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The Microbiome its Influence and Relationship with the Immune System, and Cancer

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Abstract

The paper deals with the intricate balance between the microbiome, its relationship and influence on the T-cells, and B lymphocytes on immunity, and the immune system. These cells can be modified by the influence of various changes in flora. Immune receptors play a prominent role in the function of the immune system. Although T-cell receptors are highly specific for their antigens, in some instances however, faulty receptors can lead to either an over activation, or a weak immune response. There are approximately 30 trillion bacteria, that make up the microbiome. They include the following orders, genera and species, such as *Clostridiales, Ruminococcaceae, Faecalibacterium* spp., *Akkermansia muciniphila, Bacteroides fragilis, and Bifidobacteria*. These microorganisms can modulate the immune system, in a positive or negative fashion, depending on the genetics, mutations, immune factors (cytokines, lymphokines and metabolites), and the influence can lead to the development of cancer related illness [47,48]. Cancer can resist treatment for melanoma, when cancer cells express the CD47 receptor, where they are able to cause macrophages to go to sleep. Cancer cells can alter "conventional therapy, "trigger inflammation", as well as macrophages to release molecules, that can stimulate cancer growth, and metastasis. In the case of metastatic breast cancer disease, during chemotherapy with paclitaxel and doxorubicin, this can create individuals that are more prone to metastatic disease, following chemotherapeutic therapy. In this case, there can be a release of small vesicles called exosomes. Exosomes contain a protein annexin-A-6, its release is "enhanced" after chemotherapy. In breast cancer, "luminal epithelial breast cells" can express the estrogen receptor at different levels, and can influence whether breast cells become cancerous [31,32,34,35]. Even small metabolites like methionine can affect cell growth, and metabolic pathways such as, the pentose phosphate pathway, as well as the formation of pyridoxal phosphate, the synthesis of amino acids, and nucleotides important in growth [44]. Short-chain fatty acids (SCFAs), are important since they can increase the presence of *Bifidobacterium* spp., which can act to reduce tumor growth [48].

Viruses can also be a problem for the immune system, when they are capable of converting from their single stranded formation to double stranded shape [61]. Genetic mutations do occur, and these can lead to errors in how genes are encoded, for example the enzyme tyrosine phosphatase N2 can lead to decreased levels of the enzyme PTPN2, and contribute to the development of autoimmune disease. Certain regions of the DNA sequences called TADS, can be affected in gene regulation. Thus, cancer can affect gene regulation by interfering with TADs and gene expression. In essence, even one mutation in a gene can lead to changes in the interactions within TADs [40,41].

Keywords: *Microbiome; Immune System; Cancer*

Microbiology owes much of its progress from its early beginnings, through the likes of Robert Koch, and his developments on pure culture methods. This discovery in the use of agar as a solidifying agent, made possible for pathogenic microorganisms isolated as colonies, at elevated temperatures of 37°C. Koch also is attributed for his development of Koch's postulates, and the recognition of a specific causative

agent, responsible for a disease. Pasteur also contributed greatly by his gooseneck or "swan-neck" flask, which helped to end the theory of spontaneous generation, as well as his work on pasteurization and rabies. Elie Metchnikoff also studied phagocytes and realized the importance of phagocytes, that function in the bodies protection from disease. Paul Ehrlich's is notable for his work in chemotherapy, and his "magic bullet", compound 606 (Salvarsan), for the treatment of syphilis. He also coined the term chemotherapy and developed the side chain theory of antibodies. He earned a Nobel Prize, and the title of Father of Modern Immunology. These contributions and others have given the world the foundations, for a better understanding of our immune system, and the future of immunology today [1,2].

