Environmental Research 142 (2015) 239–256

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Review Article

Microbial influences on hormesis, oncogenesis, and therapy: A review of the literature ☆

Ryan Clanton [a,c,*], David Saucier [a], John Ford [a], Gamal Akabani [a,b,c]

[a] Department of Nuclear Engineering, Texas A&M University, College Station, TX 77843, USA
[b] Department of Veterinary Integrative Biosciences, Texas A&M University, College Station, TX 77843, USA
[c] Texas A&M Institute for Preclinical Studies, Texas A&M University, College Station, TX 77843, USA

ARTICLE INFO

Article history:
Received 22 April 2015
Received in revised form
11 June 2015
Accepted 23 June 2015

Keywords:
Microbiome
Tumor microenvironment
Oncogenesis
Hormesis
Lipid peroxidation

ABSTRACT

Utilization of environmental stimuli for growth is the main factor contributing to the evolution of prokaryotes and eukaryotes, independently and mutualistically. Epigenetics describes an organism's ability to vary expression of certain genes based on their environmental stimuli. The diverse degree of dose-dependent responses based on their variances in expressed genetic profiles makes it difficult to ascertain whether hormesis or oncogenesis has or is occurring. In the medical field this is shown where survival curves used in determining radiotherapeutic doses have substantial uncertainties, some as large as 50% (Barendsen, 1990). Many *in-vitro* radiobiological studies have been limited by not taking into consideration the innate presence of microbes in biological systems, which have either grown symbiotically or pathogenically. Present *in-vitro* studies neglect to take into consideration the varied responses that commensal and opportunistic pathogens will have when exposed to the same stimuli and how such responses could act as stimuli for their macro/microenvironment. As a result many theories such as radiation carcinogenesis explain microscopic events but fail to describe macroscopic events (Cohen, 1995). As such, this review shows how microorganisms have the ability to perturb risks of cancer and enhance hormesis after irradiation. It will also look at bacterial significance in the microenvironment of the tumor before and during treatment. In addition, bacterial systemic communication after irradiation and the host's immune responses to infection could explain many of the phenomena associated with bystander effects. Therefore, the present literature review considers the paradigms of hormesis and oncogenesis in order to find a rationale that ties them all together. This relationship was thus characterized to be the microbiome.

1. Introduction

1.1. Failures in risk assessment

Utilization of acute doses of radiation to prevent cancer was first proposed over three decades ago (Doss, 2013). This hypothesis was never investigated in humans because of the dominance of the Linear No-Threshold (LNT) model and the consequent carcinogenic concerns regarding low doses (Doss, 2013). The goal of the LNT model is to limit the risk to individuals as much as reasonably possible but if we can understand how there may be radiation hormesis occurring in the body then we may be able to harness that potential and use it as an anti-neoplastic treatment. The LNT model is representative of years of data collected from nuclear accidents, nuclear bomb detonations, and *in-vitro* studies, which the International Commission on Radiological Protection (ICRP), often with the help of national and international bodies, analyzed in order to formulate radiation safety recommendations (United Nations. Scientific Committee on the Effects of Atomic Radiation, 1977; United Nations. Scientific Committee on the Effects of Atomic Radiation, 1993; United Nations Scientific Committee on the Effects of Atomic Radiation, 1996; United Nations Scientific Committee on the Effects of Atomic Radiation, 2000; United Nations Scientific Committee on the Effects of Atomic Radiation, 2010; United Nations Scientific Committee on the Effects of Atomic Radiation, 2011). The model assumes that all exposure carried a risk so there is no beneficial amount of exposure, even at low and protracted doses. Some controlled *in-vitro, in-vivo,* human, and animal studies have contradicted the LNT model by observing some effects that are consistent with a threshold, in the region originally extrapolated for (see Fig. 1) (Redpath and Elmore, 2007; Tubiana et al., 2009; Ullrich and Storer, 1979). Of all the data used to form the LNT model, the data that is most often used and

☆This data has not been presented at a conference.

* Corresponding author at: Systems Radiobiology Laboratory, Texas A&M Institute for Preclinical Studies, 800 Raymond Stotzer Parkway, College Station, TX 77843, USA.

http://dx.doi.org/10.1016/j.envres.2015.06.026
0013-9351/

considered to be the "gold standard" for estimating the radiation-induced risk of cancer is collected from Japanese atomic-bomb survivors (Cassata, 2014). This is due to the large, non-selective population that was irradiated, the wide range of radiation doses received, and the availability of long-term systemic monitoring of their health in these studies.

The problems associated with the "gold standard" are that they are deficient in data pertaining to the homeostasis of bacteria within each individual, the amount of metabolic pathways available for cellular repair, or even the quantity of radioprotective agents such as iodine, ethanol, and trimethylglycine consumed prior to radiation exposure (Rodriguez et al., 2013). The previously mentioned problems leave too many inconsistencies and unknowns in the data to consider the data representative for evaluation of radiation-induced effects; this is especially true when considering populations of different regions. For example, the stomach is considered one of the high-risk organs in these studies but the Japanese population already has a high incidence of stomach cancer due to endemic *Helicobacter pylori* infection (Yamagata et al., 2000). In fact, the percentage of Japanese men afflicted with *H. pylori* is approximately 71.5% (Yamagata et al., 2000). This is significant considering the bacterial strain, *H. pylori,* is known to contribute to 60% of stomach cancers world-wide (Correa and Piazuelo, 2011). This means that more than half of the risk associated with radiation and stomach cancer could be significantly attributable to bacteria. Since radiation is a promoter of tumorigenesis, it would only increase the incidence of or decrease the age at which these individuals would obtain stomach cancer if previously infected. The risk is thus skewed by the high coincidence of infected individuals within Japan in contrast to other regions of the world.

There are some situations in which epidemiological effects are taken into consideration but these have always been limited due to the considerable challenges associated with accomplishing such a consideration. However, it is known that there is significant correlation between genetics, environment, diet, and cancer risk based on the risk calculations associated with an individual's absorbed dose, where inconsistencies in the data have attributed to large uncertainties. The survival curves that are used in assessing radiotherapeutic doses actually have considerable uncertainties, some even as large as 50% (Barendsen, 1990). Some individuals have even tried to model utilizing *in-vitro* data, which seems to completely ignore that more information is needed in order to treat disparities associated with different regions and populations (Mackay and Hendry, 1999).

1.2. Theories of carcinogenesis

Rudolf Virchow was the first to postulate in the mid-1800s that cancer forms in areas of chronic inflammation and he based these findings on his studies of pathogens (Sanford, 2005). His studies observed that inflammatory cells would infiltrate tumors, thus he hypothesized that cancer arose from inflammatory sites (Balkwill and Mantovani, 2001; Landskron et al., 2014; Virchow, 1863). Following Virchow, Warburg hypothesized that mitochondrial dysfunction could lead to cell death or immortalization (Warburg, 1956). The main evidence for this was the observed switch from aerobic to anaerobic respiration. He also noticed significant increases in the reactive oxygen species (ROS) production of the cancer cells (Wallace, 2005). Recent studies have also shown that the mitochondrial uncoupling or the abrogation of ATP synthesis in response to the mitochondria's membrane potential promotes the Warburg effect, potentially contributing to chemoresistance (Samudio et al., 2009).

The theory of radiation carcinogenesis is related to the two components of damage, direct damage and indirect damage (Biaglow, 1981). Double strand breaks (DSBs) and cluster damage are considered to be the main culprits behind carcinogenesis; therefore, at the present, radiation biologists have continually emphasized that ROS are not the main culprit of mutagenesis because they produce many magnitudes more single strand breaks (SSBs) than they do double strand breaks. This is why damage done by radiation, which results in a significant amount of DSBs, is considered to have a higher risk of mutagenesis. DSBs also take up to an hour before a human cell will recognize them and begin the repair process. This would mean there is a significant amount of time for additional DSBs to form and inappropriate rejoining to occur.

Most research over the past decade has been placed into routinely separating and isolating subsets of tumorigenic cells or cancer stem cells (CSCs), taken from solid tumors, that had one or a couple of distinct cellular markers, such as membrane antigens representing their cluster of differentiation (CD), that separate them from non-tumorigenic cells (Al-Hajj et al., 2003; Bonnet and Dick, 1997; Haraguchi et al., 2006; Ho et al., 2007; Lapidot et al., 1994; O'Brien et al., 2007; Olempska et al., 2007; Prince et al., 2007; Ricci-Vitiani et al., 2007; Schatton et al., 2008; Seigel et al., 2007; Singh et al., 2003; Singh et al., 2004; Wang et al., 2007; Zen et al., 2007). CSCs are similar to normal stem cells in self-renewal, unlimited proliferative potential, infrequent or slow replication cycles, and resistance to toxic xenobiotics as well as radiation. They also share high DNA repair capacity and the ability to give rise to daughter cells that differentiate (Hadnagy et al., 2006; Hirschmann-Jax et al., 2004). On the other hand, CSCs differ from stem cells in that they demonstrate deregulated self-renewal or differentiation programs and have the ability to form new tumors (Hermann et al., 2007). Their daughter cells also arrest at various stages of differentiation and have limited proliferative potential. The daughter cells, which make up the bulk of a tumor, are also characterized by their rapid replication and limited metastatic potential (Bagley and Teicher, 2009). CSCs also appear to be the main culprit for cells with the ability to metastasize (Hermann et al., 2007).

Recently, other theories have begun to be developed by the author of this literature review and other researchers to bring light to certain features unexplained by the cancer stem cell theory. For example, cell fusion as a mechanism of tumorigenesis was first postulated by Otto Aichel in the 1900s (Lu and Kang, 2009). Aichel believed that the spontaneous fusion between somatic cells could lead to chromosomal abnormalities, which could propagate into cancer. To add on to what Otto Aichel first postulated, it should be pointed out that many variations of cell fusion could occur that

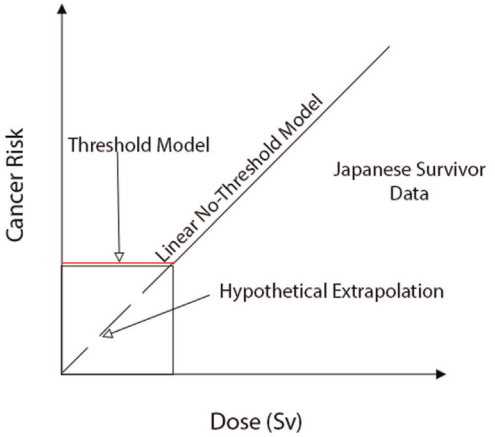

Fig. 1. The Linear-No Threshold model based on Japanese atomic bomb survivors along with the Threshold Model depicting normal incidence levels from background radiation.

could possibly contribute to the formation of diverse neoplastic cells. This is within the same tumor as well, creating opportunities for CSC populations with different CD markers to occur within the same tumor, making isolation and treatment of CSCs very arduous if based on these markers alone. The fusion of bone marrow derived cells (BMDCs) have been shown to occur with Purkinje neurons, cardiomyomycytes, and hepatocytes with evidence that trans-differentiation occurred only in these fused cells (Alvarez-Dolado et al., 2003; Chen et al., 2011). Trans-differentiation is a key characteristic of many tumors (Han et al., 2014; Shekhani et al., 2013). Since cell fusion occurs first upon the epithelial surfaces such as the blood-brain barrier, skin, lungs, and intestines where microbes thrive, it would be erroneous to ignore what potential effects they could have in cell fusion or in the complete differentiation of fused cells. There are even certain microbes with mechanisms of inducing cell fusion (Bayliss and Wolf, 1980; Kespichayawattana et al., 2000; Poste and Pasternak, 1978; Verschoor et al., 1990).

2. Reactive oxygen species

2.1. Bystander effects and carcinogenesis by reactive oxygen/nitrogen oxide/aldehyde species

The indirect reactions of ionizing radiation interacting with water have the ability to produce (ROS) in biological systems (Riley, 1994). A common characteristic of these reactions is that the body responds to ROS by perceiving it as a threat and causing more inflammation, often due to the mitochondria, in the affected tissues (Azzam et al., 2003; Leach et al., 2001; Yamamori et al., 2012). This increase is believed to be the foundation of why the bystander effect occurs in radiation treatments (Chen et al., 2009a; Shao et al., 2003).

The propagation of these radiation-induced, mitochondria-dependent responses by the cells, the electron-transport chains of bacteria, and the immune system could propagate into a hazardous situation where a large concentration of ROS, reactive nitrogen oxide species (RNOS), and aldehydes are situated within a rather localized area. Even though acute amounts are used every day for beneficial activities such as inducing stem cell differentiation, chronic exposures to ROS have never been associated with a beneficial outcome. This phenomenon is referred to as the ROS paradox in which ROS is an essential biomolecule utilized in the regulation of cellular functions and as toxic by-products of metabolism (Thannickal and Fanburg, 2000). The only difference appears to be in the ROS concentrations, where they occur, and what by-products they produce (Thannickal and Fanburg, 2000).

The downstream effects of oxidative stressors and their mutagenic capacities need to be taken into consideration as well. The primary targets of oxidative stressors are DNA, proteins, and lipids. Free radicals also have a tendency of directly attacking polyunsaturated fatty acids in the membrane and resulting in a process known as lipid peroxidation (Cabiscol et al., 2000). The most chemoresistant cancer cells have already been linked to mitochondrial uncoupling and preferential oxidation of fatty acids (Samudio et al., 2009). A primary effect of lipid peroxidation is a decrease in the cell's membrane fluidity, which alters the cell's membrane properties and bound proteins (Samudio et al., 2009). As a result, the cell's ability to receive paracrine signals becomes limited. This effect acts as an amplifier to free radical production and lipid peroxidation that will result in larger concentrations of aldehyde by-products (Samudio et al., 2009).

Aldehydes are extremely reactive, have long lives (~9 min), and can diffuse from their site of origin and attack distant sites with high lipid and DNA specificity (Cabiscol et al., 2000). The lifespan of ROS in the cytoplasm may explain why they do not cause much damage when induced in the cytoplasm. However, their ability to produce aldehydes via lipid peroxidation could demonstrate why there is a need for processes to prevent them from reacting with the cell membrane or organelle membranes. In contrast to ROS, the aldehydes can induce a significant amount of cluster damage, SSBs, and DSBs (Cabiscol et al., 2000). The most extensively researched aldehydes, such as melonaldehyde and 4-hydroxyalkenals, will actually produce SSBs and DSBs in the DNA backbone, adducts of base and sugar groups, cross-linkage to other molecules, and lesions that block replication (Cabiscol et al., 2000). Interestingly, almost every CSC and circulating tumor cell (CTC) that has been found has also been shown to have up-regulated expressions of aldehyde dehydrogenase (Charafe-Jauffret et al., 2010; Chen et al., 2009b; Marcato et al., 2011a; Marcato et al., 2011b; Ucar et al., 2009). The daughter cells of these CSCs will either die or survive based on their continued expression of these pumps or transporters.

The radiation theory of carcinogenesis fails to explain why some non-dividing cells, such as lymphocytes, apoptose after relatively limited radiation exposure while the proliferative cells of the liver appear relatively unaltered and continue to function (Biaglow, 1981). Aldehyde dehydrogenase is one important piece of evidence that contradicts the theory of radiation carcinogenesis in terms of direct interactions. For example, the liver, whose cells have a more than average expression of Aldehyde dehydrogenase, can receive doses up to 31 Gy and still continue replicating and repairing itself without any ill effects (Dawson et al., 2002). Repair proteins and cytoplasmic volume may be increased in liver cells but with such a large dose the direct interaction component (DSBs and cluster damage) of radiation carcinogenesis loses some foundation. There should also still be quite a bit of indirect damage as well.

Due to this conundrum, it would appear more likely that the liver is responding to ROS and aldehyde production induced by radiation immediately in some fashion rather than radiation-induced direct damage of the DNA. This is especially true if it can take up to an hour for the cell to recognize DSBs. Thus, it is already something expressed by liver cell that have the capabilities of removing large quantities of radiation's by-products immediately, that make them radioresistant. The aldehyde dehydrogenases of the liver are already tasked with elimination of toxins, aldehydes, and alcohols in the first place so much of the liver's radiation resistance could be due to its elimination of the aforementioned by-products of radiations indirect reactions (Bosron and Li, 1986; Koivula, 1975). This hypothesis is backed up by the overall increase in liver function that has been shown to follow up low doses of radiation exposure (Yeo et al., 2010).

2.2. The role of the mitochondria and bacteria in ROS homeostasis

As previously mentioned, Warburg was one of the first proponents of mitochondrial dysfunction for carcinogenesis. Considering the endosymbiosis hypothesis, the mitochondria were originally prokaryotes whose portions of original genes have migrated to the nucleus, it would seem flawed to assume that bacterial RNA cannot be integrated into the mitochondria or nucleus via the same mechanisms of this hypothesis (Cheng and Ivessa, 2010; Lough et al., 2008; Richly and Leister, 2004). This would explain why some researchers have noticed a surplus of modern day microbe-like (usually pathogen related) RNA, converted to DNA, within the mitochondrial genome of cancer cells (Criswell, 2009; Riley et al., 2013). The electron transport chains of the two are pretty much identical as well, establishing a link between the mitochondria of human cells and bacteria, as both will become a biological source of ROS when the cells are exposed to ionizing

radiation. This will arrest the cells in the G2/M phase, increasing ROS for mediating Bystander effects, but having potential for genotoxicity in neighboring cells in high concentrations (Chen et al., 2009a; Shao et al., 2003; Yamamori et al., 2012).

This is complicated by the replacement and/or fusion of stem cells with the damaged cells in an environment that would damage the stem cell DNA and potentially hinder their complete differentiation normally (Naka et al., 2008). This is because a common feature of stem cells is that the more pluripotent they are, the less likely they will differentiate rather than apoptose when there is surplus ROS; as such, there will actually be a higher risk of affecting the DNA, gap junctions, and corresponding cell signaling (Naka et al., 2008). Bacteria will also respond to this stress rapidly by dividing and increasing their population size and diversity. Increasing their metabolic processes will result in an overactive respiratory chain. In *E. coli* the respiratory chains are presumed to account for 87% of the total hydrogen peroxide production (Cabiscol et al., 2000). There is no clear consensus to what effect this extra production of ROS will have on surrounding mammalian cells. The leakage of single electrons from the bacterial respiratory chain has been observed at the dehydrogenase and ubiquinone sites (Cabiscol et al., 2000). This is a process that is actually very similar to the processes observed in the mitochondria of mammalian cells (Cabiscol et al., 2000).

