

Molecular Microbiology of Pathogenicity

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Abstract

This paper deals with the complex interaction of the various immune cells (dendritic cells, macrophages, and lymphatic cells), as it relates to the microbiome, its influences of the various organs, and the dysfunction of cellular components, such as mitochondria and golgo body, as they affect cancer treatments, the immune system, and autoimmune diseases.

Mitochondria disease has been linked to a number of diseases, due to mutations in the mitochondrial DNA, which are visual problems, heart disease, liver disease, gastrointestinal disorders, neurological problems, and others. These dysfunctions seem to be related to mitochondrial DNA mutations, and because of their importance in energy synthesis, they can affect many parts of the body. In regard to the microbiome, there seems to be a strong connection to the incidence of a number diseases, such as inflammatory bowel disease, diabetes, and as well as a number of autism disorders, which seem to be due to “abnormal gut microbial communities”. Although, there is evidence that probiotics can promote the growth of healthy intestinal bacteria, and those of the genus Bifidobacterial and Lactobacilli seem to be helpful, preventing disease causing bacteria, from sticking to intestinal walls. In a report by the Mayo Clinic, *Prevotella histocola* a gut Intestinal bacterium, may contribute to the prevention of multiple sclerosis, since it can drive a decrease of “pro-inflammatory cells”, while increasing fighting cells, such as, T-cells, dendritic cells, and certain macrophages.

In regard to cancer research, researchers know that a protein (Tudor-SN), which is abundant in cancer cells, and not healthy cells, can when removed, boost the presence of microRNA's, halt cell division, and thus slow cancer growth. Researchers also have discovered that by inhibiting miR25 and miR93 tumor cells, they were able to boost cGAS levels, which is important in bridging the gap between innate and adaptive immunity. A final note, because mitochondrial DNA is similar to bacterial DNA, the immune system can recognize the release of that microconidia DNA (mtDNA) as foreign, resulting in an immune attack. There is much evidence that many of the autoimmune diseases have been linked to dysfunctional mitochondrial DNA (for example Lupus), and it is the purpose of this paper to discuss many of these exciting aspects of molecular microbiology.

Keywords: *Molecular Microbiology; Pathogenicity; Immune Cells; Microbiome*

What is microbiology? Is it just the study of bacteria, fungi, and parasites, or what some people call bugs, or much more today. Microbiology has its origin in the late eighteen hundred, with the development of the microscopes, the use of antitoxins as vaccines, chemotherapy and immunology, during the era of its infancy [1]. With the development of newer and improved vaccines, the quality of life has much improved over the years. According Garcon., *et al.* [2], vaccines have been significantly helped in reducing neonatal birth defects, the iron lung (due to polio), many childhood diseases, as well as influenza [2].

In the textbook by Black, *et al.* [3], there are over 3.5 million children that die from infectious diseases, which can be prevented through immunization. Prior to the introduction of the pertussis vaccine, nearly 8,000 died from whooping cough. Vaccines in the past were of the whole cell type, composed of the whole microbial cell, including its vast array of antigenic determinants [2,4]. Today many of the vaccines are of the acellular type, only containing “purified proteins”, in order to establish immunity. Vaccine formulators believe using acellular vaccines can reduce the problems with whole cell vaccines, which can result in inflammatory reactions [4]. In the Great Flu Pandemic of 1918, it was estimated that 50 to 100 million deaths were responsible for the influenza virus. Today vaccines are not perfect, but even with current vaccines, there are expected deaths between 12,000 to 56,000 from influenza in the U.S. each year. This is because each year the virus can mutate, and current vaccines can be much less effective [5].

Microbiology encompasses many of the things we take for granted in our daily life. The very food we eat, the water we drink, as well as the supplements we take for nutrition or medication. All these things are subject to being microbiologically tested in various laboratories throughout the country. All of which must be tested in some manner, by a skilled microbiologist [7,8]. We go to the supermarket, and assume that everything is safe, but are we [8]? In 2012, compounding drugs due to poor sanitation techniques, lead to hundreds of people developed meningitis due to an infection from fungi [6].