Currently Scientists, Microbiologists and Immunologist have new insight into the unique mechanisms, of the functioning of the immune system. Today a "new light based technology" has made it possible to detect, and determine the quantify, and the release of signaling molecules, allowing the communication between cells [3]. A Fluid filled chip may also provide of a better glimpse into the tiny structures of cells, in the living state, through new fluorescent dyes, that offer more detail [4]. Other possibly new antibiotics may be in the pipeline, with the use of the CRISPR/Cas9 gene editing tool, utilizing the soil microorganism *Streptomyces sclerotialus*. By this tool genes normally silenced may be turned on, in a way, that allows for the creation of new antibiotics, enzymes, and or other biological molecules of significance [5]. This can be accomplished by using clones of DNA fragments, which are taken up by bacteria. In this manner, genes that normally are repressed, are able to be expressed upon their activation [6]. Some immune responses can be improved by "blocking proteins", that interfere with an immune response, against malignant tumors [7]. Research now centers on using CAR-T therapy, and methods that can recognize cancer surface antigens. In an effort to identify cancer surface antigens, these can serve as markers, by engineering cells to attack malignant cancer cells [8]. These methods for treating cancer through the immune system, are often referred to as immunotherapy, since this technique utilizes the bodies own cells to fight cancer. Some cancer treatments use cytokine levels (signaling molecules), as a means to monitor how well immunotherapy is proceeding as well, and if any toxin affects (rash and thyroid dysfunction) have occurred, or autoimmune disease. Therefore, these therapies do have risks, but monitoring for toxicity due to therapy, and autoimmune disease can be helpful as well [9]. Some investigations indicate that the response to an infection can be "modulated", from an inflammatory nature by HOTAIR (long noncoding RNA molecule), particularly during inflammation, which could lead to serious infections such as sepsis, or meningitis [11,13].

The National Institute Of Health (NIH) has found that some microbial populations in the gums, can lead to inflammation and periodontal disease. Their research showed thru RNA analysis, that blocking Th 17 cells can "reduce inflammation, tissue destruction and bone loss [12]. Immunologists also believe during clinical trials, that removal of senescent cells, can be beneficial for the therapy of patients, since it is believed that "semidormant cells" which occur in other areas of the body, can cause various aging conditions, from osteoporosis, diabetes, muscle weakness, and in some cases idiopathic pulmonary fibrosis (fatal condition due to senescent cells) [10,11]. This is because senescent cells may acquire damages that may impair their function, and or be the result of disease, and chronic inflammation. However, mice studies indicate that the aging cells can survive with certain drugs, in which functional genes can be activated by certain proteins [11].

Researchers at the University of Texas at Arlington have found that a "long non-coding RNA molecule referred to as "HOTAIR", are present on white blood cells, can serve as a signaling molecule from DNA, and is pivotal for an immune response. It thus can be a regulator for cytokine release during an infection, and can be a means to monitor rapid progressing infections [13]. Other regulators of the immune system include the Regulatory T cells (T- reg's), although the majority enhance an immune response to destroy cancer cells, various bacteria, and viruses. In some instances, T- reg's can damper an immune response, by controlling the expression of and a number of genes, that are involved in T cell function [14].

The University of Turku has discovered a protein that is a key regulator of T-reg's called "Hypermethylated in Cancer 1" (HIC1). HIC1 has control of a large number of genes, that are in charge of T cell function. HIC1 also has binding sites in the nucleus, providing a better understanding in the "molecular mechanisms", involved in T cell function, and in their immunological response [14]. Scientists at the Uni-

versity of Washington Health Sciences/UW Medicine have developed a protein that "mimics" another key immune regulator interleukin 2 (IL-2), with an equal ability to stimulate cancer fighting T-cells as that of IL-2, without side-affects [15]. Naturally occurring IL-2 has the problem of binding to alpha receptors, as well as beta and gamma receptors. This can lead to severe toxicity from those cells bearing those receptors. This developmental protein is said not to produce side effects, in that is not able to bind alpha receptors on T-cells, and thus lesser side effects from therapy [15]. Another form of immunotherapy, involves the extraction of a patient's blood, using a virus in order to insert modified DNA into a patients T-cells. This in turn stimulates T-cells thus to express a receptor, which will help T-cells to recognize, and destroy cancer cells. These newly modified T-cells are hybrid cells called chimeric antigen receptor T-cells, or CART cells. They are allowed to multiply in number, and re-infused back into the patient. Thus, these newly modified T-cells, are able to recognize tumors expressing the CD30 protein maker [15,16].

A new CRISPR-Cas9 genomic library has been developed identifying 20,000 genes from mouse Th2 cells, providing greater incites into the many different genes, important in the "activation of, and differentiation Th-2 cells, and the signals involved in immune regulation. They were also able to discover new regulatory genes, and a transcription factor PPARG, which is important in regulating Th2 cells. Thus providing a greater incite into a number of regulatory genes, that are important in the regulation of Th2 cells [17,18]. CRISPR which is involved in "gene editing", may also provide clues to what particular genes are responsible for antibiotic resistance, since these genes can be selected. It also provides a means to determine how resistance occurs directly, in the bacterial cell through conjugation studies. In this study "Mobile-CRISPR" made it possible to study those genes, that are important in antibiotic resistance, in these particular pathogenic species, such as *Pseudomonas, Salmonella* and *Listeria* [19]. CRISPR has also applications in skin grafts, wound healing, transplant rejection, and cosmetic surgery [20]. The gene editing tool in addition has implications of treatment for the parasitic disease Schistosomiasis, which is caused by the parasite *Opisthorchis viverrini*, where researches were able experimentally to "deactivate a gene responsible for a protein produced by the liver fluke during infection [21].