It may take up to an hour before the body will respond to radiation-induced DNA damage but bacteria react within a few seconds to radiation and other environmental stressors. Having bacteria that will respond to radiation within minutes by transcribing superoxide dismutase and catalase could be beneficial to controlling the concentration of ROS. It may not do anything to the ROS inside the cells but as we know today the ROS are very short lived and if not within the nucleus have relatively little effect (Munro, 1970). As such, interactions of bacterial ROS would occur on the cell membranes. Lipids make up 10% of human cell dry weight and 53% of these lipids make up the cell membrane (Gray and Yardley, 1975). This would give credence to a large quantity of lipid peroxidation reactions upon the cell membrane producing aldehydes. As previously mentioned, the DNA damage seen by ROS and radiation appears to be the same as those induced by aldehydes as well except that aldehydes also have preference for other lipids (to produce even more aldehydes) along with the DNA (Vaca et al., 1988). To counter ROS production within the cell itself, bacterial lipopolysaccharides or endotoxins have also been shown to increased gene expression of ROS-eliminating pathways (Spolarics, 1996).

Most of the data about radiation and ROS damage comes from controlled, antibiotics-treated, *in-vitro* studies. This may be an ineffective method because antibiotics eliminate components (bacteria and their responses) that add to the potential DNA damage and hinder the ability for cell-to-cell communication. They also fail to consider toxic interactions of antibiotics with radiation such as those seen with antibiotic interactions with radiation from the sun, not that there has been much consensus in what these reactions truly are the result of. In addition, culture experiments are missing major contributors to stem cell and immune system response. Normally, the tissues of the immune system will produce radical oxygen species (ROS) and nitrogen intermediates that damage and/or destroy other damaged cells in order to destroy possible out-growths of bacteria and any tissues that are evading apoptosis (Shacter and Weitzman, 2002). The studies would also not take into consideration that bacteria will begin effluxing rapid amounts of ROS within minutes, increasing production of catalases/superoxide dismutase while sending signals to other bacterial cells. There is also some evidence of association with the mammalian cells via gap junction intercellular communication (GJIC) (Kelly et al., 2004). This is a clear situation where bacterial communication would contribute to bystander effects.

If the body continues to produce ROS in such a confined area the cells will most likely be overwhelmed, lipid peroxidation will increase, and there will be considerable amounts of inflammation. This could result in higher quantities of damage to healthy cells and their DNA. As a result this will lead to mutagenesis, oncogene activation, and angiogenesis (Shacter and Weitzman, 2002). This is where the idea of increasing the ratio of bacteria that moderate inflammation to those that induce more damage could be a practical means of accomplishing hormesis (Kelly et al., 2004). The bacteria that would be considered good are commensal bacteria, which have the ability moderate inflammation, while some such as *Lactobacillus rhamnosus* also produce novel, soluble proteins such as p75, which limit apoptosis and increase mammalian cell survival (Ciorba et al., 2012; Ciorba and Stenson, 2009; Demirer et al., 2006; Dong et al., 1987; Kelly et al., 2004; Lin et al., 2009; Yan et al., 2007).

The bacteria that are bad are opportunistic pathogens, which have a large potential for creating ROS and inducing more damage in the environment as it grows without competition from other bacteria. This explains why many individuals exposed to large doses of radiation actually die from sepsis more often than they would from other effects (Walker, 1978). Therefore, damage induced by radiation should be considered to include the effects of radiation on the DNA, the concentration and position of produced ROS, and the ability of bacteria to control or disrupt the

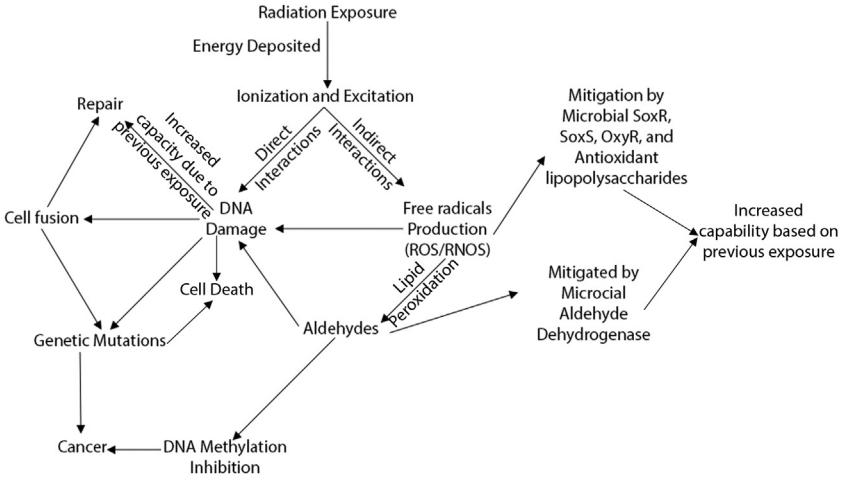

Fig. 2. The above figure represents radiations effects on cells and how bacteria can mitigate some of the risks.

homeostatic properties of the environment (see Fig. 2).

3. Hormesis and radioprotection

3.1. Bacterial radioprotection and hormesis

The human population lives in a partnership with a rich commensal microbiota on the epithelial surfaces (Trinchieri, 2013). This is an important partnership that is critical for tissue formation, metabolism, the development, and the functioning of innate/adaptive resistance. If you follow, step by step, the effects of ionizing radiation, then you will see that the commensal bacteria, such as *E. coli,* will begin transcription of OxyR, SoxR, and SoxS to produce superoxide dismutase and many other enzymes necessary for the removal of ROS (Thannickal and Fanburg, 2000). Even the previously mentioned aldehydes would be mitigated by microbial aldehyde dehydrogenase activity (see Fig. 2) (Nosova et al., 1996). If they are not commensal bacteria or if homeostasis has been disturbed, then some populations of bacteria will begin to increase their growth rate and increase their production of ROS as a result of their active electron transport chains and metabolic processes. They may even increase their production of ROS in response to an altered environment (stress) and corresponding proliferation. If the radiation disrupts the bacteria's ability to control inflammatory responses, then the immune system may respond as well. This leads to the propagation of ROS that is not beneficial to the whole organism. It would also be hard to infer whether bacteria could have acquired a mutation where they continue to just produce ROS from continued metabolic activity or impaired energy production. As previously mentioned, this would be very similar to what occurs in mitochondrial dysfunction.

One clear example of this is how the intestinal microbiota provides protective immunity in the case of mucosal infections or damage and regulates the physiological host-microbial mutualism. For example, in the human body it is believed that approximately 3 Gy of radiation is needed to harm gastrointestinal stem cells while hematopoietic stem cells are damaged at doses greater than 1 Gy. This review suggest that this is because the gastrointestinal stem cells are located inside intestinal crypts which along with other parts of the intestines are microcosms for different types of bacteria such as *Lactobacillus* and *Escherichia* (Keku et al., 2014; Yen and Wright, 2006). *Lactobacillus* probiotics have been routinely administered prior to radiation exposure and scientists have been led to believe that the bacteria were able to alleviate some of the inflammation of the gut caused by radiation therapy via repositioning of the cyclooxygenase-2 (COX-2) pathway and nuclear-cytoplasmic shuttling of peroxisome proliferator-activated receptor gamma (PPAR-γ) and V-Rel Reticuloendotheliosis Viral Oncogene Homolog A (RelA) (Ciorba et al., 2012; Dong et al., 1987; Kelly et al., 2004). RelA is also known as Nuclear Factor of Kappa Light Polypeptide Gene Enhancer in B-Cells 3 (NFKB3), which is a part of a family already hypothesized for linking inflammation and cancer development/progression (Karin and Greten, 2005). This would give some reasoning to why in-vitro studies have shown the in-vitro threshold dose of neoplastic transformation to be around 100–200 mGy with hormesis below these doses while recent *in-vivo* data shows threshold doses greater than 1000 mGy being necessary for neoplastic transformation (Redpath and Elmore, 2007).

Another interesting reaction of bacteria is the cross-talk between the microbiota and the immune system involving the innate cell types such as macrophages and dendritic cells (Trinchieri, 2013). It might seem alarming that bacteria have so much control over our inflammatory processes and yet the first thing prescribed when we have a viral infection is antibiotics, which only affect bacteria. It is also alarming that antibiotics can be the very cause of gut permeability that allow bacteria to translocate into the blood (Swank and Deitch, 1996). This was corroborated by Velicer in 2004, whose study was trying to correlate antibiotic use and risk of developing breast cancer (Velicer et al., 2004). As such, a better pursuit would be making the commensal bacteria in our body resistant to viruses utilizing transfection of genes containing conjugate RNA or proteins that bind to viral RNA or proteins.

A simple proof of how microbes contribute to radiation hormesis can be seen in a study performed by Gerber in 1974 (Gerber et al., 1979). They demonstrated a very interesting link between the effects of frequent sun exposure on bacterial colonization of the skin. Many micro-organisms are susceptible to the lethal action of light and many often have protective mechanisms against these actions (Gerber et al., 1979). In the study, organisms were collected from the forehead, forearm, upper arm, upper back, and lower back of 21 healthy female volunteers ranging in age from 22 to 41. Nine of the individuals were frequent sunbathers and 10 were infrequent sunbathers. What is relevant about the study is that both groups had approximately the same amount of bacteria everywhere and the bacteria to fungi concentration were not significantly different.

The authors' found that individuals who frequently sunbathed had a greater number of pigmented bacteria than those that sunbathed infrequently. The pigmented bacteria were also found on chemical analysis to contain carotenoid pigments. In contrast, high numbers of non-pigmented bacteria were obtained from the infrequent sunbathers. The authors neglected to assess this, but this author would have liked to see the arrangement of the bacteria on top of the skin to see whether the pigmented bacteria live on top of the non-pigmented bacteria in some type of mutualistic environment.

The most significant and important study that was able to prove that bacteria could significantly increase the radio-resistance of a tissue was performed by Daly and his colleagues in 2010 (Daly et al., 2010). This study found that *Deinococcus radiodurans* and other bacteria which are extremely resistant to ionizing radiation, ultraviolet radiation, and desiccation produced protein-free substances that could prevent the oxidation of proteins at massive doses of ionizing radiation (Daly et al., 2010). In contrast, the radiation-sensitive bacteria were found to not be protective at all. To make matters even more impressive the researchers found that the bacterial extracts or ultra filtrates were protecting *E. coli* and human Jurkat T cells from extreme doses of ionizing radiation as well (Daly et al., 2010). Thus, there are potentially radioprotective substances produced by bacteria, and with modern genetic profiling and manipulation, they can be used to engineer bacteria capable of protecting tissues from damage (see Fig. 3).

Another point to mention is that bacteria also live in a competitive environment, a healthy component for the host considering microbes that are pathogenic are usually in competition

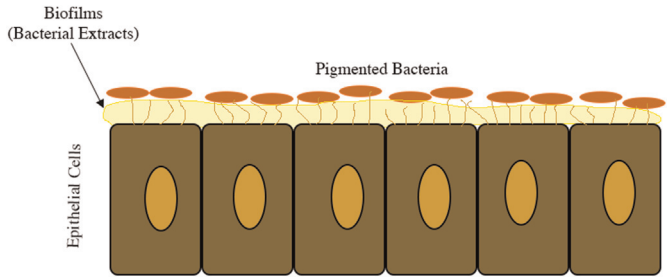

Fig. 3. The figure above depicts how pigmented bacteria, their biofilms, and bacterial extracts can be used for radioprotection.

against others. There is much diversity in the microbiome that is important to the health of the host (Abrahamsson et al., 2012; Alves et al., 2012; Azad et al., 2013; Ballor and Leadbetter, 2012; Cayrou et al., 2013; Dillon et al., 2010; Engel et al., 2012; Engel and Moran, 2013; Forno et al., 2009; Ismail et al., 2012; Kohl, 2012; Lozupone et al., 2012; Mihajlovski et al., 2010; Scanlan and Marchesi, 2008; Turroni et al., 2012). This prevents one pathogenic strain from overpopulating and thus inducing an infection or detrimental situation. Most bacteria may have a higher resistance to radiation than mammalian cells but controlled *in-vitro* studies fail to assess how competition between bacteria can be affected by radiation. From a microbial studies standpoint, it seems that only low and high levels of radiation are indicative of competition while all ranges between will allow one species to overgrow the others (Ragon et al., 2011).

For example, a study performed in Chernobyl showed that bacterial competition is drastically affected by ionizing radiation (Ragon et al., 2011). In terms of the mammalian microbiota, this would not be a beneficial situation. Opportunistic bacteria might take this as an opportunity for over-growth and invasion into the blood while at the same time, increasing local concentrations of ROS. The Chernobyl study allows an individual to see that at least three situations could occur in the gut. Either radiation hormesis will occur and the bacteria will respond to irradiation within minutes by transcribing proteins to remove ROS, the bacteria will respond as if they are endangered and begin producing more ROS to kill off the bacteria surrounding them (disrupting homeostasis), or the ROS will be over concentrated and certain populations of radioresistant bacteria will grow without competition.

3.2. Effects of nutrition and radioprotectants on the microbiome

Depending on the concentration of certain nutrients, the pH, and many other components of an individuals' diet, then their microbiota will be affected in a severe manner (Kruis et al., 1991). This is again due to the fact that microbes are always competing for dominance, which leads to problems such as irritable bowel syndrome, eczema, certain diseases, and even allergies (Abrahamsson et al., 2012; Azad et al., 2013; Bolino and Bercik, 2010; Cani et al., 2008; Forno et al., 2009; Gratz et al., 2010). An individual's microbiota will then affect their adiposity, inflammation, immune system, metabolism, energy, hypertension, and even gut permeability, which would explain how gut bacteria are found within tumors in the first place (Abou-Donia et al., 2008; Bolino and Bercik, 2010; Cani and Delzenne, 2009; Cani and Delzenne, 2010; Cani et al., 2008; DiBaise et al., 2008; Hugot, 2004; Iwamoto et al., 2010; Kadooka et al., 2010; Kirjavainen et al., 1999; Kruis et al., 1991; Leyer et al., 2009; Lye et al., 2009; Majamaa and Isolauri, 1997; Mcfarland and Bernasconi, 1993; Rao et al., 2009; Selvam et al., 2009; Soler et al., 1999; Sullivan et al., 2009; Wang et al., 2014). The correlation between nutrition, the microbiome, and cancer is most significantly illustrated in western society where obesity is one of the leading causes of cancer in non-smokers with liver disease being the largest cancer risk for individuals above 35 BMI (Calle and Kaaks, 2004; Calle and Thun, 2004). Interestingly, changes in the intestinal microbiota by alcohol has been linked to the progression of alcoholic liver disease via bacterial translocation and the production of certain microbial metabolites (Yan and Schnabl, 2012; Yoshimoto et al., 2013). Even the lung tumors of smokers has considerable association with microbes as well (Cummins and Tangney, 2013). The microbiome has also been shown to secrete metabolites that promote liver cancer through the senescence secretome (Cani and Delzenne, 2010; DiBaise et al., 2008; Kadooka et al., 2010; Pischon et al., 2008; Wang et al., 2014; Yoshimoto et al., 2013).

Turnbaugh performed an interesting study where he was able to demonstrate significant effects of diet on the microbiome by transplanting fresh or frozen adult fecal microbial communities into germ-free c57BL/6 J mice (Turnbaugh et al., 2009b). He showed that the microbial environment and the genes they expressed changed within one day after switching from a low fat, plant polysaccharide-rich diet to a high-fat/high-sugar "Western" diet (Turnbaugh et al., 2009b). There is also a profound effect of nutrition on the genes expressed and the concentration of certain bacteria in the gut microbiome of distinct human populations and even those of different body mass indexes (BMIs) (De Filippo et al., 2010; Muegge et al., 2011; Turnbaugh et al., 2009a). The study demonstrated that bacterial ingestion could affect the lateral gene transfer of genes from one bacterium to another, affecting the gene expression of the microbiome. Hehemann showed the lateral gene transfer of genes coding for porphyranases, agarases, and associated proteins from *Zobellia galactanivorans* living on seaweed to the gut bacterium *Bacteroides plebius* (Hehemann et al., 2010). These are carbohydrate-active enzymes, which could overtime significantly enhance carbohydrate digestion, especially when seaweed makes up 14.2 g per person per day of the daily diet in japan (Cantarel et al., 2009; Fukuda et al., 2007; Hehemann et al., 2010). This could explain why the non-obese Japanese population can have such a high-carbohydrate diet tolerance.

Along with nutrition, the inclusion of antibiotics in meat, produce, and many other consumable products has significantly affected the virulence of bacteria and disrupted the growth of beneficial bacteria that could help prevent infections. Many individuals will suggest the ingestion of yogurt or fermented foods for bacterial content but this fails to assess the homeostasis of each type of bacteria or the quantities that will actually reach the gut (Rambaud et al., 1993). These are important considerations that are needed in order to induce a favorable environment for radiation protection. This review suggests that we also need to find the correct proportion of bacteria needed for competition with/regulation of opportunistic pathogens that have the ability to induce cancer (Chang and Parsonnet, 2010).

Furthermore, many of the radioprotectants that we use are actually compounds that have a beneficial effect on the bacteria as well. Trimethylglycine, for example, has multiple applications in which it may be beneficial in mammalian cells. First, it acts as an osmotic regulator controlling osmotic stressors and limiting membrane damage (Bucuvalas et al., 1995). Second, is the fact that trimethylglycine acts as a chemical chaperone that will actually use its methylating groups to repair DNA damage as well as proteins denatured by ROS or radiation (Diamant et al., 2001; Rodriguez et al., 2013; Sharma et al., 2013). These are also the same situations and effects found in bacteria as well. The effects are significantly increased though since bacteria don't have a nucleus. This is why it would be very beneficial if aims were to increase the survival of bacteria producing catalases and superoxide dismutase. Since trimethylglycine or betaine also acts as an antioxidant it is extremely important in moderating lipid peroxidation since it seems that peroxidation occurs when the antioxidant defenses are overcome (Alirezaei et al., 2012). Trimethylglycine or its substituent choline and ethanol also seem to have direct effects on the ability of human and bacterial cells to resist aldehydes (Holmström et al., 1994; Steinmetz et al., 1997).