Currently microbiologists today are working on a number of problems, whether it's the environment, the water we drink, the trash we accumulate, either at home or even in the oceans [9]. A microbiologist is trying to solve it. As scientists we are delving into the very essence of life, by probing even more into cells, by using presence of even more powerful microscopes. We are beginning to be able to see any of our cells in just vivid detail, such as the very cell receptors, as well as exosomes, which function in the communication between +cells, and even the illumination of brain tumors, by new fluorescent dyes [10,11,17,21,22].

Current Research

Today's research seems to relate to the delicate balance between the immune cells, their relationships, and how they relate to the body in fighting disease, cancer and autoimmune diseases. There seems to be a relationship between the various autoimmune diseases, in regard to the fitness of the mitochondria of the cell, where mitochondrial myopathy is typically due to a mutation in the mitochondria DNA, and can be associated with a number of clinical diseases, such as anemia, dementia, hypertension, lymphoma, seizures, and neuro-developmental disorders [12].

Current research seems to document that many of the autoimmune diseases have a detrimental effect on the mitochondria. There also seems to be a common association of the mitochondria with the autoimmune diseases. There is a connection between the immune system, and the mitochondria which can serve as a “signaling platform”, in response to various types of cellular damage, stress, and or types of infections [13,14].

In addition, there seems to be a relationship between mitochondrial activity with some cancers. Some cancers can greatly accelerate mitochondria functional levels. These particular functions can be due to the fusion of a pair of genes, and lead to a cascade of events, that can cause the mitochondria to go into overdrive. When gene fusion occurs, there is a wave of mitochondrial activity, due in part to a gene called FGFR3-TACC3. This gene in turn can activate a protein called PIN4, where it is taken up by peroxisomes, which release oxidants (PGC-1alpha), and regulates an increase in the activity of mitochondria and energy production [14]. Mitochondria also can sound the alarm that intruding DNA from bacteria and viruses, signaling that the cell needs to be on alert. A variety of white blood cells are able to react to small fragments of DNA, that are similar to microbial DNA (bacterial and viral). When white blood cells are confronted with an antigen, they release a web of Mitochondrial DNA (mtDNA), which alerts other surrounding white blood cells, to be really for an attack. This web of mitochondrial DNA causes other white blood cells to release interferon type 1. and can result in an unwanted inflammatory reaction [15].

The chemical alarm from cancers during immunotherapy is related to the release of mitochondria DNA, in which the chemical messenger lies in the molecule cGAS. cGAS plays significant role also, in serving as a “bridge” between innate, and adaptive immunity. Allowing the duality of the immune system, to step up to produce an anti-tumor response. Also, to note, elevated levels of interferon type 1 as a result of mtDNA, also occurs with many autoimmune diseases [17].

Immunological progress

Over the years immunology has become more and more specific in terms of the interactions between immune cells, with a better insight into the balance between immune cells, as it relates to the interaction between pathogens, microbiome, cancer and autoimmune cells. Today immunologists are able to target *cancer cells, and or program immune cells, to seek out and attack cancer cells anywhere in the body, and there also seems to be a commonality in some cancers in the relationship in the way they operate genetically [18,19]. Researchers are trying to gain a better control of immune cells, not only in a way to control them, but also regulate the immune system, in an effort to either slow down an immune response through regulatory T cells (suppress an immune response), or by unmasking the immune cancer control by allowing killer T cells to fight cancer. Cancer cells also produce an abundance of the protein Tudor-SN, which influences the cell cycle. It has been found by removing it from human cells, one can greatly increase the levels of many dozen microRNAs, and encourage genes that are involved in cell growth. Thus, blocking the protein Tudor-SN also found in human cells, increases the levels of microRNAs, and thus cells undergoes their phases of cell division more slowly. Offering a possible method for slowing the growth of cancer cells [24]. Other researchers also are attempting to prevent cancer from masking the immune system, by the use of “checkpoint inhibitors. Checkpoint inhibitors are pharmaceutical drugs They are frequently are composed of antibodies that prevent cancer, from dampening an immune response. A method which allows cancer cells hiding from the immune system [23-25,28,29].