According to recent assessments, on the whole we have approximately 30 trillion bacteria that inhabit our body, as a community, or microbiome. These various orders, family, genera and species such as *Clostridiales*, *Ruminococcaceae*, *Faecalibacterium spp.*, *Akkermansia muciniphila*, *Bacteroides fragilis* and *Bifidobacteria*. These microorganisms may modulate the immune system, in a positive or negative fashion, depending on the genetics, mutations, immune factors (cytokines, lymphokines and metabolites), and their influence relating to the development of growth cancer related illness [47,48].

Other means of immunotherapy include the use of regulatory proteins, such as SATAB1, which can regulate the "transcription of several genes". According to the University of Turku this information may provide additional methods for treating multiple sclerosis, and or arthritis, by having a better understanding how these proteins affect the functioning of T cells, The function of T cells may change over time, as it relates to the process of inflammation [22]. Immune receptors are also prominent function of the immune system, and immunotherapy, although their receptors are highly specific, and sensitive towards the antigens they respond towards. However, in some cases T-cells can have faulty receptors, which can lead to an over activation, and a "chronic proinflammatory state". The status of constant activation can have a detrimental affect on organs and tissues. This can occur in HIV patients, with the SLAMF7 immune receptor [24]. The inositol 1,4,5-trisphosphate receptor (IP3Rs), and choline which its "mimics" are both important in the release of calcium, where "choline activation of sigma-1 receptor potentiated, the calcium-releasing actions of IP3R". Therefore, choline works as well as IP3 to stimulate calcium release, where choline activates sigma-1 receptors, and affects "uptake by transporters at synapses, where calcium is important in nerve transmission [25,67]. In essence, calcium is important in nerve transmission. Although T-cells were once considered to be static, they have molecules that are constantly moving. It also seems that the health of T-cell receptors does have an impact on the quality of the function of the immune system [23-25].

It seems possible in the future with the development of current techniques, to be able to utilize pluripotent stem cells, in such a manner making it possible to process, and produce any cell type in the body. These new techniques can create hope with creating T-cells, which can be engineered to produce fully functional T-cells, capable of being directed toward fighting cancers. The University of California is working on these new techniques, that involve using pluripotent stem cells, to produce engineered T-cells with specific receptors, which are functional for individuals, and should in the future serve as a reservoir of cells for many others [26].

Some methods of immunotherapy utilize various drugs, and the engineering of immune cells, in order to give the immune system, an opportunity to be able to recognize, and attack any cancer cells, that may occur within the body [48]. This is also true that genetic mutations can occur, and can lead to errors that can induce the onset of cancer and autoimmune disease [27]. Mutations for example that occur, in the "encoding gene" for the enzyme tyrosine phosphatase N2 (PTPN2), can lead to decreased levels of the enzyme PTPN2, and can contribute to in the development of autoimmune disease, Type 1 diabetes, Crohn's Disease, and rheumatoid arthritis. Decreased levels of the enzyme can contribute to T-cells which may attack other cells of the body [27,28]. Other mechanisms that occur with cancer, particularly with melanoma cancer for example, include mutations in the BRAF gene, during the genetic pathway MAPK, which can drive tumor growth. Proteins like ERK a part of the MAPK pathway, have a significant mechanism that can provide a means for cancer resistance. This can occur when ERK can move from the cytoplasm to the endoplasmic reticulum and called ER translocation. In so doing, reactivation of ERK can occur, and increase autophagy. Therefore, cancer resistance can occur when the protein ERK reactivates, and when cancer cells "recycle" cells, after cells undergo autophagy [31].

Immunotherapy as can be easily explained, is whereby treatments whether for immune cell problems, mutations, or genetic aberrations, involves trying to train the immune system to eradicate cancers. In Leukemia, cancer cells can in some instances, try to interfere with the regulation of the consumption of glucose by cells. Cancer's "strategies" is also insulin dependent". Cancer can interfere with insulin levels, by particularly affecting the "over production of a protein called IGFBP. This makes healthy cells less sensitive to insulin, and when IGFBP is high, it takes more insulin to use glucose, than it does when IGFBP1 is low. Cancer also can inactivate incretins, which help to reduce glucose levels, after a good meal. Cancer also can attack serotonin, and by reducing serotonin, it also reduces the insulin levels. Cancer therefore "undercuts" the ability of cells to consume glucose in a normal fashion [29,30].