4. Microbial effects on neoplasms

4.1. Bacteria in the microenvironment of the tumor

Bacteria-in-the-blood is another name for acute bacteremia, which is a situation that, although often considered medical heresy to say, appears to occur normally and very often in people

as well as animals without any noticeable symptoms (Dahlinger et al., 1997; Domingue and Schlegel, 1977; Greene, 2006; McLaughlin et al., 2002; Tedeschi and Amici, 1972; Tedeschi et al., 1976b; Tedeschi et al., 1978). Bacteria in the blood can occur through various methods such as bug bites, oral cavities, antibiotics, chemotherapeutics, and superficial wounds (Amar et al., 2011; Berg, 1983; Gendron et al., 2000; McLaughlin et al., 2002; Nakayama et al., 1997; Swank and Deitch, 1996). As mentioned previously, an individual just needs to look at how the American diet is contributing to leaky gut syndromes to see how bacteria could enter the blood as well (Kiefer and Ali-Akbarian, 2004). Bacteria in the blood and leaky guts create many complications such as osteomyelitis, depression, chronic fatigue syndrome, eczema, obesity, and even cancer as presented in this paper (Cani and Delzenne, 2009; Forno et al., 2009; Gutierrez, 2005; Lewis et al., 1978; Maes et al., 2007; Mass et al., 2008).

Therefore, it is not surprising that the effects of bacteria continue in the microenvironment of the tumor as well. This may be either good or bad depending on the balance of bacteria and the type of bacteria within and around the tumor (Boleij et al., 2012; Iida et al., 2013; Lokody, 2014; Trinchieri, 2013; Viaud et al., 2013; Yan et al., 2007). Most bacteria live in a dynamic environment where temperature, availability of nutrients, and presence of various chemicals vary (Ron, 2006). Tumors, CTCs, and metastasized tumors are all microenvironments in which many bacteria have the ability to survive and thrive due to the produced growth factors and local immunosuppression (Morrissey et al., 2010). This was clearly shown in a study performed by Yu, which found that bacteria could be injected straight into the blood stream, without any modification, and still be specific to the neoplasm (Yu et al., 2004). In fact, they were highly effective at using light emitting bacteria to see the preferred target neoplasms (Yu et al., 2004). This thus means that bacteria can also be used as tumor-targeting vectors, an idea that was first being investigated over 150 years ago when doctors were noticing shrinkage in tumor volume after purposeful infection with bacteria (Pawelek et al., 2003). Therefore, studies of bacteria and cancer have ultimately lead to the study of immunomodulation, in fact, the cell wall components of *Bifidobacterium,* lipopolysaccharides from *Salmonella*, and the toxins produced by *Clostridium* have all been used to target, enhance immune response, and increase the efficacy of treatments such as chemotherapy (Pawelek et al., 2003).

4.2. Hypoxia and angiogenesis

As mentioned previously, Warburg hypothesized that mitochondrial dysfunction was occurring in cancer due to his observation of the switch from aerobic to anaerobic respiration (Warburg, 1956). This anaerobic switch leads to or is due in part to the formation of a hypoxic region. It has been routinely shown that bacteria can be used to target these areas of hypoxia in order to digest necrotic tissue and slow growth (Yu et al., 2012). However, not much research has been successfully made into why the hypoxic regions are occurring besides the fact that proliferation may induce stress that causes the arteries to collapse. The problems this author has with these theories are that they do not explain how cysts and other growths such as moles can undergo active proliferation with increased blood flow instead of hypoxia. However, activation of Hypoxia Inducible Factor 1 (HIF-1α) is a general phenomenon associated with the hypoxic regions of neoplasms while also being induced by lipopolysaccharides and other compounds produced by bacteria (Werth et al., 2010). This is because HIF-1α is associated with the host's innate immune functions in order to help the specialized phagocytic cells function in the hypoxic microenvironments of infected tissues (Nizet and Johnson, 2009; Zinkernagel et al., 2007). Thus, bacteria in the microenvironment of the tumor would effectively prepare the neoplasm against hypoxia as well as inflammation, since HIF-1α also has a positive association with the expression of the previously discussed aldehyde dehydrogenase (Tiezzi et al., 2013).

The relationship between the two is rather complex, but it would seem that the CSCs are manipulating the host immune responses to the bacteria attracted to it for further growth and development. Considering how Virchow first noticed the infiltration of inflammatory cells into tumors, it's no wonder that fusion of macrophages with tumor cells could occur leading to the expression of macrophage antigens by tumor cells (Lazova et al., 2011; Powell et al., 2011; Shabo and Svanvik, 2011). Noting how the immune system seems to promote the tumor growth, it is also relevant to note the studies showing bacterial influences on TLR5 signaling and galectin-1-producing γδ-T cells, which therefore significantly affect distal malignant progression through tumor-promoting inflammation (Rutkowski et al., 2015).

Even after hypoxia, bacteria's influence could continue with the angiogenesis that follows. The connection between hypoxia and angiogenesis has been extensively investigated as a form of "supply and demand" or delayed negative feedback (Moeller et al., 2004). In other words, the hypoxia induces a lack of oxygen available to the cells which results in the expression of pro-angiogenic substances (Krock et al., 2011). However, when looking at bacteria in the tumor microenvironment, it must be taken into consideration what those bacteria do in other environments as well, to see if those roles are transferred. Therefore, one can see their influence in angiogenesis as the microbiota also induce intestinal vascular remodeling (Reinhardt et al., 2012). Even the mechanisms they use, such as tissue factor (TF) glycosylation, have been linked to tumor angiogenesis (Belting et al., 2004; Reinhardt et al., 2012). This alone shows that bacteria in the microenvironment of the tumor would have direct influence on angiogenesis.

However, there are even more influences that microbes could have in the microenvironment of the tumor to promote angiogenesis as well. For example, *Bartonella hensalae* has been shown to promote angiogenic lesions as a result of the production of IL-8 by monocytes and endothelial cells (McCord et al., 2006). Interestingly enough, *B. hensalae* has also been shown to induce vascular endothelial growth factor (VEGF), one of the main contributors to tumor angiogenesis, in carcinomas (Kempf et al., 2001; Kirby, 2004). Furthermore, bacterial lipopolysaccharides have also shown the capability of inducing angiogenesis along with their potential in metastatic growth of tumors (see Fig. 4) (Harmey et al., 2002; Pollet et al., 2003).

4.3. Abscopal effects

Bacteria are also quick adapters to any type of stress but what truly makes them interesting is that their response is not localized. They have global regulatory networks that control the simultaneous expression of a large number of genes and the level of response is proportional to the extent of the change (Ron, 2006). This is not to claim that abscopal effects are completely controlled by bacteria but it is difficult to find a research article showing the body's immune system only responding to the unique cell markers on CSCs and not to the potential unique cell markers or exogenous gene expressions of the bacteria present in that tumor as well. The most effective cancer treatments have actually always increased expression of immune responses.

The whole concept of unique cell markers on the CSCs is fundamentally limited by whether or not there is a mutation that results in a foreign protein or lipid that is produced and whether or not it is noticeable by the immune system. It is also limited by whether distal sites of metastasis will have these unique expressions as well. The most fundamental limit to this theory is

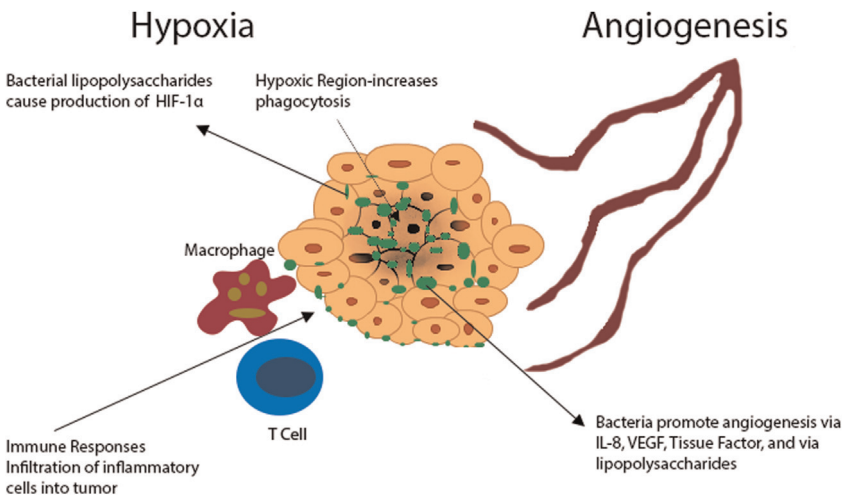

Fig. 4. The figure above depicts microbial influences in the development of hypoxia on the left and angiogenesis on the right.

assuming that these "unique" cell differentiation markers are not expressed by the normal stem cell populations, which they often are. The immune system will probably be able to notice the daughter cells of CSCs and be able to control the tumors growth but the CSCs don't express unique cell markers induced by transcription errors in large quantities. They are not usually easily recognized as foreign cells and targeted by the host immune system rapidly. Many CSCs express the same markers as embryonic and tissue stem cells but in different amounts so it makes perfect sense that the body would not recognize them as foreign. Tumors are not homogeneous either so it is rather difficult to assess how irradiating one tumor could reduce the growth of tumors in other regions of the body based on immune response to the same cell differentiation marker transcription errors.

There is a greater probability that the immune system would send antibodies systemically after perceiving an infection. Some of these processes may take time but utilizing a bacterium that the body has already been exposed to and can therefore target within a couple of days would drastically enhance the ability for the immune system to target the cancer. There will probably be an even greater probability that a combined immune response to a bacterial infection and the foreign proteins in cancer would induce a strong systemic immune response, increasing the treatments effectiveness. This increased immune response from multiple agents can be seen in how successful the Diphtheria, Tetanus, and acellular Pertussis (DTAP) vaccine, has become at immunizing against these microbes or the illnesses they produce.

It may be that the immune system is targeting the apparent "bacterial infection" that is a component of the microenvironment of the tumor, thus inducing an abscopal reaction systematically (see Fig. 5). Bacteria are mutated by ionizing radiation and free radicals faster and more readily than mammalian cells so it is questionable why these considerations have not had more prominence. Commensal or opportunistic bacteria could be easily mutated, or create a localized infection to the point at which the immune system would consider them a foreign identity.

Many bacteria are usually opportunistic so when tumors begin growing there is a marked change in the microenvironment that may allow only certain strains to preferentially proliferate. The reverse may also be true. There is no indication that the tumor has to occur first and that it is not the pre-existing imbalance of certain strains of bacteria that are contributing to tumor growth. This was exactly what Virchow was first postulating and seeing in his studies (Chang and Parsonnet, 2010). He noticed that there was indeed chronic irritation stimulating cancer cells to grow (Chang and Parsonnet, 2010). He came to this after seeing the inflammatory reaction in schistosome-related bladder cancers (Chang and Parsonnet, 2010). He thus believed that it was the

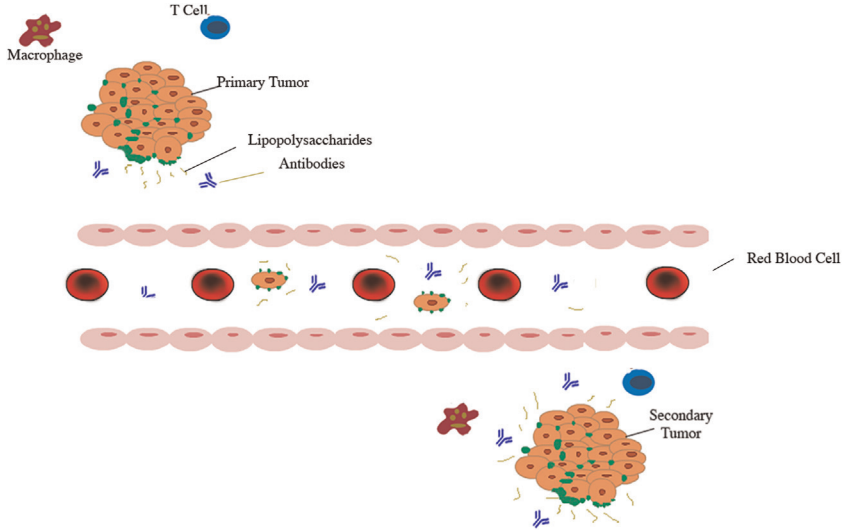

Fig. 5. The figure above depicts how it could be the host's immune response to pathogens in the tumor that contribute to abscopal effects.

inflammatory process characterized by the host's immune response to infection rather than by the infecting organism itself (Chang and Parsonnet, 2010).The immune system is a very complex system so the authors find it intriguing to discern whether the immune system perceives the bacteria of the tumor as an infection and begins releasing antibodies and cytokines to help limit and control the outgrowth. The only item required for this reaction is some of the lipopolysaccharides of the bacteria that died from treatment with harsh antibiotics or chemotherapeutics to be noticed.

4.4. Therapy

There are two other studies that when combined suggest that there is a direct correlation between bacteria and radiation-induced damage in mammalian cells (Bleehen et al., 1974; Jørgensen, 1972). In the first paper by Jorgensen in 1971 a time dose relationship in combined bleomycin (BLM, a radiomimetic and radioprotectant at small doses) treatment and radiotherapy was assessed. In the study it was seen that the inhibition of tumor growth obtained by the combined treatment given simultaneously was higher than by BLM treatment alone. The biological effects of the treatment were assessed to be similar to radiotherapy and a synergistic effect was expected (Jørgensen, 1972). An additional interesting feature was that intermittent treatment with BLM increased the reduction of tumor growth at a rate faster than the combined treatment.

However, these results were not what Bleehen found in 1974. Bleehen observed that the mammalian cells had no potentiation effect induced by the combination of BLM and radiation therapy in clinical practice (Bleehen et al., 1974). Bleehen was on to something in his experiment but did not appear to note it. In every case, the number of bacteria was affected by BLM. BLM also had a significant effect on the survival of *E. Coli* B/r strains, especially when given BLM after irradiation. What is interesting about this study is that the mammalian cells (EMT6/M/CC) were not affected by the presence of BLM before, during, or after irradiation (Bleehen et al., 1974). As such, there was no significant statistical change in cell survival.

What Jorgensen and Bleehen found, creates a very important question that needs to be analyzed further in depth. How does a drug that is considered radiomimetic have any radioprotective properties when it does not appear to have any effect on mammalian cell death or survival independently but seems to rather significant effect on bacteria? This also makes the authors curious to whether compounds that produce certain reactions in bacteria can be used to increase the effectiveness of cancer therapeutics used today. One of the most interesting proofs of this concept is a paper written by Noriho Iida in 2013 (Iida et al., 2013). What Iida found is that in antibiotics-treated or germ-free mice, tumor-infiltrating myeloid-derived cells responded poorly to CpG-oligonucleotide immunotherapy and platinum chemotherapy, resulting in lower cytokine production/tumor necrosis and deficient production of ROS/cytotoxicity, respectively.

This paper significantly shows the apparent effects bacteria have on anti-cancer treatments and what this could mean for normal tissues. If bacteria control the efficacy of a treatment then it would seem reasonable that the treatments affect the bacterial population in such a way that they are stressed. With bacterial stress comes bacterial ROS production and bacterial death followed by immune responses, thus creating a highly localized inflammatory region where there is higher host cell death. If microbes have the ability to increase cell death then efforts should be placed into inducing stress in the bacterial strains associated with the tumor microenvironment during treatment as well. It should also be assessed to what type of stress the treatment is inducing in the bacteria or what their responses actually are.

In another study by Viaud in 2013, cyclophosphamide was studied because it is one of several clinically important cancer drugs whose therapeutic efficacy is due in part to its ability to stimulate antitumor immune responses (Viaud et al., 2013). What they found is that when cyclophosphamide was given to germ-free mice or mice that were treated with antibiotics to kill gram-positive bacteria, their tumors were resistant to cyclophosphamide. This was because they realized that it was actually bacteria stimulating the generation of a specific subset of "pathogenic" T helper (pT_H17) cells and memory T_H1 immune response (Viaud et al., 2013). Viaud correctly noted that the gut microbiome modulates the chemotherapeutic treatment but what he did not fully consider was that the bacteria of the gut are also routinely found in the microenvironment of the tumor as well. Another influence not considered is that the chemotherapeutic used, cyclophosphamide, has been associated with the translocation of *E. coli* to non-intestinal regions of the body such as the liver and blood (Nakayama et al., 1997). These results have also been corroborated by other chemotherapeutics and various other bacteria as well (Berg, 1983).

Cyclophosphamide has also been extremely useful in understanding what is truly killing the tumor. This is because of a study done by John Hilton in 1984, which found that cyclophosphamide-resistant L1210 have abnormally high aldehyde dehydrogenase activity (Hilton, 1984). This would mean that it is not just ROS, but the downstream reactants such as aldehydes that play a major role in carcinogenesis and tumor killing. As mentioned previously, many of the CSCs and most importantly those that are invasive actually show significantly increased aldehyde dehydrogenase expression (Charafe-Jauffret et al., 2010; Chen et al., 2009b; Landen et al., 2010; Marcato et al., 2011a).

Most chemotherapeutics are primarily microbial antibiotics that were assumed to have the similar effects on mammalian cells due to their toxicity. However, why does utilizing antibiotics beforehand or performing the treatment in a germ-free animal cause the treatments to be less effective if they are presumed to have the same effects? What could bacteria be doing in that environment that causes this variance from norm? One possibility is that it is the immune response to the dead bacteria. Another possibility is precisely what Dwyer hints at in his paper using antibiotics that directly induce the production of ROS (Dwyer et al., 2009). Dwyer wanted to know the role of ROS in antibiotic action and resistance so that new antibiotics for antibiotic resistant bacteria could be made that rely on these mechanisms. The first drug that he mentions is the widely used fluoroquinolone antibiotic, norfloxacin, which contributes to bacterial cell death via DNA gyrase inhibition. This inhibition then results in the breakdown of iron regulatory dynamics, which in the Fenton reaction is used to remove free radicals, and as a result there was an increase in the production of ROS (Dwyer et al., 2009).