The use of toxins has been used before by Conan in the 1800’s in order to fight cancer. Salmonella has been engineered for the “over-expression” of the production of flagellin B, in an effort to enhance an immune response. In this case it was found that macrophages could be switched from immunosuppression to induce an “inflammatory phenotype”. In essence, it was found through genetic experiments, the presence of the host protein called Toll-like receptor 4 is responsible for stimulating an innate immune response, and resulting in an anti-cancer activity. This immunity was the result of the flagellin enhanced Salmonella, just as William Colley had experimented in the 1891 [26].

Microbiome

It seems that genes not only affect the heredity of an organism, but also play an important role in shaping the gut microbiome during early development. In experimental mice, there a seemed to be a relationship between the presence of several genes, and the presence of Lactobacillales (probiotic strain). The level of this probiotic strain was found in experimental mice, to affect the microbial level of a special strain of Lactobacillales (probiotic strain), and a subsequent increase in the number of T-helper cells [31,34].

Every day it seems there’s always a mention either by email, or on the television, using the term microbiome. What is the microbiome? Is it the sum total of microorganisms found throughout the body, or just the intestinal gut microbes? Well, it seems its all of the above. It’s the 40 trillion microbial cells that make up the flora, that inhabit throughout our body. The human gut itself is made up a 1000 different species of bacteria alone. Baylor College of Medicine, has noted that the use of *Lactobacillus reuteri* in the presence of glycerol, has been noticed to reduce the risk of *Clostridium difficile* infections, by the production of reuterin [30,31]. Recent research on probiotics indicates its use may help to reduce inflammation, and suppress tumors associated in colon cancer. Other recent on inflammation has found that macrophages which are responsible for inflammation can be stimulated to produce itaconate. Itaconate is a biochemical that can put a halt “switching off” the proteins involved in the inflammation [33,35].

Today much of the research on the mechanisms of pathogenic microorganisms has centered around the interactions of the immune cells, as they relate to their interactions of the microbiome. This new knowledge has led to a better understanding of the basis of pathogenicity, probiotic microorganisms, and in their relationship in the monitoring, and hope for the prevention of autoimmune diseases. In some cases, it is believed changes in the microbiome can promote tissue repair and regeneration [46]. It has become very apparent that the physiological processes that occur within the body, can be modified either through genetics, the nutrition, and the bacteria that make up the various parts of the body. However, changes, that damage mitochondria, or resulting from faulty regulations of T cells, or macrophages can be the result of immunological changes, or affect other immunological processes [30,32-35,44].

Immunological changes

These immunological changes in the function of the immune system, can lead to diseases such as pancreatic cancer, and are reflected in the rapid increase in a bacterial level (1,000 fold), with various genera (proteobacteria, actinobacteria, and fusobacteria), that can reduce the immune system from being able to attack the tumors [36]. Although in other instances, the gut bacteria have been reported to be beneficial and protect. They have been reported to the help to prevent against sepsis, by increasing the levels of IgA and IgG, which can be protective against sepsis [30,36-38]. There is also some evidence that certain bacteria (*Prevotella histicola*) can provide protection of the myelin sheath (membrane protects brain and spinal cord), by reducing the presence of “two types of pro-inflammatory cells” by increasing the cells the level of T-cells, dendritic cells and certain macrophages, that can fight against the autoimmune disease multiple sclerosis [38,39].