Other mechanisms that allow for cancers to resist treatment, occur in melanoma [31]. Macrophages can also be put to sleep by cancer in some instances, when these cancer cells express the CD47 receptor. Researchers at the Pennsylvania School of Medicine found that these macrophages, could be activated, and primed to attack cancer cells, with the use of CpG, a toll-receptor "agonist", which can send a signal for attacking cancer tumors [32]. Cancer cells killed after conventional therapy can also "paradonically trigger inflammation", and trigger macrophages to release chemicals that promote new cancer growth, and metastasis. However, the anti-inflammatory drug called PTUPB, has been found to block the release of "tumor-promoting chemicals", that macrophages release during conventional cancer treatment [33,66].

Cancers that affect women, and those of a serious nature such as breast cancers for example, after "neoadjuvant therapy", can in some entances be more prone to metastatic disease. This can occur after chemotherapy, with paclitaxel and doxorubicin. There can be the release of small vesicles called exosomes, which can contain a protein called protein annexin-A6, and where exosomes are "enhanced", as a result of chemotherapy [34]. In the case of breast cancer, the luminal epithelial breast cells can "express" the estrogen receptor at different levels, and can affect whether breast cells will become cancerous or not [35]. With child care cancers, immunotherapy in this case does not often succeed. The use of checkpoint inhibition is mainly to affect gene mutations, and as such is of limited value. Research by Stanford Medicine has found that by using six types of engineered CAR-T cells (chimeric antigen receptor T cells), and targeting the surface maker B7-H3, they were able to irradicate osteosarcoma, or Ewing sarcoma (both bone tumors), from "xenograft models of pediatric cancer". They hope that this research can provide another mechanism, for treatments of brain tumor cancer patients [36].

In the case of skin cancer, approximately 2 - 5% of cancer patients go on to develop squamous cell carcinoma. It appears in these cases a signaling pathway MET and the gene Tpl2, contribute to continued develop of cancer disease [38]. With other forms of cancer, it seems that the CDK9, a DNA transcription regulator (a kinase), can be inhibited by MC180295 a new drug and in so turn genes on, that are epigenetically silenced due to cancer [37]. Other interesting facts of immune cells would include certain aspects of macrophages and neutrophils, in their regulation of phagocytosis of these immune cells, by a "critical regulator called myoferlin. Myoferlin is a "key regulator" of the exocytosis of these cells, which can contain particularly more vesicles and lysosomes. Making those cells more capable of attacking cancer cells, since the immune cells are able to secrete large amounts of cytolytic enzymes, "and expulsion of indigestible debris [39]".

Cancer in essence is caused by changes such as mutations in the DNA. These include the exposure to UV radiation, chemical exposure, smoking, as well as changes that can occur during cell division [27]. DNA that is Chromatin is "wrapped around proteins" and very tightly packed, and in the form of a complex in a 3D structure. Chromatin protects the DNA from damage, and as well is important in its organization, and "regulating gene expression in three dimensions". When the DNA in its three-dimensional structure, it also has "certain regions" that are called topologically associating domains, or TADs. TADs are certain DNA sequences that are able to "interact" [40,41]. In this way various regions of the DNA are able to "interact" with each other, and implying that individual genes are able to act on each other. Therefore, interrupting TADs affects the operation of gene control. Cancer can "affect" gene regulation by interfering with TADs, and thus gene expression. Recent discoveries show that a mutation of a gene, can lead to changes in the interactions within TADs. Normal gene transcription can be repressed by the gene EZH2. Mutations can occur with the EZH2 gene, and this can lead potentially to the onset of cancer, since repression of this gene particularly can lead to tumor growth. Mutations of the EZH2 gene can turn off a complete domain, and turn off genes that would normally be operating to suppress tumor growth. In this situation a multitude of genes may be turned off, and in so doing, create an atmosphere of increased tumor development. New Pharmaceutical drugs that can inhibit this tendency of the EZH2 to promote cancer, are being considered for its potential in cancer therapy [40,41].