There was a very interesting study performed by Choi in 2006, where *Lactobacillus acidophilus* 606 and *Lactobacillus casei* (ATCC 393) exhibited profound inhibitory effects on all of their tested cell lines (Choi et al., 2006). The soluble polysaccharides were actually able to inhibit Human Esophageal Fibroblasts (hEF) growth by 20%. The authors came to the conclusion that the soluble polysaccharide may constitute a novel anticancer agent, which manifests a high degree of selectivity for human cancer, as well as an antioxidant agent in cells (Choi et al., 2006). The polysaccharide acted as a rather potent antioxidant, which seems to have created a situation in which it shouldn't have according to Watson in 2013 (Watson, 2013). Watson stated that antioxidants cause cancer, interferes with its treatments (which would make sense since many of the treatments induce higher concentrations of ROS), and that antioxidants actually promote the growth of late stage

metastatic cancer (Watson, 2013). However, it could actually be the fact that some antioxidants such as vitamin C will act as pro-oxidants as well, depending on their environment (Casciari et al., 2001; Riordan et al., 1995). If that is the case than bacteria could be the key delivery method to producing lipopolysaccharides in the body that will both act as an antioxidant in healthy tissues while acting as a pro-oxidant in neoplasms.

4.5. Bacterial influence on progression, invasion, and metastasis

There are two complex features of CSCs, where the full mechanism is hard to determine. The first is Matrix Metalloprotease (MMPs) production and the second is the niches that CTCs choose for deposition and recurrence/progression. It is suggested that bacteria may be able to provide some insight into both of these if their interactions, needs, and effects are studied further. MMPs are believed to be the main contributor to the invasiveness of certain cancers by giving it the ability to degrade the tissues surrounding it (Duffy et al., 2000; Xiaofeng et al., 2013). MMPs are expressed due to the presence of mouse double minute 2 (MDM2) which have been repeatedly found to slow the proliferation of the many cancers when inhibited (Coll-Mulet et al., 2006; Gu et al., 2008; Kojima et al., 2006; Kojima et al., 2005; Shi et al., 2014; Tabe et al., 2009; Tovar et al., 2006; Vassilev et al., 2004; Watanabe et al., 1994; Watanabe et al., 1996; Xiaofeng et al., 2013). One such study that provides a little light is one performed by Hiroshi Maeda in 1998 that described how bacterial infections induce human MMP activation by insults involving proteases and free radicals (Maeda et al., 1998). In other words, it could mean that the bacteria within the microenvironment could be contributing to CSCs production of MMPs, promoting invasiveness. This is corroborated by another study, performed by Weibel, that found that once *E. coli* entered the tumor, it altered the tumor microenvironment in murine breast tumors by vascular remodeling, focal concentration of tumor associated macrophages, and focal expression of MMP-9 and TNF-α around bacterial colonies (Leschner et al., 2009; Weibel et al., 2008). As such, there is also evidence of metastasis and invasion because of the previously mentioned microbial inducement of HIF-1α (Jing et al., 2012).

Another study was performed by Beuth in 1993, where they found that the mediators for adhesion of both CTCs and bacteria were lectins, which could explain why some CSCs are selective for certain tissues while others are not (Beuth et al., 1993). The fact that so many CTCs are produced while only a small fraction are able to metastasize, all being in specific niches, leads to the suggestion that there is something unique going on that is not being considered (Cristofanilli et al., 2004; Jones and Wagers, 2008). This is why this review suggests that bacteria potentially contribute to where the CTCs metastasize (see Fig. 6). This reasoning comes from looking at how the metastasis of melanoma to the lung follows the same path as the pathogenic bacteria of the skin, *Staphylococcus aureus,* spreading to the breast and causing infection (Behari et al., 2004; Daum, 2007; Gutierrez, 2005; Lewis et al., 1978).

Breast cancer metastasizes to the bone and some of the common bacteria of osteomyelitis are Sal*monella, Streptococcus,* and *Staphylococcus,* which will also produce an infection in the breast (Ciampolini and Harding, 2000; Gutierrez, 2005; Lew and Waldvogel, 2004; Lewis et al., 1978). There is also evidence that breast metastasis could be coming from malignant melanoma in the nose which makes *S. aureus* and many others, once more, viable culprits (Tanaka et al., 2012). Following this logic it may be rather easy to associate certain cancers with the bacteria that follow the same patterns of niche colonization.

If a mechanism of how bacteria can increase CTC niche choosing is required than the paper by Swanson and his colleagues is an excellent source. It has been previously shown by Swanson and his colleagues that enteric commensal microbiota of the human host influenced the maturation and repair of epithelial linings by generating ROS, which induces oxidation of target cysteines in the redox-sensitive tyrosine phosphatases, resulting in increased phosphorylation of Focal Adhesion Kinase (FAK) substrate proteins (Swanson et al., 2011). This shows that focal adhesion formation and cell migration are all significantly enhanced by bacterial contact (Swanson et al., 2011). What is known for sure is that bacteria have high affinity for the bone and are exponentially harder to treat once they are there, just like many cancers that metastasize to the bone are. This similarity in tissue preference is why there may be a plausible and casual association between which bacteria induced or inhabit the neoplasm and where the CTCs are capable spreading. It would make sense that the receptors that bacteria utilize to attach to the tissues are the same receptors that the CSCs would attach to during metastasis. Considering the autophagic/phagocytic nature of the of the CTCs/CSCs,

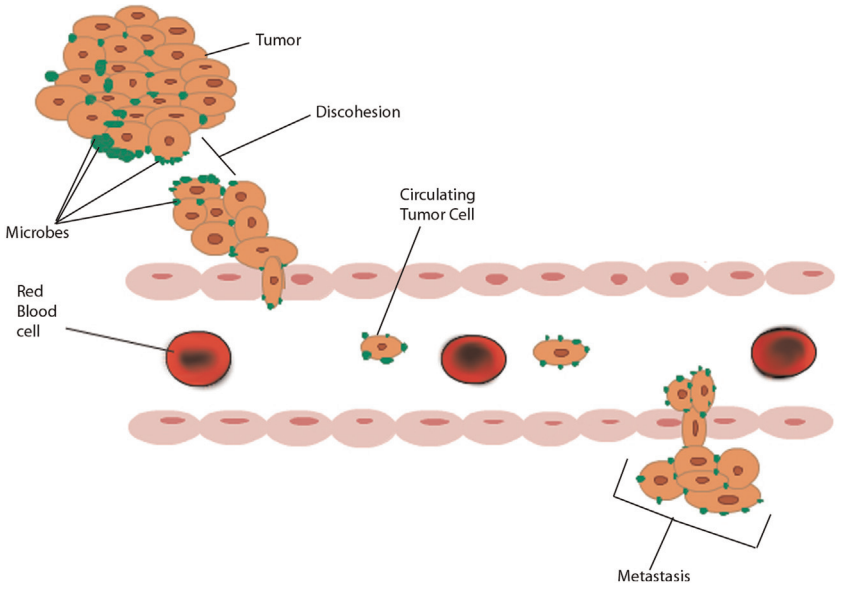

Fig. 6. The figure above shows how bacteria influence discohesion of tumor cells, travel with the CTCs in the blood, and metastasize with the CTCs to other regions of body.

as previously mentioned, this process could then lead to cell fusion and transdifferentiation resulting in the secondary tumors.

Another proof of this concept can be found in a study, as previously mentioned, by Yu et al. in 2004 (Yu et al., 2004). This study was particularly interesting in their tests of bacterial circulation within the blood. What they found was that all of the luminescent bacteria in the blood within a normal rat would be removed by the immune system within 48 h. However, once they injected them into a rat with a tumor; the tumor was the only environment in which they could inhabit. When the researchers placed another tumor in the rat, the light-emitting bacteria were unable to colonize the other tumor. This is interesting because when they used a cancer that they knew would metastasize the bacteria were found in all new tumors that developed (Yu et al., 2004). This means the bacteria were traveling along with the CTCs (see Fig. 6).

4.6. Lateral gene transfer (genetic effects)

So far all this review has talked about is the reactions induced by ROS, RNOS, and aldehydes while ignoring genetic effects. The only problem associated with genetics is that we have been evolving for hundreds of thousands of years and yet as soon as cancer rates increase we jump to the conclusion that it is genetic. This is erroneous because it ignores all of the other contributors and only looks at vertical gene transfer for answers. Many of the genes we express are due to our environment (Hunter, 2005). Even genetic mutations induced by the environment, such as from the radiation that atomic bomb survivors were exposed to, appear to have little influence on the offspring (Nakamura, 2006; Neel et al., 1990). Vertical gene transfer would not change significantly enough to allow for a predicted increase in global cancer rates by 50% from 2003 to 2020 (Rassool, 2003). However, bacteria and viruses would have the ability to change our genetics within two decade by inserting or producing DNA or RNA that are taken up via lateral gene transfer. Lateral gene transfer is the transmission of genetic material by means other than direct vertical transmission from progenitors to their offspring (Riley et al., 2013).

Viral DNA is most known to integrate in the human genome, but David Riley went on in 2013 to examine the integration of bacterial DNA in human cells. What he found is that there is evidence for bacterial DNA in the somatic genome with the highest concentration of bacterial DNA actually being found more frequently in tumors (Riley et al., 2013). They were also found more frequently in RNA than DNA samples and in the mitochondrial genome rather than nuclear genome. What was most interesting is that hundreds of thousands of paired sequence reads support the random integration of *Acinetobacter*-like DNA into the mitochondrial genome of acute myeloid leukemia samples (Riley et al., 2013). There was numerous stomach adenocarcinoma samples supporting the integration of *Pseudomonas*-like DNA in the 5′-UTR and 3′-UTR of the four proto-oncogenes that are up-regulated in their transcription, which were consistent with conversion to an oncogene (Riley et al., 2013).

The mitochondria are not the only issues and it is clear by other studies that the bacterial RNA will be transcribed and taken into the nuclear genome as well (Lebkowski et al., 1984; Robinson et al., 2013). There has been significant evidence that bacteria can adapt to the blood cells and try to live with and within mammalian cells (Domingue and Schlegel, 1977; Tedeschi and Amici, 1972; Tedeschi et al., 1976b; Tedeschi et al., 1978). This would make lateral-like gene transfer occur even if the actual DNA is not within the nucleus or mitochondria. The most interesting of these were those performed by G.G. Tedeschi, who found that there was not only cell wall deficient (CWD) forms of gram positive cocci in human subjects, but in the fetal blood drawn at birth as well, and that it could be bacteria as common as *Staphylococcus epidermidis* (Tedeschi and Amici, 1972; Tedeschi et al., 1976a; Tedeschi et al., 1976b). Continuing with this concept, there was also significant evidence presented by Nikkari and colleagues in 2001 which used real-time PCR with primers and a probe for conserved regions of the bacterial 16 S ribosomal DNA (rDNA) which revealed a significant amount of this rDNA in the blood samples of healthy individuals (Nikkari et al., 2001). There was also significantly more rDNA in the blood samples than there were in the matched reagent controls (Nikkari et al., 2001).

Bacteria and viruses may have the ability to affect the genetics of mammalian cells and cause cancer but another possible effect of lateral gene transfer is disruption of the diversity of bacteria due to bacteriophages (Ventura et al., 2011). When the bacteriophages lyse bacteria, they significantly influence global biological cycles, which could contribute to adverse diversity (Thingstad and Lignell, 1997). Having bacterial populations that are not only competing with bacteria but with phages or bacteria that have acquired an advantage due to lateral gene transfer could drastically affect the biodiversity of the gut ecosystem. This is why diversity can go both ways, good or bad. The most important thing is the ratio of good bacteria that are helping the host to those that are not.

Another aspect of DNA that is completely ignored is what happens to the bacterial nucleotides that are damaged by oxidative stress such as 8-oxoguanine. If these are taken up by the host cell it can lead to potential problems based on kinetics and concentration (Macpherson et al., 2005). It is the stability of these modified nucleotides that makes them more often favored than the normal ones. This is especially true if there are not enough antioxidants such as vitamin C in the blood to compensate for reduced production of catalase, glutathione peroxidase, and superoxide dismutase as found in Leukemia (Cooke et al., 2003). It was found by Honda et al. that decreasing vitamin C intake from 250 mg/day to 5 mg/day led to a corresponding 50% increase in sperm DNA levels of 8-OH-dG (Kim et al., 2004). This most likely demonstrates that increases in antioxidants decreased the uptake of oxidative DNA damage. Since this study examined the presence of oxidative DNA damage in semen then it is also plausible that this would correlate to increased genetic defects in offspring. Therefore, increasing vitamin C levels should be a definite consideration for all radiation workers or patients exposed to radiation on a continual basis.

5. Microbial carcinogenesis

5.1. Examples of microbial carcinogenesis

When exposed to radiation it seems that bacteria thrive and as a result some of the leading causes of death after exposure actually end up being due to bacterial infections and not the radiation. This is due, in part, to the fact that bacteria are opportunistic and if the populations composing a microbiome are changed then this could lead to an increase in pathogenic strains. Suppose that an individual has mycoplasma in their body but it is being controlled. If that population of mycoplasma increases then the increased production of mycoplasma p37 will be released, which will directly inhibit the p53 of the cells nearby contributing to tumorigenesis (Chang and Parsonnet, 2010).

In 1994, the International Agency for Research on Cancer was overwhelmed with the accumulation data showing *H. pylori*'s connection to stomach cancer. It has thus been linked to 60% of all stomach cancers (Chang and Parsonnet, 2010). *H. pylori* cause inflammation by epithelial cell release of ROS, RNOS, and interleukin-8 (IL-8). This could cause the production of various chemokines, which will also attract and activate neutrophils and macrophages that will release ROS and RNOS. This could result in

the activation of lymphocytes and the induction of Th1-predominant cellular immune responses that includes secretion of pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and gamma interferon (Ganesh et al., 2011; Mogensen, 2009). Interestingly, this mechanism (Th1-predominant cellular immune responses) appears very similar to what Viaud describes to be as the treatment efficacy behind cyclophosphamide (Viaud et al., 2013).The interesting thing about cancers produced by *H. pylori* in animal studies is that as soon as the animals were treated with antibiotics the cancer went away (Chang and Parsonnet, 2010). This was also true in Japanese patients with early gastric cancer (Chang and Parsonnet, 2010). This makes Viaud's treatment results even more explicative since many chemotherapeutics, such as cyclophosphamide, are often potent antibiotics as well (Peiris and Oppenheim, 1993). More support comes from a study performed by Dove in 1997 which showed germ-free mice developed half as many adenomas than conventional controls which were a family of mice explicitly bred to develop this type of cancer (Dove et al., 1997). This means that even though an organism is genetically prone to cancer, if you change the environment, then you can mitigate the predisposition of the organism to that particular cancer. There have been further studies that came to the same conclusion that germ-free mice that were explicitly bred for a certain type of cancer, did not get it in contrast to normal mice that were not germ-free (Chang and Parsonnet, 2010).

Enterotoxins or exotoxins are also potential contributors to carcinogenesis. One such example is that of Enterotoxigenic *Bacteroides fragilis* (ETBF), which produces a metalloprotease toxin that will cause colitis and colonic tumors in just four weeks after injection while mice infected with the non-toxin-producing *Bacteroides fragilis* do not develop any cancer in the colon (Wu et al., 2009). Another example would include the Rho-activating cytotoxic necrotizing factor 1 (CNF1), which would also implicate the toxin in cellular migration and invadopodia formation at the invasive front of specific types of cancer (Jin et al., 2012; Sakurai-Yageta et al., 2008; Travaglione et al., 2008). There have also been bacterial toxins produced that induce DNA damage or have interfered with cell signaling processes (Lax, 2007; Li et al., 2002; Nath et al., 2010; Nougayrede et al., 2006; Schiavo and van der Goot, 2001; Seo et al., 2000). There is even evidence that lipopolysaccharides (endotoxins) produced by bacteria have the ability to potentiate the effects of staphylococcal enterotoxins (Beno et al., 2001; Stiles et al., 1993). However, enterotoxins are not necessarily a bad thing, in fact it has been shown that an individuals' exposure to these enterotoxins is actually linked to their resistance to colon cancer (Pitari et al., 2003). This can either be linked to how the toxins affect the tumor cells or hormesis by inducing small amounts of damage to the cells that ultimately lead to the cells activation of reparative mechanisms. In fact, this would be eerily similar to the previously mentioned radiomimetic/radio-protectant BLM which also shows antitumor/antimicrobial activities and is produced by the bacterium *Streptomyces verticullus* (Du et al., 2000).

Therefore, cancer prevention should begin to emphasize limiting potential promoters and manipulating microbial homeostasis to allow for stimulation or low dose exposure. Radiation is a potential promoter as it decreases competition (allowing for localization of pathogenic colonies) and allows for overexposure to enterotoxins. Another example is Phorbol 12-Myristate 13-Acetate which causes inflammation but not necessarily cancer by itself (DiGiovanni, 1992; Fürstenberger et al., 1981). However, when it is combined with a sub-carcinogenic dose of an agent such as 7, 12-dimethylbenz [a} anthracene, then cancer is more likely to follow (DiGiovanni, 1992; Fürstenberger et al., 1981). If an individual has certain strains of bacteria that act as promoters than the risk of cancer induced by radiation or the environment would increase the cancer rates. This also appears to be extremely relevant in Japan where the men consume alcohol (promoter) while *H. pylori* also acts as a promoter/inducer of cancer in the stomach. Therefore, there could be a direct correlation to why stomach cancer is so predominant in their culture.