Skin cancer is a type of cancer can be "more invasive", because cancer cells can release molecules that promote tumor growth, as well as the spread of cancer to other parts of the body. It seems that the chemicals released from Myosin II rich cells called interleukin 1A, can be significant to the spread of cancer cells, and in the particular situation of melanoma. Therefore, the blocking Myosin II activity, and interleukin 1A, these researchers found that this could reduce the chances of malignant cells surviving after surgery [42]. Experiments with interleukin-27 alpha by the University of Munich, which is an important mediator, can be important as a key biochemical messenger, for the immune system, since an engineered interleukin-27 molecule can be recognized, and released by human cells. These experimenters believe their research may lead to important key signal molecules, by biochemical synthetic methods, and new treatments for sepsis [43]. Even small metabolites like methionine can be important in the cell growth, and in metabolic pathways, like the pentose phosphate pathway, the formation of pyridoxal phosphate, the synthesis of amino acids, and nucleotides important in growth [44]. In the case of Leukemia, a protein called Beta-catenin can be involved in the "activation of genes", that is important in the occurrence of leukemia. With Acute myeloid leukemia F691L mutations can occur, after therapy with FLT3 inhibitors. Purdue researchers have found that both the drugs alkynyl-aminoisoquinoline and alkynyl naphthyridine (new class of FLT3 inhibitors) in preclinical studies, seem to be affective against drug-resistant secondary mutations such as, the "problematic F691 mutation" [45,46].

According to current research, there are approximately 30 trillion bacteria that are harbored by our body. Some are from orders, families, of bacteria, as well as genera and species, and include for example, the *Clostridiales, Ruminococcaceae, Faecalibacterium* spp., *Akkermansia muciniphila, B. fragilis* and *Bifidobacteria.* These groups of microorganisms may modify the immune system, in a positive or negative fashion (more susceptible), depending on the release of immune factors, (cytokinin's, interleukins, metabolites), mutations, genetics, and cancer [47]. There seems to be a link between the 20% of global disease. The species, *Helicobacter pylori*, *Fusobacterium nucleatum*, Epstein-Barr virus, and human papilloma virus, are all related with cancer. It seems clear, that the microbiome plays a significant role, in relationship in various diseases as well [48]. There does seem to be a relationship between changes in the microbiome, in regards to various types of cancers. Microbiome examples include, oral, branchial, intestinal, and vaginal microbiotas are changed in head, neck, lung, with colorectal and cervical carcinomas [48]. Some cancers may release soluble factors, such as CC-chemokine ligand 25 (CCL25), that affect metabolism in a general way. Other mechanisms may influence Toll-like receptors (TLR3-5), and can "affect anticancer immunosurveillance, in the way the immune system responds to the microbiome" [48]. Microbial genomes have also been found in what has been generally considered "sterile sites", namely some tissues, and body fluids such as plasma and cerebrospinal fluid [48].

Other aspects that influence the immune system, also include the "translocation" of *Enterococcus hirae* and *Lactobacillus johnsonii*, through the "intestinal barrier" into lymphoidal organs. That is, following the chemotherapeutic treatment with cyclophosphamide (CTX).

Plus injections with the immune checkpoint blockade monoclonal antibody "ipilimumab", melanoma patients can lead to better targeting of cytotoxic T lymphocyte protein 4 (CTLA4), which can lead to better anti-melanoma therapy. However, with shifts in the microbiome, there can be a greater risk of gastrointestinal toxicity. Therefore, the loss of microbiome, can be as serious as the complete loss of the cytotoxic T lymphocytes, and can have a detrimental effect on the efficiency of the immune system [48].

It also seems that antibiotic treatment can make individuals more susceptible to cancer, by altering ones surveillance capabilities, by "antibiotic induced changes in the microbiome". In the case of vancomycin, there can be a shift from gram positive bacteria to gram negative bacteria, of the order Bacteroidales. This medical procedural treatment with vancomycin can be detrimental, or useful in the effort to improve immunotherapy, by targeting CTLA4 (cytotoxic T-lymphocyte antigen protein4). Yet by inducing the increase in the presence of bacteria of the order Bacteroidales, can help to "trigger type 1 T helper immune responses, by improving the effectiveness of CTLA 4 blockade". Some treatments methods of immunotherapy, which include the inhibiting enzymes, which can potentially lead to convert anticancer chemicals, into toxic products [48]. An example can occur with the enzyme Beta glucuronidases produced by *E. coli, Bacteroides* spp. and *Clostridium perfringens*, since it prevents "reactivation of glucuronidated irinotecan metabolites", and the release of toxic products [48]. Other methods that can promote the growth, and activity of health facilitating microorganisms, is the metabolism of "non-digestible polysaccharides, by gut bacteria, resulting in the production of short-chain fatty acids (SCFAs). SCFAs seem to increase the presence of *Bifidobacterium* spp., which can act to reduce tumor growth [48]. SCFAs also seem in conjunction with diet, can help to reduce the incidence of "colorectal carcinogenesis". Prebiotics such as oligofructose, and inulin can serve as "adjuvants" to cytotoxic cancer drugs and increase the antitumor affects. Even the diabetes drug metformin has anticancer properties, and may be considered as a prebiotic [48]. Diet restriction has been a consideration, and does seem to favor in the reducing the presence of pathogenic bacteria. However, these claims have not been substantiated, whether changing one's diet can lead to beneficial changes in the microbial floral [48]. The use of Calmette-Guerin (BCG) after bladder surgery, does seem to reduce the incidence of cancer relapse. The Lactic Acid bacteria of various species have been reported to be useful, particular through natural killer cell activation, dendritic maturation, and "probiotic-derived ferrichrome (an iron-scavenging peptide) release". Prohep has been useful in shifting the natural intestinal flora towards *Prevotella* spp. *Oscillibacter* spp., and facilitating the growth of *Bacteroides fragilis, Alistipes shahii, Parabacteroides distasonis* and *A. muciniphila* species. These particularly species have the reducing proinflammatory property of Th 17cells and differentiation of T regs, and T regulatory type 1 cells, in the intestinal tract [48]. There can also be an increase in the presence of *Alistipes shahii* after antibody treatment, against interleukin -10 receptor, with CpG oligodeoxy nucleotides, and a subsequent improvement in immunotherapy. *A. shahii* in addition also improved immunotherapy by an increase in the release of tumour necrosis factor [48].

Bacteroides fragilis on the other hand, can "stimulate "pro-inflammatory Th 17 cells, and rapid increase in the greater risk of cancer in tumor predisposed mice [48]. However, *B. fragilis* may in the right circumstances (after blockade of immune checkpoint) have anticancer properties, in the regards to the "context of anti-CTLA4 immunotherapy", since this microorganism can stimulate T memory cells [48]. Other microorganisms besides *B. fragilis* may also stimulate IL-12 production by dendritic cells, for example *Burkholderia cepacia*, which in combination with *B. fragilis*, can mediate an enhanced anticancer effect in the "context of CTLA4 blockage". Furthermore, the microorganism *Barnesiella intestinihominis* commonly found near the intestinal colon, when associated with tumour-bearing wildtype mice, and associated with *B. intestinihominis* can stimulate a greater number of multifunctional CD4+, CD8+, and gamma sigma T-cells, as well as a greater production of interferon-sigma T-cells. Therefore, *B. intestinihominis* during CTX-based chemotherapy, reduced the cancer growth in mice, by involving pathways of Th1 cells, Type 1 CD8+ T cells, TNF (tumor necrosis factor) and IFNγ23. Some microorganisms such as *E. hirae*, can have a greater capacity to move from the intestine to lymphoid organs during CTX-based chemotherapy, and essence also reduce the immunosuppressive T regs, and IL-17 producing gamma sigma T-cells [48].

In relation to pathogen associated molecular patterns (PAMPs), for example, such as bacterial endotoxin, may with radiation treatment, cause an inhibition of tumor growth by activating T cells. PAMPs also has been used as a vaccine adjuvate, particularly against

cancer causing viruses. Lipid A from *Salmonella enteric* has also been approved in a peptide-based vaccine, for "cervical carcinoma-associated strains of the human papillomavirus". Imiquimod a TLR7 a "synthetic agonist ", in addition is approved for the treatment of superficial basal carcinoma. Various genera can contribute to the differentiation, and rise in the number of T reg cells, and help to increase "anti-inflammatory effects [48]". When it comes to cellular metabolites, acetate may increase the growth of some cancer types, since it converts acetate to acetyl-Coenzyme A, which can favor anaerobic growth, and cancer. The metabolite butyrate however, may contribute to tumor suppression. Vitamin A may can also be helpful in the prevention, and treatment of colorectal cancer [48]. A new tool called Unveiling RNA Sample Annotation, provides a way to determine the weight of differences in gene activity, whereby these differences in gene activity, can be used to "describe distinct tissues, and diseases" [49].