5.2. Microbial theory of carcinogenesis

When the commensal bacteria are unable to modulate inflammation or when opportunistic pathogens are unhindered from proliferation, then inflammatory signals such as cytokines will propagate, causing the migration of the hematopoietic stem cells, tissue stem cells, and other bone-marrow derived stem cells in response to damage. They will respond to the signal to repair the damage that is there. However, these cells do not know or perhaps are overwhelmed by inflammatory signals to avoid the area full of ROS. If these cells are damaged in such a way that they can't differentiate or are unable to receive the signals to fully differentiate then it could explain how stem cells can be turned into CSCs. In essence, this could potentially be the perfect environment for breeding a disease of differentiation, a disease of the stem cells, a disease of the mitochondria, and "oncogeny as partially blocked ontogeny" (Potter, 1978; Trosko, 2005). This is where this review would like to modify Potter's holistic and biologically-based hypothesis that "The cancer problem is not merely a cell problem, it is a problem of cell interaction [and homeostasis], not only within tissues [and in microbiota], but also with distal cells [and microbes] in other tissues" (Potter, 1978).

It seems unlikely that many of the CSCs have cell membranes associated with differentiated cells or possess a lack of GJIC while maintaining plasticity, simply by chance (Loewenstein and Kanno, 1966). There is an emphasis on hematopoietic stem cells because they are very sensitive to ROS. ROS in these cells will cause detrimental effects to endogenous growth signals, cell survival, proliferation, and differentiation along with the production of cytokines (Yamaguchi and Kashiwakura, 2013). This is clearly shown by Yamaguchi who irradiated mitochondrial dysfunctional hematopoietic stem cells with X-rays and showed that there was a significant increase in intracellular ROS, which inhibited their ability to proliferate and differentiate (Yamaguchi and Kashiwakura, 2013).

One hallmark of CSCs that is under appreciated in carcinogenesis, is the absence of connexin gene expression which could result in dysfunction of GJIC (Shao et al., 2003). GJIC is important for differentiation, apoptosis, and even wound healing. GJIC are also suppressed by ROS coming from the neutrophils (Nishida et al., 2001). This is again a situation where the bacterial production of ROS or the bacteria's inability to modulate ROS can have an effect on stem cell differentiation, thus promoting neoplasia.

6. Conclusion

The role of microbes in carcinogenesis is a very complex and long neglected area of research. However, this review suggests that this information is highly important if treatments for cancer or even its prevention are to be more effective. This is especially true since some cancer rates were expected to rise somewhere between 50% and 60% within 2003 and 2020 (Rassool, 2003). One such example is pancreatic cancer that is the only one expected to increase in Europe while other cancer rates decrease. As such, studies have also found a convincing link between *Porphyromonas gingivalis* and pancreatic cancer since high antibody levels for the microbe correlated to a 2-fold increase in pancreatic cancer risk (Farrell et al., 2012; Michaud et al., 2013). This could mean that

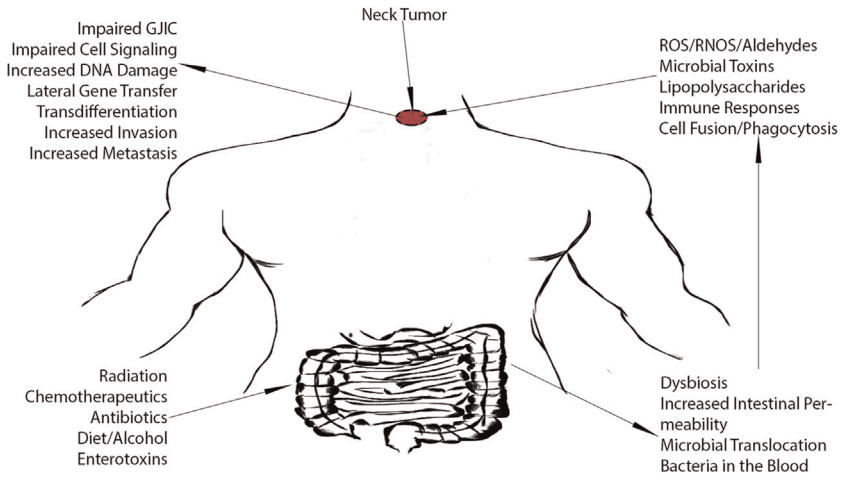

Fig. 7. Representation of how the environment can influence the microbial homeostasis, which influences many features of neoplasia.

pathogenic bacteria could enter the blood just by forming an oral cavity (Gendron et al., 2000).

Conversely, another study noted that high antibody levels for some kinds of harmless commensal, oral bacteria where associated with a 45% lower risk of pancreatic cancer (Michaud et al., 2013). This is why broad spectrum antibiotics are not the answer, even though they kill a broad range of bacteria, the ones that continue to flourish are usually the opportunistic or pathogenic bacteria along with fungi such as *Candida albicans* that will disrupt homeostasis. This is why there is also strong evidence that even though antibiotics will kill the *H. pylori* in the stomach, there may actually be an increase of cancer in the throat due to disruption of its microbial environment (Velicer et al., 2004). There is evidence of this in breast tissue as well (Velicer et al., 2004). Instead of producing damage all over the body we should focus on creating an environment in which the bacteria could be injected into the blood to prime an immune response against the tumors when treatment is performed. As mentioned before we already know what bacteria can be used to due to a study performed by Yu in order to see cancer *in-vivo* using a light emitting bacteria (Yu et al., 2004). There are also many other papers that have tabulated the bacteria that are found in and can be used to target certain tumors as well (Morrissey et al., 2010; Pawelek et al., 2003). This type of treatment could also allow for booster shots to be used to activate immune response against recurring tumors without the need for surgery.

Bacteria seem to be able to contribute to not only CSC production via degradation of the cell membrane and genetic defects but also to the immune responses to treatments and cancer progression. They even appear to have the ability to promote human MMP production for the degradation of tissues in the most invasive cancers. This is why cancer studies involing microbes are so important to radiotherapy and cancer prevention. This review suggests bacteria along with other microbes, such as viruses and fungi, contibute to a systemic view of carcinogenesis. Hormesis and carcinogenesis are two sides of the same coin. If you increase an individuals protection against carcinogens via hormesis than you potentially also increase their protection against cancer. This is why including the microbiome in all theories of carcinogenesis is significant in that it can systematically addresses hormesis and supplements almost every other paradigm of oncogenesis as well.

It is through a complete understanding of what can contribute to cancer that will allow us to prevent or reduce the rise in some cancer rates, especially until effective treatments are found. There is much potential in utilizing bacterial homeostasis for cancer prevention, radioprotection, and as a possible means of cancer therapeutics/diagnostics. It is time to consider the role of bacteria along with other microbes in the human microbiome for their ability to induce cancer, increase/decrease risks of cancer, modulate inflammation, and increase immune response to treatment (see Fig. 7). It is therefore suggested that controlling the microbiota has the greatest potential of increasing well-being and cancer prevention.

Conflict of interest

None of the authors have a conflict of interest.

Funding sources

There are no funding sources to report and this paper did not use any human subjects or experimental animals.

Acknowledgments

There are no funding sources or acknowledgments of individuals.

References

Abou-Donia, M.B., El-Masry, E.M., Abdel-Rahman, A.A., McLendon, R.E., Schiffman, S.S., 2008. Splenda alters gut microflora and increases intestinal p-glycoprotein and cytochrome p-450 in male rats. J. Toxicol. Environ. Health A 71, 1415–1429.

Abrahamsson, T.R., Jakobsson, H.E., Andersson, A.F., Bjorksten, B., Engstrand, L., Jenmalm, M.C., 2012. Low diversity of the gut microbiota in infants with atopic eczema. J. Allergy Clin. Immunol. 129, 434–440.

Al-Hajj, M., Wicha, M.S., Benito-Hernandez, A., Morrison, S.J., Clarke, M.F., 2003. Prospective identification of tumorigenic breast cancer cells. Proc. Natl. Acad. Sci. USA 100, 3983–3988.

Alirezaei, M., Reza Gheisari, H., Reza Ranjbar, V., Hajibemani, A., 2012. Betaine: a promising antioxidant agent for enhancement of broiler meat quality. Br. Poult. Sci. 53, 699–707.

Alvarez-Dolado, M., Pardal, R., Garcia-Verdugo, J.M., Fike, J.R., Lee, H.O., Pfeffer, K., Lois, C., Morrison, S.J., Alvarez-Buylla, A., 2003. Fusion of bone-marrow-derived cells with Purkinje neurons, cardiomyocytes and hepatocytes. Nature 425, 968–973.

Alves, E.A., Minagawa, C., Santos, S., Rodrigues, D.M., Pegolo-Alves, D., Gilioli, R., 2012. Importance of the microbiota species diversity in the gut tract of C3H/HePasUnib Mouse Strain. J. Am. Assoc. Lab. Anim. Sci. 51, 690.

Amar, J., Chabo, C., Waget, A., Klopp, P., Vachoux, C., Bermudez-Humaran, L.G., Smirnova, N., Berge, M., Sulpice, T., Lahtinen, S., Ouwehand, A., Langella, P., Rautonen, N., Sansonetti, P.J., Burcelin, R., 2011. Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes:

molecular mechanisms and probiotic treatment. EMBO Mol. Med. 3, 559–572.
Azad, M.B., Konya, T., Maughan, H., Guttman, D.S., Field, C.J., Sears, M.R., Becker, A.B., Scott, J.A., Kozyrskyj, A.L., Investigators, C.S., 2013. Infant gut microbiota and the hygiene hypothesis of allergic disease: impact of household pets and siblings on microbiota composition and diversity. Allergy Asthma Clin. Immunol. 9.
Azzam, E.I., de Toledo, S.M., Little, J.B., 2003. Oxidative metabolism, gap junctions and the ionizing radiation-induced bystander effect. Oncogene 22, 7050–7057.
Bagley, R.G., Teicher, B.A., 2009. Stem Cells and Cancer. Humana, Totowa, N.J.
Balkwill, F., Mantovani, A., 2001. Inflammation and cancer: back to Virchow? Lancet 357, 539–545.
Ballor, N.R., Leadbetter, J.R., 2012. Analysis of extensive [FeFe] hydrogenase gene diversity within the gut microbiota of insects representing five families of dictyoptera. Microb. Ecol. 63, 586–595.
Barendsen, G.W., 1990. Mechanisms of cell reproductive death and shapes of radiation dose-survival curves of mammalian cells. Int. J. Radiat. Biol. 57, 885–896.
Bayliss, G.J., Wolf, H., 1980. Epstein–Barr virus-induced cell fusion. Nature 287, 164–165.
Behari, P., Englund, J., Alcasid, G., Garcia-Houchins, S., Weber, S.G., 2004. Transmission of methicillin-resistant Staphylococcus aureus to preterm infants through breast milk. Infect. Control Hosp. Epidemiol. 25, 778–780.
Belting, M., Dorrell, M.I., Sandgren, S., Aguilar, E., Ahamed, J., Dorfleutner, A., Carmeliet, P., Mueller, B.M., Friedlander, M., Ruf, W., 2004. Regulation of angiogenesis by tissue factor cytoplasmic domain signaling. Nat. Med. 10, 502–509.
Beno, D.W., Uhing, M.R., Goto, M., Chen, Y., Jiyamapa-Serna, V.A., Kimura, R.E., 2001. Staphylococcal enterotoxin B potentiates LPS-induced hepatic dysfunction in chronically catheterized rats. Am. J. Physiol. Gastrointest. Liver Physiol. 280, G866–G872.
Berg, R., 1983. Bacterial translocation from the gastrointestinal tracts of mice receiving immunosuppressive chemotherapeutic agents. Curr. Microbiol. 8, 285–292.
Beuth, J., Ko, H.L., Pichlmaier, H., Pulverer, G., 1993. Lectins-mediators of adhesion for tumor-cells in metastasis and for bacteria in infectious-diseases. Zent. Chir. 118, 145–152.
Biaglow, J.E., 1981. The effects of ionizing radiation on mammalian cells. J. Chem. Educ. 58, 144.
Bleehen, N.M., Gillies, N.E., Twentyman, P.R., 1974. The effect of bleomycin and radiation in combination on bacteria and mammalian cells in culture. Br. J. Radiol. 47, 346–351.
Boleij, A., Dutilh, B.E., Kortman, G.A., Roelofs, R., Laarakkers, C.M., Engelke, U.F., Tjalsma, H., 2012. Bacterial responses to a simulated colon tumor microenvironment. Mol. Cell. Proteomics 11, 851–862.
Bolino, C.M., Bercik, P., 2010. Pathogenic factors involved in the development of irritable bowel syndrome: focus on a microbial role. Infect. Dis. Clin. N. Am. 24961.
Bonnet, D., Dick, J.E., 1997. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat. Med. 3, 730–737.
Bosron, W.F., Li, T.K., 1986. Genetic polymorphism of human liver alcohol and aldehyde dehydrogenases, and their relationship to alcohol metabolism and alcoholism. Hepatology 6, 502–510.
Bucuvalas, J.C., Bezerra, J.A., Schmidt, C., Burnham, C.E., 1995. N-trimethylglycine (betaine) transport is critical to protect HEPG2 cells from hyperosmotic stress. Gastroenterology 108, A1040.
Cabiscol, E., Tamarit, J., Ros, J., 2000. Oxidative stress in bacteria and protein damage by reactive oxygen species. Int. Microbiol. 3, 3–8.
Calle, E.E., Kaaks, R., 2004. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat. Rev. Cancer 4, 579–591.
Calle, E.E., Thun, M.J., 2004. Obesity and cancer. Oncogene 23, 6365–6378.
Cani, P.D., Delzenne, N.M., 2009. The role of the gut microbiota in energy metabolism and metabolic disease. Curr. Pharm. Des. 15, 1546–1558.
Cani, P.D., Delzenne, N.M., 2010. Involvement of the gut microbiota in the development of low grade inflammation associated with obesity: focus on this neglected partner. Acta Gastro-Enterol. Belg. 73, 267–269.
Cani, P.D., Rottier, O., Goiot, Y., Neyrinck, A., Geurts, L., Delzenne, N., 2008. Changes in gut microbiota control intestinal permeability-induced inflammation in obese and diabetic mice through unexpected dependent mechanisms. Diabetologia. 51, S34–S35.
Cantarel, B.L., Coutinho, P.M., Rancurel, C., Bernard, T., Lombard, V., Henrissat, B., 2009. The Carbohydrate-Active EnZymes database (CAZy): an expert resource for Glycogenomics. Nucl. Acids Res. 37, D233–D238.
Casciari, J.J., Riordan, N.H., Schmidt, T.L., Meng, X.L., Jackson, J.A., Riordan, H.D., 2001. Cytotoxicity of ascorbate, lipoic acid, and other antioxidants in hollow fibre in vitro tumours. Br. J. Cancer 84, 1544–1550.
Cassata, J., 2014. Radiation dose and the impacts on exposed populations: summary Q&A. Health Phys. 106 329 10.1097/HP.0000000000000031.
Cayrou, C., Sambe, B., Armougom, F., Raoult, D., Drancourt, M., 2013. Molecular diversity of the Planctomycetes in the human gut microbiota in France and Senegal. Apmis 121, 1082–1090.
Chang, A.H., Parsonnet, J., 2010. Role of bacteria in oncogenesis. Clin. Microbiol. Rev. 23, 837–857.
Charafe-Jauffret, E., Ginestier, C., Iovino, F., Tarpin, C., Diebel, M., Esterni, B., Houvenaeghel, G., Extra, J.-M., Bertucci, F., Jacquemier, J., 2010. Aldehyde dehydrogenase 1–Positive cancer stem cells mediate metastasis and poor clinical outcome in inflammatory breast cancer. Clin. Cancer Res. 16, 45–55.
Chen, K.A., Cruz, P.E., Lanuto, D.J., Flotte, T.R., Borchelt, D.R., Srivastava, A., Zhang, J., Steindler, D.A., Zheng, T., 2011. Cellular fusion for gene delivery to SCA1 affected Purkinje neurons. Mol. Cell. Neurosci. 47, 61–70.
Chen, S., Zhao, Y., Zhao, G., Han, W., Bao, L., Yu, K.N., Wu, L., 2009a. Up-regulation of ROS by mitochondria-dependent bystander signaling contributes to genotoxicity of bystander effects. Mutat. Res. 666, 68–73.
Chen, Y.-C., Chen, Y.-W., Hsu, H.-S., Tseng, L.-M., Huang, P.-I., Lu, K.-H., Chen, D.-T., Tai, L.-K., Yung, M.-C., Chang, S.-C., Ku, H.-H., Chiou, S.-H., Lo, W.-L., 2009b. Aldehyde dehydrogenase 1 is a putative marker for cancer stem cells in head and neck squamous cancer. Biochem. Biophys. Res. Commun. 385, 307–313.
Cheng, X., Ivessa, A.S., 2010. The migration of mitochondrial DNA fragments to the nucleus affects the chronological aging process of Saccharomyces cerevisiae. Aging Cell 9, 919–923.
Choi, S.S., Kim, Y., Han, K.S., You, S., Oh, S., Kim, S.H., 2006. Effects of Lactobacillus strains on cancer cell proliferation and oxidative stress in vitro. Lett. Appl. Microbiol. 42, 452–458.
Ciampolini, J., Harding, K., 2000. Pathophysiology of chronic bacterial osteomyelitis. Why do antibiotics fail so often? Postgrad. Med. J. 76, 479–483.
Ciorba, M.A., Riehl, T.E., Rao, M.S., Moon, C., Ee, X., Nava, G.M., Walker, M.R., Marinshaw, J.M., Stappenbeck, T.S., Stenson, W.F., 2012. Lactobacillus probiotic protects intestinal epithelium from radiation injury in a TLR-2/cyclo-oxygenase-2-dependent manner. Gut 61, 829–838.
Ciorba, M.A., Stenson, W.F., 2009. Probiotic therapy in radiation-induced intestinal injury and repair. Ann. N. Y. Acad. Sci. 1165, 190–194.
Cohen, B.L., 1995. Test of the linear-no threshold theory of radiation carcinogenesis for inhaled radon decay products. Health Phys. 68, 157–174.
Coll-Mulet, L., Iglesias-Serret, D., Santidrian, A.F., Cosialls, A.M., de Frias, M., Castano, E., Campas, C., Barragan, M., de Sevilla, A.F., Domingo, A., Vassilev, L.T., Pons, G., Gil, J., 2006. MDM2 antagonists activate p53 and synergize with genotoxic drugs in B-cell chronic lymphocytic leukemia cells. Blood 107, 4109–4114.
Cooke, M.S., Evans, M.D., Dizaroglu, M., Lunec, J., 2003. Oxidative DNA damage: mechanisms, mutation, and disease. FASEB J. 17, 1195–1214.
Correa, P., Piazuelo, M.B., 2011. Helicobacter pylori infection and gastric adenocarcinoma. US Gastroenterol. Hepatol. Rev. 7, 59–64.
Cristofanilli, M., Budd, G.T., Ellis, M.J., Stopeck, A., Matera, J., Miller, M.C., Reuben, J. M., Doyle, G.V., Allard, W.J., Terstappen, L.W.M.M., Hayes, D.F., 2004. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N. Engl. J. Med. 351, 781–791.
Criswell, D.C., 2009. A review of mitoribosome structure and function does not support the serial endosymbiotic theory. Answ. Res. J. 2, 107–115.
Cummins, J., Tangney, M., 2013. Bacteria and tumours: causative agents or opportunistic inhabitants? Infect. Agents Cancer 8, 11 11.
Dahlinger, J., Marks, S.L., Hirsh, D.C., 1997. Prevalence and identity of translocating bacteria in healthy dogs. J. Vet. Intern. Med. 11, 319–322.
Daly, M.J., Gaidamakova, E.K., Matrosova, V.Y., Kiang, J.G., Fukumoto, R., Lee, D.-Y., Wehr, N.B., Viteri, G.A., Berlett, B.S., Levine, R.L., 2010. Small-Molecule Antioxidant Proteome-Shields in Deinococcus radiodurans. PLoS One 5, e12570.
Daum, R.S., 2007. Skin and soft-tissue infections caused by methicillin-resistant Staphylococcus aureus. N. Engl. J. Med. 357, 380–390.
Dawson, L.A., Normolle, D., Balter, J.M., McGinn, C.J., Lawrence, T.S., Ten Haken, R.K., 2002. Analysis of radiation-induced liver disease using the Lyman NTCP model. Int. J. Radiat. Oncol. Biol. Phys. 53, 810–821.
De Filippo, C., Cavalieri, D., Di Paola, M., Ramazzotti, M., Poullet, J.B., Massart, S., Collini, S., Pieraccini, G., Lionetti, P., 2010. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc. Natl. Acad. Sci. 107, 14691–14696.
Demirer, S., Aydintug, S., Aslim, B., Kepenekci, I., Sengul, N., Evirgen, O., Gerceker, D., Andrieu, M.N., Ulusoy, C., Karahuseyinoglu, S., 2006. Effects of probiotics on radiation-induced intestinal injury in rats. Nutrition 22, 179–186.
Diamant, S., Eliahu, N., Rosenthal, D., Goloubinoff, P., 2001. Chemical Chaperones Regulate Molecular Chaperones in Vitro and in Cells under Combined Salt and Heat Stresses. J. Biol. Chem. 276, 39586–39591.
DiBaise, J.K., Zhang, H., Crowell, M.D., Krajmalnik-Brown, R., Decker, G.A., Rittmann, B.E., 2008. Gut microbiota and its possible relationship with obesity. Mayo Clin. Proc. 83, 460–469.
DiGiovanni, J., 1992. Multistage carcinogenesis in mouse skin. Pharmacol. Ther. 54, 63–128.
Dillon, R.J., Webster, G., Weightman, A.J., Charnley, A.K., 2010. Diversity of gut microbiota increases with aging and starvation in the desert locust. Antonie Van Leeuwenhoek Int. J. Gen. Mol. Microbiol. 97, 69–77.
Domingue, G.J., Schlegel, J.U., 1977. Novel bacterial structures in human blood: cultural isolation. Infect. Immun. 15, 621–627.
Dong, M.Y., Chang, T.W., Gorbach, S.L., 1987. Effects of feeding lactobacillus GG on lethal irradiation in mice. Diagn. Microbiol. Infect. Dis. 7, 1–7.
Doss, M., 2013. Linear no-threshold model vs. radiation hormesis. Dose Response 11, 480–497.
Dove, W.F., Clipson, L., Gould, K.A., Luongo, C., Marshall, D.J., Moser, A.R., Newton, M.A., Jacoby, R.F., 1997. Intestinal neoplasia in the ApcMin mouse: independence from the microbial and natural killer (beige locus) status. Cancer Res. 57, 812–814.
Du, L., Sánchez, C., Chen, M., Edwards, D.J., Shen, B., 2000. The biosynthetic gene cluster for the antitumor drug bleomycin from Streptomyces verticillus ATCC15003 supporting functional interactions between nonribosomal peptide synthetases and a polyketide synthase. Chem. Biol. 7, 623–642.
Duffy, M.J., Maguire, T.M., Hill, A., McDermott, E., O'Higgins, N., 2000. Metalloproteinases: role in breast carcinogenesis, invasion and metastasis. Breast Cancer Res. 2, 252.
Dwyer, D.J., Kohanski, M.A., Collins, J.J., 2009. Role of reactive oxygen species in

antibiotic action and resistance. Curr. Opin. Microbiol. 12, 482–489.
Engel, P., Martinson, V.G., Moran, N.A., 2012. Functional diversity within the simple gut microbiota of the honey bee. Proc. Natl. Acad. Sci. USA 109, 11002–11007.
Engel, P., Moran, N.A., 2013. The gut microbiota of insects-diversity in structure and function. FEMS Microbiol. Rev. 37, 699–735.
Farrell, J.J., Zhang, L., Zhou, H., Chia, D., Elashoff, D., Akin, D., Paster, B.J., Joshipura, K., Wong, D.T., 2012. Variations of oral microbiota are associated with pancreatic diseases including pancreatic cancer. Gut 61, 582–588.
Forno, E., Onderdonk, A.B., McCracken, J., Litonjua, A.A., Laskey, D., Delaney, M.L., DuBois, A.M., Gold, D.R., Ryan, L.M., Weiss, S.T., Celedon, J.C., 2009. Diversity of the gut microbiota and eczema in infants. Am. J. Respir. Crit. Care Med. 179.
Fukuda, S., Saito, H., Nakaji, S., Yamada, M., Ebine, N., Tsushima, E., Oka, E., Kumeta, K., Tsukamoto, T., Tokunaga, S., 2007. Pattern of dietary fiber intake among the Japanese general population. Eur. J. Clin. Nutr. 61, 99–103.
Fürstenberger, G., Berry, D.L., Sorg, B., Marks, F., 1981. Skin tumor promotion by phorbol esters is a two-stage process. Proc. Natl. Acad. Sci. 78, 7722–7726.
Ganesh, B.B., Bhattacharya, P., Gopisetty, A., Prabhakar, B.S., 2011. Role of cytokines in the pathogenesis and suppression of thyroid autoimmunity. J. Interf. Cytokine Res. 31, 721–731.
Gendron, R., Grenier, D., Maheu-Robert, L.-F., 2000. The oral cavity as a reservoir of bacterial pathogens for focal infections. Microbes Infect. 2, 897–906.
Gerber, D., Mathews-Roth, M., Fahlund, C., Hummell, D., Rosner, B., 1979. Effect of frequent sun exposure on bacterial colonization of skin. Int. J. Dermatol. 18, 571–574.
Gratz, S.W., Mykkanen, H., El-Nezami, H.S., 2010. Probiotics and gut health: A special focus on liver diseases. World J. Gastroenterol. 16, 403–410.
Gray, G.M., Yardley, H.J., 1975. Lipid compositions of cells isolated from pig, human, and rat epidermis. J. Lipid Res. 16, 434–440.
Greene, C., 2006. Cardiovascular infections, Infectious diseases of the dog and cat. Saunders Elsevier, Missouri, 1.
Gu, L., Zhu, N., Findley, H.W., Zhou, M., 2008. MDM2 antagonist nutlin-3 is a potent inducer of apoptosis in pediatric acute lymphoblastic leukemia cells with wild-type p53 and overexpression of MDM2. Leukemia 22, 730–739.
Gutierrez, K., 2005. Bone and Joint Infections in Children. Pediatr. Clin. N. Am. 52, 779–794.
Hadnagy, A., Gaboury, L., Beaulieu, R., Balicki, D., 2006. SP analysis may be used to identify cancer stem cell populations. Exp. Cell Res. 312, 3701–3710.
Han, X., Li, F., Fang, Z., Gao, Y., Li, F., Fang, R., Yao, S., Sun, Y., Li, L., Zhang, W., Ma, H., Xiao, Q., Ge, G., Fang, J., Wang, H., Zhang, L., Wong, K.-k, Chen, H., Hou, Y., Ji, H., 2014. Transdifferentiation of lung adenocarcinoma in mice with Lkb1 deficiency to squamous cell carcinoma. Nat. Commun. 5.
Haraguchi, N., Inoue, H., Tanaka, F., Mimori, K., Utsunomiya, T., Sasaki, A., Mori, M., 2006. Cancer stem cells in human gastrointestinal cancers. Hum. Cell 19, 24–29.
Harmey, J.H., Bucana, C.D., Lu, W., Byrne, A.M., McDonnell, S., Lynch, C., Bouchier-Hayes, D., Dong, Z., 2002. Lipopolysaccharide-induced metastatic growth is associated with increased angiogenesis, vascular permeability and tumor cell invasion. Int. J. Cancer 101, 415–422.
Hehemann, J.H., Correc, G., Barbeyron, T., Helbert, W., Czjzek, M., Michel, G., 2010. Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota. Nature 464 908-U123.
Hermann, P.C., Huber, S.L., Herrler, T., Aicher, A., Ellwart, J.W., Guba, M., Bruns, C.J., Heeschen, C., 2007. Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. Cell Stem Cell 1, 313–323.
Hilton, J., 1984. Role of aldehyde dehydrogenase in cyclophosphamide-resistant L1210 leukemia. Cancer Res. 44, 5156–5160.
Hirschmann-Jax, C., Foster, A.E., Wulf, G.G., Nuchtern, J.G., Jax, T.W., Gobel, U., Goodell, M.A., Brenner, M.K., 2004. A distinct "side population" of cells with high drug efflux capacity in human tumor cells. Proc. Natl. Acad. Sci. USA 101, 14228–14233.
Ho, M.M., Ng, A.V., Lam, S., Hung, J.Y., 2007. Side population in human lung cancer cell lines and tumors is enriched with stem-like cancer cells. Cancer Res. 67, 4827–4833.
Holmström, K.O., Welin, B., Mandal, A., Kristiansdottir, I., Teeri, T.H., Lamark, T., Strøm, A.R., Palva, E.T., 1994. Production of the Escherichia coli betaine-aldehyde dehydrogenase, an enzyme required for the synthesis of the osmoprotectant glycine betaine, in transgenic plants. Plant J. 6, 749–758.
Hugot, J.P., 2004. Inflammatory bowel disease: a complex group of genetic disorders. Best Pract. Res. Clin. Gastroenterol. 18, 451–462.
Hunter, D.J., 2005. Gene-environment interactions in human diseases. Nat. Rev. Genet. 6, 287–298.
Iida, N., Dzutsev, A., Stewart, C.A., Smith, L., Bouladoux, N., Weingarten, R.A., Molina, D.A., Salcedo, R., Back, T., Cramer, S., Dai, R.M., Kiu, H., Cardone, M., Naik, S., Patri, A.K., Wang, E., Marincola, F.M., Frank, K.M., Belkaid, Y., Trinchieri, G., Goldszmid, R.S., 2013. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science 342, 967–970.
Ismail, I.H., Oppedisano, F., Joseph, S.J., Boyle, R.J., Robins-Browne, R.M., Tang, M.L.K., 2012. Prenatal administration of Lactobacillus rhamnosus has no effect on the diversity of the early infant gut microbiota. Pediatr. Allergy Immunol. 23, 255–258.
Iwamoto, T., Suzuki, N., Tanabe, K., Takeshita, T., Hirofuji, T., 2010. Effects of probiotic Lactobacillus salivarius WB21 on halitosis and oral health: an open-label pilot trial. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endodontol. 110, 201–208.
Jin, Q., Pulipati, N.R., Zhou, W., Staub, C.M., Liotta, L.A., Mulder, K.M., 2012. Role of km23-1 in RhoA/actin-based cell migration. Biochem. Biophys. Res. Commun. 428, 333–338.
Jing, S.W., Wang, Y.D., Kuroda, M., Su, J.W., Sun, G.G., Liu, Q., Cheng, Y.J., Yang, C.R., 2012. HIF-1alpha contributes to hypoxia-induced invasion and metastasis of esophageal carcinoma via inhibiting E-cadherin and promoting MMP-2 expression. Acta Med. Okayama 66, 399–407.
Jones, D.L., Wagers, A.J., 2008. No place like home: anatomy and function of the stem cell niche. Nat. Rev. Mol. Cell Biol. 9, 11–21.
Jørgensen, S.J., 1972. Time-dose relationships in combined bleomycin treatment and radiotherapy. Eur. J. Cancer (1965) 8, 531–534.
Kadooka, Y., Sato, M., Imaizumi, K., Ogawa, A., Ikuyama, K., Akai, Y., Okano, M., Kagoshima, M., Tsuchida, T., 2010. Regulation of abdominal adiposity by probiotics (Lactobacillus gasseri SBT2055) in adults with obese tendencies in a randomized controlled trial. Eur. J. Clin. Nutr. 64, 636–643.
Karin, M., Greten, F.R., 2005. NF-[kappa]B: linking inflammation and immunity to cancer development and progression. Nat. Rev. Immunol. 5, 749–759.
Keku, T.O., Dulal, S., Deveaux, A., Jovov, B., Han, X., 2014. The Gastrointestinal Microbiota and Colorectal Cancer. Am. J. Physiol. Gastrointest. Liver Physiol., ajpgi.00360.2012
Kelly, D., Campbell, J.I., King, T.P., Grant, G., Jansson, E.A., Coutts, A.G., Pettersson, S., Conway, S., 2004. Commensal anaerobic gut bacteria attenuate inflammation by regulating nuclear-cytoplasmic shuttling of PPAR-gamma and RelA. Nat. Immunol. 5, 104–112.
Kempf, V.A., Volkmann, B., Schaller, M., Sander, C.A., Alitalo, K., Riess, T., Autenrieth, I.B., 2001. Evidence of a leading role for VEGF in Bartonella henselae-induced endothelial cell proliferations. Cell Microbiol. 3, 623–632.
Kespichayawattana, W., Rattanachetkul, S., Wanun, T., Utaisincharoen, P., Sirisinha, S., 2000. Burkholderia pseudomallei induces cell fusion and actin-associated membrane protrusion: a possible mechanism for cell-to-cell spreading. Infect. Immun. 68, 5377–5384.
Kiefer, D., Ali-Akbarian, L., 2004. A brief evidence-based review of two gastrointestinal illnesses: irritable bowel and leaky gut syndromes. Altern. Ther. Health Med. 10, 22–30, quiz 31, 92.
Kim, J.Y., Mukherjee, S., Ngo, L.C., Christiani, D.C., 2004. Urinary 8-hydroxy-2′-deoxyguanosine as a biomarker of oxidative DNA damage in workers exposed to fine particulates. Environ. Health Perspect. 112, 666–671.
Kirby, J.E., 2004. In Vitro Model of Bartonella henselae-Induced Angiogenesis. Infect. Immun. 72, 7315–7317.
Kirjavainen, P.V., Apostolou, E., Salminen, S.J., Isolauri, E., 1999. New aspects of probiotics-a novel approach in the management of food allergy. Allergy 54, 909–915.
Kohl, K.D., 2012. Diversity and function of the avian gut microbiota. J. Comp. Physiol. B: Biochem. Syst. Environ. Physiol. 182, 591–602.
Koivula, T., 1975. Subcellular distribution and characterization of human liver aldehyde dehydrogenase fractions. Life Sci. 16, 1563–1569.
Kojima, K., Konopleva, M., McQueen, T., O'Brien, S., Plunkett, W., Andreeff, M., 2006. Mdm2 inhibitor Nutlin-3a induces p53-mediated apoptosis by transcription-dependent and transcription-independent mechanisms and may overcome Atm-mediated resistance to fludarabine in chronic lymphocytic leukemia. Blood 108, 993–1000.
Kojima, K., Konopleva, M., Samudio, I.J., Shikami, M., Cabreira-Hansen, M., McQueen, T., Ruvolo, V., Tsao, T., Zeng, Z., Vassilev, L.T., Andreeff, M., 2005. MDM2 antagonists induce p53-dependent apoptosis in AML: implications for leukemia therapy. Blood 106, 3150–3159.
Krock, B.L., Skuli, N., Simon, M.C., 2011. Hypoxia-induced angiogenesis: good and evil. Genes Cancer 2, 1117–1133.
Kruis, W., Forstmaier, G., Scheurlen, C., Stellaard, F., 1991. Effect of diets low and high in refined sugars on gut transit, bile-acid metabolism, and bacterial fermentation. Gut 32, 367–371.
Landen, C.N., Goodman, B., Katre, A.A., Steg, A.D., Nick, A.M., Stone, R.L., Miller, L.D., Mejia, P.V., Jennings, N.B., Gershenson, D.M., Bast, R.C., Coleman, R.L., Lopez-Berestein, G., Sood, A.K., 2010. Targeting aldehyde dehydrogenase cancer stem cells in ovarian cancer. Mol. Cancer Ther. 9, 3186–3199.
Landskron, G., De la Fuente, M., Thuwajit, P., Thuwajit, C., Hermoso, M.A., 2014. Chronic inflammation and cytokines in the tumor microenvironment. J. Immunol. Res. 2014, 19.
Lapidot, T., Sirard, C., Vormoor, J., Murdoch, B., Hoang, T., Caceres-Cortes, J., Minden, M., Paterson, B., Caligiuri, M.A., Dick, J.E., 1994. A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature. 367, 645–648.
Lax, A.J., 2007. New genotoxin shows diversity of bacterial attack mechanisms. Trends Mol. Med. 13, 91–93.
Lazova, R., Chakraborty, A., Pawelek, J.M., 2011. Leukocyte-cancer cell fusion: initiator of the warburg effect in malignancy? Adv. Exp. Med. Biol. 714, 151–172.
Leach, J.K., Van Tuyle, G., Lin, P.-S., Schmidt-Ullrich, R., Mikkelsen, R.B., 2001. Ionizing radiation-induced, mitochondria-dependent generation of reactive oxygen/nitrogen. Cancer Res. 61, 3894–3901.
Lebkowski, J.S., Dubridge, R.B., Antell, E.A., Greisen, K.S., Calos, M.P., 1984. Transfected DNA is mutated in monkey, mouse, and human-cells. Mol. Cell. Biol. 4, 1951–1960.
Leschner, S., Westphal, K., Dietrich, N., Viegas, N., Jablonska, J., Lyszkiewicz, M., Lienenklaus, S., Falk, W., Gekara, N., Loessner, H., 2009. Tumor invasion of salmonella enterica serovar typhimurium is accompanied by strong hemorrhage promoted by tnf-α. PLoS One 4, e6692.
Lew, D.P., Waldvogel, F.A., 2004. Osteomyelitis. Lancet 364, 369–379.
Lewis, R.P., Sutter, V.L., Finegold, S.M., 1978. Bone infections involving anaerobic bacteria. Medicine 57, 279–306.
Leyer, G.J., Li, S.G., Mubasher, M.E., Reifer, C., Ouwehand, A.C., 2009. Probiotic effects