Many diseases seem to have a molecular basis, or as a result of a protein that allows a microorganism an advantage, either in its ability to initiate an infection, or cause a disease state. *Chlamydia trachomatis* for example, can "hijack part of the cells protective layers, in an effort to perpetuate itself". It's able to "manipulate human cells" by its *Chlamydia* protein, ChlaDuB1. *Chlamydia* interesting enough, is able to surround itself with pieces of the Golgi apparatus. Apparently, ubiquitin (signaling protein) which is produced by human cells, can be removed by the ability of the protein ChiaDUB1, which can protect the organism from the "host inflammatory response" [50]. *Legionella pneumophila* can "alter the dynamics" of the mitochondria, by "impairing" mitochondria respiration. It does this by a host protein called DNM1L, that fragments the mitochondria, and ultimately results in cell death, as it impairs respiration, and glycolysis [51]. With the case of tularemia (caused by *Francisella tularensis*), this pathogenic microorganism uses a sneaky approach to invade host cells. It apparently likes to avoid the toll-like receptors on the surface of the monocyte, and instead uses a "sack" called a phagosome on monocytes. In this method the organism can access to the host cell, initiate infection, and hinder the release of IL-1B from the cell, and prevent the cell from recognizing its under attack [52]. A Rickettsial-like microorganism called *Anaplasma phagocytophilum* the cause of granulocytic anaplasmosis is second only to Lyme disease (*Borrelia burgdorferi*) in appearance in the United States. Its trick is that it uses a particular sugar residue on the cell surface, and its protein called OmpA, as a key in order to attach, and invade the host cell [53]. *Borrelia burgdorferi* the cause of Lyme disease, is able to disarm the bodies innate immunity, by a protein that disables the immune system. The disease is primarily due to the intense inflammatory response, as a result of the intense reaction, due to the presence of the microorganisms. There are approximately 300,000 cases in the Unites States annually, and is transmitted by the tick Ixodes [54].

There are at risk approximately 500 million people in the case of Leishmaniasis, particularly Africa, Asia, and America. This microorganism begins its infectivity, by infecting macrophages. It makes an initiation of infection by entering a vacuole, and in part the result of the enzyme GP63, a "zinc-dependent metalloprotease", which occurs on the surface of Leishmania. The microorganism enters the macrophage, and "hijacks the host cell membrane fusion machinery. *Leishmania* "evades LC3-associate phagocytosis", which helps it to evade an increase in the antimicrobial properties of macrophages. Leishmania's ability to a cause disease is in part by GP63 and CPB proteases [55-57]. In the case of the tropical disease Chagas disease, approximately 8 - 10 million people are affected by this disease caused by *Trypanosoma cruzi*, including 300,000 people here in the United States. It is commonly found in Mexico, Central and South America. This microorganism is able to sustain its presence in infected cells, by the presence of a protein called parasite-derived neurotrophic factor (PDNF) on its surface, by promoting the survival of its cells. PDNF is important since it serves as a substrate, and prolongs activation for a key enzyme Akt kinase, an enzyme that is necessary for cell survival. Akt is an enzyme that "promotes nutrient uptake," and also inhibits cell death [58].

Mycobacterium tuberculosis the cause of tuberculosis, releases RNA causing a "chain reaction" within the macrophage, resulting in the release of interferon beta. Thus, helping in the survival of the microorganism, by a secretion system called SecA2, which mediates the release of RNA, by these organisms [59]. With the yeast *Candida* which can cause a chronic mucocutaneous candidiasis (CMS), or vaginal candidosis (thrush), it can be difficult to treat medically if there is a mutation, in either the genes Dectin-1, and or CARD9. Dectin-1 is important in the detection in the presence of fungi, and sends signals that help to set up a molecular initiation of the immune system. Research in this case is in an effort to help to have a better perspective how fungi, and the human immune system interact [60]. Viruses that

are also capable of hijacking the immune system. They are able to do this, because they can convert their single strand to double stranded RNA, by an ADAR1 protein (adenosine deaminases), so that the immune system is not activated. In this way some viruses are not seen by the immune system. Human cells do recognize ADAR1 protein, but have to make a choice between "detecting the virus or preventing autoimmune disease" [61].