on cold and influenza-like symptom incidence and duration in children. Pediatrics 124, E172–E179.
Li, L., Sharipo, A., Chaves-Olarte, E., Masucci, M.G., Levitsky, V., Thelestam, M., Frisan, T., 2002. The Haemophilus ducreyi cytolethal distending toxin activates sensors of DNA damage and repair complexes in proliferating and non-proliferating cells. Cell. Microbiol. 4, 87–99.
Lin, P.W., Myers, L.E., Ray, L., Song, S.C., Nasr, T.R., Berardinelli, A.J., Kundu, K., Murthy, N., Hansen, J.M., Neish, A.S., 2009. Lactobacillus rhamnosus blocks inflammatory signaling in vivo via reactive oxygen species generation. Free Radic. Biol. Med. 47, 1205–1211.
Loewenstein, W.R., Kanno, Y., 1966. Intercellular communication and the control of tissue growth: lack of communication between cancer cells. Nature 209, 1248–1249.
Lokody, I., 2014. Tumour microenvironment: bacterial balance affects cancer treatment. Nat. Rev. Cancer 14, 10.
Lough, A.N., Roark, L.M., Kato, A., Ream, T.S., Lamb, J.C., Birchler, J.A., Newton, K.J., 2008. Mitochondrial DNA transfer to the nucleus generates extensive insertion site variation in maize. Genetics 178, 47–55.
Lozupone, C.A., Stombaugh, J.I., Gordon, J.I., Jansson, J.K., Knight, R., 2012. Diversity, stability and resilience of the human gut microbiota. Nature 489, 220–230.
Lu, X., Kang, Y., 2009. Cell fusion as a hidden force in tumor progression. Cancer Res. 69, 8536–8539.
Lye, H.S., Kuan, C.Y., Ewe, J.A., Fung, W.Y., Liong, M.T., 2009. The Improvement of Hypertension by Probiotics: Effects on Cholesterol, Diabetes, Renin, and Phytoestrogens. Int. J. Mol. Sci. 10, 3755–3775.
Mackay, R.I., Hendry, J.H., 1999. The modelled benefits of individualizing radiotherapy patients' dose using cellular radiosensitivity assays with inherent variability. Radiother. Oncol. 50, 67–75.
Macpherson, P., Barone, F., Maga, G., Mazzei, F., Karran, P., Bignami, M., 2005. 8-Oxoguanine incorporation into DNA repeats in vitro and mismatch recognition by MutSα. Nucl. Acids Res. 33, 5094–5105.
Maeda, H., Okamoto, T., Akaike, T., 1998. Human matrix metalloprotease activation by insults of bacterial infection involving proteases and free radicals. Biol. Chem. 379, 193–200.
Maes, M., Coucke, F., Leunis, J.-C., 2007. Normalization of the increased translocation of endotoxin from gram negative enterobacteria (leaky gut) is accompanied by a remission of chronic fatigue syndrome. Neuroendocrinol. Lett. 28, 739–744.
Majamaa, H., Isolauri, E., 1997. Probiotics: a novel approach in the management of food allergy. J. Allergy Clin. Immunol. 99, 179–185.
Marcato, P., Dean, C.A., Giacomantonio, C.A., Lee, P.W.K., 2011a. Aldehyde dehydrogenase: Its role as a cancer stem cell marker comes down to the specific isoform. Cell Cycle 10, 1378–1384.
Marcato, P., Dean, C.A., Pan, D., Araslanova, R., Gillis, M., Joshi, M., Helyer, L., Pan, L., Leidal, A., Gujar, S., 2011b. Aldehyde dehydrogenase activity of breast cancer stem cells is primarily due to isoform ALDH1A3 and its expression is predictive of metastasis. Stem Cells 29, 32–45.
Mass, M., Kubera, M., Leunis, J.-C., 2008. The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. Neuroendocr. Lett. 29, 117–124.
McCord, A.M., Resto-Ruiz, S.I., Anderson, B.E., 2006. Autocrine role for interleukin-8 in bartonella henselae-induced angiogenesis. Infect. Immun. 74, 5185–5190.
Mcfarland, L.V., Bernasconi, P., 1993. Saccharomyces-boulardii: a review of an innovative biotherapeutic agent. Microb. Ecol. Health Dis. 6, 157–171.
McLaughlin, R.W., Vali, H., Lau, P.C.K., Palfree, R.G.E., De Ciccio, A., Sirois, M., Ahmad, D., Villemur, R., Desrosiers, M., Chan, E.C.S., 2002. Are there naturally occurring pleomorphic bacteria in the blood of healthy humans? J. Clin. Microbiol. 40, 4771–4775.
Michaud, D.S., Izard, J., Wilhelm-Benartzi, C.S., You, D.-H., Grote, V.A., Tjønneland, A., Dahm, C.C., Overvad, K., Jenab, M., Fedirko, V., 2013. Plasma antibodies to oral bacteria and risk of pancreatic cancer in a large European prospective cohort study. Gut 62, 1764–1770.
Mihajlovski, A., Dore, J., Levenez, F., Alric, M., Brugere, J.F., 2010. Molecular evaluation of the human gut methanogenic archaeal microbiota reveals an age-associated increase of the diversity. Environ. Microbiol. Rep. 2, 272–280.
Moeller, B.J., Cao, Y., Vujaskovic, Z., Li, C.Y., Haroon, Z.A., Dewhirst, M.W., 2004. The relationship between hypoxia and angiogenesis. Semin. Radiat. Oncol. 14, 215–221.
Mogensen, T.H., 2009. Pathogen recognition and inflammatory signaling in innate immune defenses. Clin. Microbiol. Rev. 22, 240–273.
Morrissey, D., O'Sullivan, G.C., Tangney, M., 2010. Tumour targeting with systemically administered bacteria. Curr. Gene Ther. 10, 3–14.
Muegge, B.D., Kuczynski, J., Knights, D., Clemente, J.C., Gonzalez, A., Fontana, L., Henrissat, B., Knight, R., Gordon, J.I., 2011. Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans. Science 332, 970–974.
Munro, T.R., 1970. The relative radiosensitivity of the nucleus and cytoplasm of Chinese hamster fibroblasts. Radiat. Res. 42, 451–470.
Naka, K., Muraguchi, T., Hoshii, T., Hirao, A., 2008. Regulation of reactive oxygen species and genomic stability in hematopoietic stem cells. Antioxid. Redox Signal. 10, 1883–1894.
Nakamura, N., 2006. Genetic effects of radiation in atomic-bomb survivors and their children: past, present and future. J. Radiat. Res. 47 (Suppl B), B67–B73.
Nakayama, M., Itoh, K., Takahashi, E., 1997. Cyclophosphamide-induced bacterial translocation in escherichia coli c25-monoassociated specific pathogen-free mice. Microbiol. Immunol. 41, 587–593.
Nath, G., Gulati, A.K., Shukla, V.K., 2010. Role of bacteria in carcinogenesis, with special reference to carcinoma of the gallbladder. World J. Gastroenterol.: WJG 16, 5395–5404.
Neel, J.V., Schull, W.J., Awa, A.A., Satoh, C., Kato, H., Otake, M., Yoshimoto, Y., 1990. The children of parents exposed to atomic bombs: estimates of the genetic doubling dose of radiation for humans. Am. J. Hum. Genet. 46, 1053–1072.
Nikkari, S., McLaughlin, I.J., Bi, W., Dodge, D.E., Relman, D.A., 2001. Does blood of healthy subjects contain bacterial ribosomal DNA? J. Clin. Microbiol. 39, 1956–1959.
Nishida, M., Morita, I., Murota, S.-I., 2001. Mechanism of inhibitory effect of hypoxia/reoxygenation on gap junctional intercellular communication of vascular endothelial cells in culture. In: Fukuuchi, Y., Tomita, M., Koto, A. (Eds.), Ischemic Blood Flow in the Brain. Springer, Japan, pp. 49–56.
Nizet, V., Johnson, R.S., 2009. Interdependence of hypoxic and innate immune responses. Nat. Rev. Immunol. 9, 609–617.
Nosova, T., Jokelainen, K., Kaihovaara, P., Jousimies-Somer, H., Siitonen, A., Heine, R., Salaspuro, M., 1996. Aldehyde dehydrogenase activity and acetate production by aerobic bacteria representing the normal flora of human large intestine. Alcohol Alcohol. 31, 555–564.
Nougayrede, J.P., Homburg, S., Taieb, F., Boury, M., Brzuszkiewicz, E., Gottschalk, G., Buchrieser, C., Hacker, J., Dobrindt, U., Oswald, E., 2006. Escherichia coli induces DNA double-strand breaks in eukaryotic cells. Science 313, 848–851.
O'Brien, C.A., Pollett, A., Gallinger, S., Dick, J.E., 2007. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. Nature 445, 106–110.
Olempska, M., Eisenach, P.A., Ammerpohl, O., Ungefroren, H., Fandrich, F., Kalthoff, H., 2007. Detection of tumor stem cell markers in pancreatic carcinoma cell lines. Hepatobiliary Pancreat. Dis. Int. 6, 92–97.
Pawelek, J.M., Low, K.B., Bermudes, D., 2003. Bacteria as tumour-targeting vectors. Lancet Oncol. 4, 548–556.
Peiris, V., Oppenheim, B.A., 1993. Antimicrobial activity of cytotoxic drugs may influence isolation of bacteria and fungi from blood cultures. J. Clin. Pathol. 46, 1124–1125.
Pischon, T., Nöthlings, U., Boeing, H., 2008. Obesity and cancer. Proc. Nutr. Soc. 67, 128–145.
Pitari, G.M., Zingman, L.V., Hodgson, D.M., Alekseev, A.E., Kazerounian, S., Bienengraeber, M., Hajnóczky, G., Terzic, A., Waldman, S.A., 2003. Bacterial enterotoxins are associated with resistance to colon cancer. Proc. Natl. Acad. Sci. 100, 2695–2699.
Pollet, I., Opina, C.J., Zimmerman, C., Leong, K.G., Wong, F., Karsan, A., 2003. Bacterial lipopolysaccharide directly induces angiogenesis through TRAF6-mediated activation of NF-kappaB and c-Jun N-terminal kinase. Blood 102, 1740–1742.
Poste, G., Pasternak, C., 1978. Virus-induced cell fusion. Cell Surf. Rev. 5, 305–367.
Potter, V.R., 1978. Phenotypic diversity in experimental hepatomas: the concept of partially blocked ontogeny. The 10th Walter Hubert Lecture. Br. J .Cancer 38, 1–23.
Powell, A.E., Anderson, E.C., Davies, P.S., Silk, A.D., Pelz, C., Impey, S., Wong, M.H., 2011. Fusion between Intestinal epithelial cells and macrophages in a cancer context results in nuclear reprogramming. Cancer Res. 71, 1497–1505.
Prince, M.E., Sivanandan, R., Kaczorowski, A., Wolf, G.T., Kaplan, M.J., Dalerba, P., Weissman, I.L., Clarke, M.F., Ailles, L.E., 2007. Identification of a subpopulation of cells with cancer stem cell properties in head and neck squamous cell carcinoma. Proc. Natl. Acad. Sci. USA 104, 973–978.
Ragon, M., Restoux, G., Moreira, D., Moller, A.P., Lopez-Garcia, P., 2011. Sunlight-exposed biofilm microbial communities are naturally resistant to chernobyl ionizing-radiation levels. PLoS One 6, e21764.
Rambaud, J.-C., Bouhnik, Y., Marteau, P., Pochart, P., 1993. Manipulation of the human gut microflora. Proc. Nutr. Soc. 52, 357–366.
Rao, A.V., Bested, A.C., Beaulne, T.M., Katzman, M.A., Iorio, C., Berardi, J.M., Logan, A. C., 2009. A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. Gut Pathogens 1.
Rassool, G.H., 2003. Global cancer rates could increase by 50% to 15 million by 2020. J. Adv. Nurs. 44, 7–8.
Redpath, J.L., Elmore, E., 2007. Radiation-induced neoplastic transformation in vitro, hormesis and risk assessment. Dose-Response 5, 123–130.
Reinhardt, C., Bergentall, M., Greiner, T.U., Schaffner, F., Ostergren-Lunden, G., Petersen, L.C., Ruf, W., Backhed, F., 2012. Tissue factor and PAR1 promote microbiota-induced intestinal vascular remodelling. Nature 483, 627–631.
Ricci-Vitiani, L., Lombardi, D.G., Pilozzi, E., Biffoni, M., Todaro, M., Peschle, C., De Maria, R., 2007. Identification and expansion of human colon-cancer-initiating cells. Nature 445, 111–115.
Richly, E., Leister, D., 2004. NUPTs in sequenced eukaryotes and their genomic organization in relation to NUMTs. Mol. Biol. Evol. 21, 1972–1980.
Riley, D.R., Sieber, K.B., Robinson, K.M., White, J.R., Ganesan, A., Nourbakhsh, S., Dunning Hotopp, J.C., 2013. Bacteria-human somatic cell lateral gene transfer is enriched in cancer samples. PLoS Comput. Biol. 9, e1003107.
Riley, P., 1994. Free radicals in biology: oxidative stress and the effects of ionizing radiation. Int. J. Radiat. Biol. 65, 27–33.
Riordan, N.H., Riordan, H.D., Meng, X., Li, Y., Jackson, J.A., 1995. Intravenous ascorbate as a tumor cytotoxic chemotherapeutic agent. Med. Hypotheses 44, 207–213.
Robinson, K.M., Sieber, K.B., Dunning Hotopp, J.C., 2013. A review of bacteria-animal lateral gene transfer may inform our understanding of diseases like cancer. PLoS Genet. 9, e1003877.