There is continual documented scientific evidence that our microbiome play an important role even in the early child development, with dominate floral, of *Lactobacillus, Prevotella*, or *Sneathia*. After one year age of birth, the normal gut flora, will more represent adult flora from the phyla of *Bacteroides*, *Faecalibacterium, Clostridium*, and *Ruminococcus* [62]. The microbiome does not only affect immunity during early stages of life, but affects how the body responds to stress, bacterial pathogens, the immune system, cancer, genetics, as well as antibiotics. Microorganisms can influence the body by releasing chemical molecules like short-chain fatty acids (SCFAs), that provide anti-inflammatory activity, which can be important during cancer treatment [48]. Microorganisms may also modulate the immune system by their metabolites, such as acetate, butyrate, and propionate. Some *Clostridium, Eubacterium, Roseburia, Faecalibacterium* and *Coprococcus*, may be involved. The Short-chain fatty acids notably propionate and butyrate, contribute to the differentiation, the quantity of T reg cells, and thereby provide an anti-inflammatory contribution [48]. Acetate however can contribute to several types of cancers, glioblastoma, breast, ovarian, and lung cancers [48]. Butyrate producing species of *Clostridia,* can help to reduce graft-versus-host, during "allogenetic bone marrow transplantation". Butyrate also can stimulate the differentiation of CD4+ T cells into anti-inflammatory Tregs, related to the concentration present. Indoxyl 3-suflate produced by microorganisms using tryptophan, have "immune regulatory functions" [48,63]. These two metabolites butyrate and propionate seem to be significant in the mediation of immune interactions, and important in the expression of the genes, that "encode them" [63]. Thus, microorganisms can influence metabolites, in a fashion that can be conducive to immune health, or in terms of contributing to tumor growth [47,48].

Various intestinal microorganisms also produce various anti-inflammatory, and "pro-inflammatory cytokines, metabolites, in addition to antimicrobial substances, that also can either contribute, or detour cancer [47]. Microorganisms also have present on their surface antigens, peptides, and or lipids, that can be important in the contact with T-cell receptors. In this way, alter how therapeutic drugs are affective treatment during immunotherapy [47]. Some bacteria are believed to be important in "mediating" the response to cancer treatments, include the *Lactobacillus* spp. For example, *Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus GG*, and *Lactobacillus acidophilus*, seem to mediate anticancer affects, by activation of natural killer cells, and maturing dendritic cells [48]. The mixture of *L. rhamnosus GG*, *E. coli Nissle 1917*, and heat-inactivated VSL#3 called Prohep, can cause a shift in the gut flora, to *Prevotella* spp., *Oscillibacter* spp., and enriching for a selective increase in the presence of *Bacteroides fragilis, Alistipes shahii, Parabacteroides distasonis* and *A. muciniphila*. Thus, setting up conditions that favor the reduction of gut proinflammatory conditions, and differentiation of Treg cells, Tr-1 cells, and the reduction of "inflammatory metabolites as well [48]. Enterotoxigenic *B. fragilis* alone has been shown experimentally, to induce the presence of pro-inflammatory TH 17 cells, and in so doing promote tumor development in "tumor-prone mice" [48]. Regulatory proteins like SATAB1 can influence how these proteins can affect how T cells are able to function [22,48]. Faulty T cell receptors can also affect whether these cells over function or contribute to a "chronic proinflammatory state". Receptors on T- cells are not "static, "but have molecules on their surface, that are continually in motion [23,24,48]. Of course genetics play a key interaction whether with the microbiome, the various immune cells, and by various treatments of immunotherapy. *Burkholderia ambifaria* which produces lectins can target white blood cells, that display a ligand (B-cell antigen receptor) on their surface. The lectin BAmbl is able to bind to the B-cell antigen receptor on white blood cells [64].

Genetic factors such as HOTAIR are important as a "signaling molecule from DNA", and important for the initiation of an immune response [13]. Other measures of control of an immune response, involve the regulation of a number of genes by Hypermethylated in Cancer1 (HIC1), which also regulates T-reg's [14]. Genetic mutations in general, and or in receptors also can play a significant role, for example in how genes are encoded, which can lead to lower levels of enzymes, resulting in cells that may attack other cell types, and contribute to autoimmune disease. Engineered CAR-T cells have been successfully used to target a surface maker B7-H3 and "irradicate osteosarcoma

[36]. Cancer can also affects TADSs (topologically associating domains), which are important in the regulation of genes. Cancer can interfere with the TADs, and thus gene control. Mutations in the EZH2 gene can lead to the initiation of cancer, since some silent genes may be turned on, or normally functional genes, may be turned off, or nonfunctional [40,41,48]. Therefore, genetics, the microbiome, and the immune system must work in close association, and integrate there collaborative function, in order for an appropriate immune response, either to inflammation, infection, recovery, cancer and or autoimmune disease [48,63,65,66].

Conclusion

In summary, the occurrence of cancer, and related health issues and its progression, can therefore be related in relationship to changes in the microbiome, which can affect the immune response, genetics, mutations, reaction to antibiotic therapy, the presence of pathogens, and other issues, such issues as fasting, diet and stress, all of which can affect or influence the outcomes of immunotherapy, and the presence of cancer [48,65,66].

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