Rodriguez, S.D., Brar, R.K., Drake, L.L., Drumm, H.E., Price, D.P., Hammond, J.I., Urquidi, J., Hansen, I.A., 2013. The effect of the radio-protective agents ethanol, trimethylglycine, and beer on survival of X-ray-sterilized male Aedes aegypti. Parasites Vectors 6, 211.
Ron, E.Z, 2006. Bacterial Stress Response. In: Dworkin, M., Falkow, S., Rosenberg, E., Schleifer, E., Stackebrandt, E. (Eds.), The Prokaryotes. Springer, New York, pp. 1012–1027.
Rutkowski, M.R., Stephen, T.L., Svoronos, N., Allegrezza, M.J., Tesone, A.J., Perales-Puchalt, A., Brencicova, E., Escovar-Fadul, X., Nguyen, J.M., Cadungog, M.G., Zhang, R., Salatino, M., Tchou, J., Rabinovich, G.A., Conejo-Garcia, J.R., 2015. Microbially driven TLR5-dependent signaling governs distal malignant progression through tumor-promoting inflammation. Cancer Cell. 27, 27–40.
Sakurai-Yageta, M., Recchi, C., Le Dez, G., Sibarita, J.-B., Daviet, L., Camonis, J., D'Souza-Schorey, C., Chavrier, P., 2008. The interaction of IQGAP1 with the exocyst complex is required for tumor cell invasion downstream of Cdc42 and RhoA. J. cell Biol. 181, 985–998.
Samudio, I., Fiegl, M., Andreeff, M., 2009. Mitochondrial uncoupling and the Warburg effect: Molecular basis for the reprogramming of cancer cell metabolism. Cancer Res. 69. http://dx.doi.org/10.1158/0008-5472.CAN-08-3722.
Sanford, K., 2005. Reintroduction to nutrition and cancer treatment. Semin. Oncol. Nurs. 21, 164–172.
Scanlan, P.D., Marchesi, J.R., 2008. Micro-eukaryotic diversity of the human distal gut microbiota: qualitative assessment using culture-dependent and -independent analysis of faeces. ISME J. 2, 1183–1193.
Schatton, T., Murphy, G.F., Frank, N.Y., Yamaura, K., Waaga-Gasser, A.M., Gasser, M., Zhan, Q., Jordan, S., Duncan, L.M., Weishaupt, C., Fuhlbrigge, R.C., Kupper, T.S., Sayegh, M.H., Frank, M.H., 2008. Identification of cells initiating human melanomas. Nature 451, 345–349.
Schiavo, G., van der Goot, F.G., 2001. The bacterial toxin toolkit. Nat. Rev. Mol. Cell Biol. 2, 530–537.
Seigel, G.M., Hackam, A.S., Ganguly, A., Mandell, L.M., Gonzalez-Fernandez, F., 2007. Human embryonic and neuronal stem cell markers in retinoblastoma. Mol. Vis. 13, 823–832.
Selvam, R., Maheswari, P., Kavitha, P., Ravichandra, M., Sas, B., Ramchand, C.N., 2009. Effect of Bacillus subtilis PB6, a natural probiotic on colon mucosal inflammation and plasma cytokines levels in inflammatory bowel disease. Indian J. Biochem. Biophys. 46, 79–85.
Seo, B., Choy, E.W., Maudsley, S., Miller, W.E., Wilson, B.A., Luttrell, L.M., 2000. Pasteurella multocida toxin stimulates mitogen-activated protein kinase via G (q/11)-dependent transactivation of the epidermal growth factor receptor. J. Biol. Chem. 275, 2239–2245.
Shabo, I., Svanvik, J., 2011. Expression of macrophage antigens by tumor cells. Adv. Exp. Med. Biol. 714, 141–150.
Shacter, E., Weitzman, S.A., 2002. Chronic inflammation and cancer. Oncology 16 (217–26), 229, discussion 230-2.
Shao, C., Furusawa, Y., Aoki, M., Ando, K., 2003. Role of gap junctional intercellular communication in radiation-induced bystander effects in human fibroblasts. Radiat. Res. 160, 318–323.
Sharma, S., Sarkar, S., Paul, S.S., Roy, S., Chattopadhyay, K., 2013. A small molecule chemical chaperone optimizes its unfolded state contraction and denaturant like properties. Sci. Rep. 3.
Shekhani, M.T., Jayanthy, A.-S., Maddodi, N., Setaluri, V., 2013. Cancer stem cells and tumor transdifferentiation: implications for novel therapeutic strategies. Am. J. Stem Cells 2, 52–61.
Shi, W., Meng, Z., Chen, Z., Hua, Y., Gao, H., Wang, P., Lin, J., Zhou, Z., Luo, J., Liu, L., 2014. RNA interference against MDM2 suppresses tumor growth and metastasis in pancreatic carcinoma SW1990HM cells. Mol. Cell. Biochem. 387, 1–8.
Singh, S.K., Clarke, I.D., Terasaki, M., Bonn, V.E., Hawkins, C., Squire, J., Dirks, P.B., 2003. Identification of a cancer stem cell in human brain tumors. Cancer Res. 63, 5821–5828.
Singh, S.K., Hawkins, C., Clarke, I.D., Squire, J.A., Bayani, J., Hide, T., Henkelman, R.M., Cusimano, M.D., Dirks, P.B., 2004. Identification of human brain tumour initiating cells. Nature 432, 396–401.
Soler, A.P., Miller, R.D., Laughlin, K.V., Carp, N.Z., Klurfeld, D.M., Mullin, J.M., 1999. Increased tight junctional permeability is associated with the development of colon cancer. Carcinogenesis 20, 1425–1432.
Spolarics, Z., 1996. Endotoxin stimulates gene expression of ROS-eliminating pathways in rat hepatic endothelial and Kupffer cells. Am. J. Physiol. 270, G660–G666.
Steinmetz, C.G., Xie, P., Weiner, H., Hurley, T.D., 1997. Structure of mitochondrial aldehyde dehydrogenase: the genetic component of ethanol aversion. Structure 5, 701–711.
Stiles, B.G., Bavari, S., Krakauer, T., Ulrich, R.G., 1993. Toxicity of staphylococcal enterotoxins potentiated by lipopolysaccharide: major histocompatibility complex class II molecule dependency and cytokine release. Infect. Immun. 61, 5333–5338.
Sullivan, A., Nord, C.E., Evengard, B., 2009. Effect of supplement with lactic-acid producing bacteria on fatigue and physical activity in patients with chronic fatigue syndrome. Nutr. J. 8.
Swank, G.M., Deitch, E.A., 1996. Role of the gut in multiple organ failure: bacterial translocation and permeability changes. World J. Surg. 20, 411–417.
Swanson, P.A., Kumar, A., Samarin, S., Vijay-Kumar, M., Kundu, K., Murthy, N., Hansen, J., Nusrat, A., Neish, A.S., 2011. Enteric commensal bacteria potentiate epithelial restitution via reactive oxygen species-mediated inactivation of focal adhesion kinase phosphatases. Proc. Natl. Acad. Sci. USA 108, 8803–8808.
Tabe, Y., Sebasigari, D., Jin, L., Rudelius, M., Davies-Hill, T., Miyake, K., Miida, T., Pittaluga, S., Raffeld, M., 2009. MDM2 antagonist nutlin-3 displays antiproliferative and proapoptotic activity in mantle cell lymphoma. Clin. Cancer Res. 15, 933–942.
Tanaka, S., Sato, N., Fujioka, H., Takahashi, Y., Kimura, K., Iwamoto, M., Uchiyama, K., 2012. A case of solitary breast metastasis from malignant melanoma of the nasal cavity. Oncol. Lett. 4, 889–892.
Tedeschi, G.G., Amici, D., 1972. Mycoplasma-like microorganisms probably related to L forms of bacteria in the blood of healthy persons. Cultural, morphological and histochemical data. Ann. Sclavo 14, 430–442.
Tedeschi, G.G., Amici, D., Santarelli, I., 1976a. Unstable L-forms of micrococci in human foetal blood. Experientia 32, 925–927.
Tedeschi, G.G., Amici, D., Sprovieri, G., Vecchi, A., 1976b. Staphylococcus epidermidis in the circulating blood of normal and thrombocytopenic human subjects: Immunological data. Experientia 32, 1600–1602.
Tedeschi, G.G., Bondi, A., Paparelli, M., Sprovieri, G., 1978. Electron microscopical evidence of the evolution of corynebacteria-like microorganisms within human erythrocytes. Experientia 34, 458–460.
Thannickal, V.J., Fanburg, B.L., 2000. Reactive oxygen species in cell signaling. Am. J. Physiol. Lung Cell Mol. Physiol. 279, L1005–L1028.
Thingstad, T.F., Lignell, R., 1997. Theoretical models for the control of bacterial growth rate, abundance, diversity and carbon demand. Aquat. Microb. Ecol. 13, 19–27.
Tiezzi, D.G., Clagnan, W.S., Mandarano, L.R.M., de Sousa, C.B., Marana, H.R.C., Tiezzi, M.G., de Andrade, J.M., 2013. Expression of aldehyde dehydrogenase after neoadjuvant chemotherapy is associated with expression of hypoxia-inducible factors 1 and 2 alpha and predicts prognosis in locally advanced breast cancer. Clinics 68, 592–598.
Tovar, C., Rosinski, J., Filipovic, Z., Higgins, B., Kolinsky, K., Hilton, H., Zhao, X., Vu, B. T., Qing, W., Packman, K., Myklebost, O., Heimbrook, D.C., Vassilev, L.T., 2006. Small-molecule MDM2 antagonists reveal aberrant p53 signaling in cancer: implications for therapy. Proc. Natl. Acad. Sci. USA 103, 1888–1893.
Travaglione, S., Fabbri, A., Fiorentini, C., 2008. The Rho-activating CNF1 toxin from pathogenic E. coli: a risk factor for human cancer development? Infect Agent Cancer 3, 4.
Trinchieri, G., 2013. L06.03Gut commensal bacteria determine cancer response to treatment by modulating systemic inflammation. Ann. Oncol. 24, i12.
Trosko, J.E., 2005. The role of stem cells and cell-cell communication in radiation carcinogenesis: ignored concepts. Brit. J. Radiol. Supplement 27, 132–138.
Tubiana, M., Feinendegen, L.E., Yang, C., Kaminski, J.M., 2009. The linear no-threshold relationship is inconsistent with radiation biologic and experimental data. Radiology 251, 13–22.
Turnbaugh, P.J., Hamady, M., Yatsunenko, T., Cantarel, B.L., Duncan, A., Ley, R.E., Sogin, M.L., Jones, W.J., Roe, B.A., Affourtit, J.P., Egholm, M., Henrissat, B., Heath, A.C., Knight, R., Gordon, J.I., 2009a. A core gut microbiome in obese and lean twins. Nature 457, 480–484.
Turnbaugh, P.J., Ridaura, V.K., Faith, J.J., Rey, F.E., Knight, R., Gordon, J.I., 2009b. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Sci. Transl. Med. 1, 6ra14.
Turroni, F., Peano, C., Pass, D.A., Foroni, E., Severgnini, M., Claesson, M.J., Kerr, C., Hourihane, J., Murray, D., Fuligni, F., Gueimonde, M., Margolles, A., De Bellis, G., O'Toole, P.W., van Sinderen, D., Marchesi, J.R., Ventura, M., 2012. Diversity of bifidobacteria within the infant gut microbiota. PLoS One 7.
Ucar, D., Cogle, C.R., Zucali, J.R., Ostmark, B., Scott, E.W., Zori, R., Gray, B.A., Moreb, J. S., 2009. Aldehyde dehydrogenase activity as a functional marker for lung cancer. Chem.-Biol. Interact. 178, 48–55.
Ullrich, R.L., Storer, J.B., 1979. Influence of gamma irradiation on the development of neoplastic disease in mice: III. Dose-rate effects. Radiat. Res. 80, 325–342.
United Nations. Scientific Committee on the Effects of Atomic Radiation, 1977. Sources and effects of ionizing radiation: 1977 report to the General Assembly, with annexes. United Nations, New York.
United Nations. Scientific Committee on the Effects of Atomic Radiation, 1993. Sources and effects of ionizing radiation: United Nations Committee on the Effects of Atomic Radiation: UNSCEAR 1993 report to the General Assembly, with scientific annexes. United Nations, New York.
United Nations. Scientific Committee on the Effects of Atomic Radiation, 1996. Sources and effects of ionizing radiation: UNSCEAR 1996 report to the General Assembly, with scientific annex. United Nations, New York.
United Nations. Scientific Committee on the Effects of Atomic Radiation, 2000. Sources and effects of ionizing radiation: United Nations Scientific Committee on the Effects of Atomic Radiation: UNSCEAR 2000 report to the General Assembly, with scientific annexes. United Nations, New York.
United Nations. Scientific Committee on the Effects of Atomic Radiation, 2010. Sources and effects of ionizing radiation: United Nations Scientific Committee on the Effects of Atomic Radiation: UNSCEAR 2008 report to the General Assembly, with scientific annexes. United Nations, New York.
United Nations. Scientific Committee on the Effects of Atomic Radiation, 2011. Hōshasen no sengen to eikyō: Genshi Hōshasen no Eikyō ni Kansuru Kokuren Kagaku Iinkai: UNSCEAR 2008-nen hōkokusho. Hōshasen Igaku Sōgō Kenkyūjo, Chiba-shi.
Vaca, C.E., Wilhelm, J., Harms-Ringdahl, M., 1988. Interaction of lipid peroxidation products with DNA: a review. Mutat. Res./Rev. Genet. Toxicol. 195, 137–149.
Vassilev, L.T., Vu, B.T., Graves, B., Carvajal, D., Podlaski, F., Filipovic, Z., Kong, N., Kammlott, U., Lukacs, C., Klein, C., Fotouhi, N., Liu, E.A., 2004. In vivo activation of the p53 pathway by small-molecule antagonists of MDM2. Science 303, 844–848.
Velicer, C.M., Heckbert, S.R., Lampe, J.W., Potter, J.D., Robertson, C.A., Taplin, S.H.,

2004. Antibiotic use in relation to the risk of breast cancer. JAMA 291, 827–835.
Ventura, M., Sozzi, T., Turroni, F., Matteuzzi, D., van Sinderen, D., 2011. The impact of bacteriophages on probiotic bacteria and gut microbiota diversity. Genes Nutr. 6, 205–207.
Verschoor, J.A., Boshoff, C.H., Coetzee, L., Van Wyngaardt, S., Visser, L., 1990. Spontaneous fusion between splenocytes and myeloma cells induced by bacterial immunization. Hybridoma 9, 511–518.
Viaud, S., Saccheri, F., Mignot, G., Yamazaki, T., Daillere, R., Hannani, D., Enot, D.P., Pfirschke, C., Engblom, C., Pittet, M.J., Schlitzer, A., Ginhoux, F., Apetoh, L., Chachaty, E., Woerther, P.L., Eberl, G., Berard, M., Ecobichon, C., Clermont, D., Bizet, C., Gaboriau-Routhiau, V., Cerf-Bensussan, N., Opolon, P., Yessaad, N., Vivier, E., Ryffel, B., Elson, C.O., Dore, J., Kroemer, G., Lepage, P., Boneca, I.G., Ghiringhelli, F., Zitvogel, L., 2013. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science 342, 971–976.
Virchow, R.L.K., Die Krankhaften Geschwülste, Bd. 1.Verlag von August Hirschwald, Berlin, 1863, 369–434.
Walker, R.I., 1978. The contribution of intestinal endotoxin to mortality in hosts with compromised resistance: a review. Exp. Hematol. 6, 172–184.
Wallace, D.C., 2005. Mitochondria and Cancer: Warburg Addressed. Cold Spring Harb. Symp. Quant. Biol. 70, 363–374.
Wang, J., Guo, L.P., Chen, L.Z., Zeng, Y.X., Lu, S.H., 2007. Identification of cancer stem cell-like side population cells in human nasopharyngeal carcinoma cell line. Cancer Res. 67, 3716–3724.
Wang, J.H., Bose, S., Kim, G.C., Hong, S.U., Kim, J.H., Kim, J.E., Kim, H., 2014. Flos lonicera ameliorates obesity and associated endotoxemia in rats through modulation of gut permeability and intestinal microbiota. PLoS One 9.
Warburg, O., 1956. On the origin of cancer cells. Science 123, 309–314.
Watanabe, T., Hotta, T., Ichikawa, A., Kinoshita, T., Nagai, H., Uchida, T., Murate, T., Saito, H., 1994. The MDM2 oncogene overexpression in chronic lymphocytic leukemia and low-grade lymphoma of B-cell origin. Blood 84, 3158–3165.
Watanabe, T., Ichikawa, A., Saito, H., Hotta, T., 1996. Overexpression of the MDM2 oncogene in leukemia and lymphoma. Leuk. Lymphoma 21, 391–397.
Watson, J., 2013. Oxidants, antioxidants and the current incurability of metastatic cancers. Open Biol. 3.
Weibel, S., Stritzker, J., Eck, M., Goebel, W., Szalay, A.A., 2008. Colonization of experimental murine breast tumours by Escherichia coli K-12 significantly alters the tumour microenvironment. Cell. Microbiol. 10, 1235–1248.
Werth, N., Beerlage, C., Rosenberger, C., Yazdi, A.S., Edelmann, M., Amr, A., Bernhardt, W., von Eiff, C., Becker, K., Schäfer, A., Peschel, A., Kempf, V.A.J., 2010. Activation of hypoxia inducible factor 1 is a general phenomenon in infections with human pathogens. PLoS One 5, e11576.
Wu, S., Rhee, K.J., Albesiano, E., Rabizadeh, S., Wu, X., Yen, H.R., Huso, D.L., Brancati, F.L., Wick, E., McAllister, F., Housseau, F., Pardoll, D.M., Sears, C.L., 2009. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17T cell responses. Nat. Med. 15, 1016–1022.
Xiaofeng, C., Jinrong, Q., Dapeng, Y., Jianlei, L., Caiyun, Y., Xiaoming, Z., Yongmei, Y., 2013. MDM2 promotes invasion and metastasis in invasive ductal breast carcinoma by inducing matrix metalloproteinase-9. PLoS One 8.
Yamagata, H., Kiyohara, Y., Aoyagi, K., Kato, I., Iwamoto, H., Nakayama, K., Shimizu, H., Tanizaki, Y., Arima, H., Shinohara, N., Kondo, H., Matsumoto, T., Fujishima, M., 2000. Impact of Helicobacter pylori infection on gastric cancer incidence in a general Japanese population: the Hisayama study. Arch. Intern. Med. 160, 1962–1968.
Yamaguchi, M., Kashiwakura, I., 2013. Role of reactive oxygen species in the radiation response of human hematopoietic stem/progenitor cells. PLoS One 8, e70503.
Yamamori, T., Yasui, H., Yamazumi, M., Wada, Y., Nakamura, Y., Nakamura, H., Inanami, O., 2012. Ionizing radiation induces mitochondrial reactive oxygen species production accompanied by upregulation of mitochondrial electron transport chain function and mitochondrial content under control of the cell cycle checkpoint. Free Radic. Biol. Med. 53, 260–270.
Yan, A.W., Schnabl, B., 2012. Bacterial translocation and changes in the intestinal microbiome associated with alcoholic liver disease. World J. Hepatol. 4, 110–118.
Yan, F., Cao, H., Cover, T.L., Whitehead, R., Washington, M.K., Polk, D.B., 2007. Soluble proteins produced by probiotic bacteria regulate intestinal epithelial cell survival and growth. Gastroenterology 132, 562–575.
Yen, T.H., Wright, N.A., 2006. The gastrointestinal tract stem cell niche. Stem Cell Rev. 2, 203–212.
Yeo, S.G., Kim, D.Y., Kim, T.H., Kim, S.Y., Hong, Y.S., Jung, K.H., 2010. Whole-liver radiotherapy for end-stage colorectal cancer patients with massive liver metastases and advanced hepatic dysfunction. Radiat. Oncol. 5.
Yoshimoto, S., Loo, T.M., Atarashi, K., Kanda, H., Sato, S., Oyadomari, S., Iwakura, Y., Oshima, K., Morita, H., Hattori, M., 2013. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Nature 499, 97–101.
Yu, B., Yang, M., Shi, L., Yao, Y., Jiang, Q., Li, X., Tang, L.-H., Zheng, B.-J., Yuen, K.-Y., Smith, D.K., Song, E., Huang, J.-D., 2012. Explicit hypoxia targeting with tumor suppression by creating an "obligate" anaerobic Salmonella Typhimurium strain. Sci. Rep. 2.
Yu, Y.A., Shabahang, S., Timiryasova, T.M., Zhang, Q., Beltz, R., Gentschev, I., Goebel, W., Szalay, A.A., 2004. Visualization of tumors and metastases in live animals with bacteria and vaccinia virus encoding light-emitting proteins. Nat. Biotechnol. 22, 313–320.
Zen, Y., Fujii, T., Yoshikawa, S., Takamura, H., Tani, T., Ohta, T., Nakanuma, Y., 2007. Histological and culture studies with respect to ABCG2 expression support the existence of a cancer cell hierarchy in human hepatocellular carcinoma. Am. J. Pathol. 170, 1750–1762.
Zinkernagel, A.S., Johnson, R.S., Nizet, V., 2007. Hypoxia inducible factor (HIF) function in innate immunity and infection. J. Mol. Med. 85, 1339–1346.