However, there are benefits in many cases to the normal gut flora, however there are also times in which the immune can be coerced by pathogens, to attack various tissues. For example, in the case of Legionellosis the pathogen can affect host metabolism, in such way in order to facilitate its own replication, by influencing the “mitochondrial respiration” [40]. The pathogen Chlamydia (*C. trachomatis*) is able to “manipulate” the mitochondria and prevent cell death. The organism also is able to prevent the activity of a tumor suppressor protein p53 in infected cells. P53 protein is involved in DNA repair, and therefore maintaining the activity of P53 is believed to allow for the capability of the cell, to destroy the infecting microorganism [41]. In the case of leprosy there is damage to the myelin sheath, as a result of the macrophages which no longer are able repair the myelin sheath. Macrophages can be “reprogrammed” (by PGL1 a surface protein) of “*Mycobacterium leprae*” that is responsible for the production of nitric oxide, where its production can damage mitochondria [42]. With the Superbug gonorrhoea, it forms membrane vesicles that can attack immune cells such the macrophages, which are commonly involved in killing bacteria and viruses [43].

Biofilms

Various microorganisms have over time developed mechanisms in order to penetrate host defenses. Many bacteria are capable of surviving by the formation of biofilms. Biofilms allow some microorganisms the means to developing layers and layers of microorganisms, in a manner that provides protection, nutrition, and the ability to resist antibiotic treatment [47,48]. Such microorganisms as coagulase negative *Staphylococci*, *Pseudomonas aeruginosa*, *Enterococci*, *Staphylococcus aureus*, *Burkholderia cepacia*, *Aspergillus fumigatus*, and *Candida albicans* are known to form biofilms, that adhere to medical devices. Other microorganisms that are pathogenic would include again *Staphylococci*, Group A *Streptococci*, Gram positive cocci, and gram-negative bacilli [47,48]. Some microorganisms also utilize unique methods for forming biofilms with the help of enzymes that help them glue together, and for the “bioform matrix, whereas some use of so called quorum sensing [47-50]. However an enzyme of *Mycobacterium fortuitum*, called pyocyanin demethylase (PodA) could be added to growing cultures of *Pseudomonas aeruginosa*, and this could prevent the formation of biofilms by this particular microorganism. The significance is that in hard to treat patients (with chronic infections) with associated microorganisms, could be a significant way to prevent biofilm formations, in these particular types of patients [51].

Microorganisms have over the years evolved in their ability to overcome the immune system. Along with creating biofilms, *Haemophilus influenzae* (nontypeable) for example, has the ability to create not only a biofilm, but also can “shuttle DNA through what is called a “inner membrane complex,” thus providing a source of DNA, for the biofilm itself [52]. The superbug gonorrhoea is able to react with macrophages, by forming “bacterial membrane blebs”, that initiates a process that results in the death, of these important immune cells. Thus giving the microbial organism a better footing, for greater growth, and multiplication [43-53]. In the case of *Legionella pneumophila*, this pathogen has the ability to produce a protein called DNM1L, which can cause “fragmentation of the mitochondria”. It causes changes in the morphology of the mitochondria, which disrupts respiration, but facilitates glycolysis. This mechanism of the organism insures the replication of the organism, by controlling the activity of mitochondria [40-54]. *Clostridium difficile* which can be a very important cause of recurrent infections (mrCD) World Wide, has the ability to multiply rapidly during antibiotic treatments, and produce toxins. Research has demonstrated even by impacting the S-layer of the cell, does not prevent the organism from multiplying, but could reduce the large amount of toxins produced by the microorganism, as a result of antibiotic (Avidocin-CD killing) treatment [55,56,57]. Other research on “C. difficile” has found that calcium, and the bile salt taurocholate are essential for the germination of this endospore. This could allow for better antibiotic treatment, since all spores would germinate at the same time, and be “vulnerable” and more treatable [56,57].

Pathogenic Mechanisms

Listeria monocytogenes which is an intracellular parasite, induces its own phagocytosis into macrophages, based on the internalin operon, which produces both internalin A and InlB. Both of which may bind to receptors found on the cell wall of a target cell. Both internalin A and B are capable of inducing phagocytosis. Internalin is a surface protein which interacts with a cell adhesion receptor, called E-cadherin on epithelial cells, resulting in the induction of phagocytosis. Cadherins are transmembrane glycoproteins, that promote binding of *L. monocytogenes* to epithelial cells. Another toxin called Listeriolysin O (LLO) is able to act by binding to membrane cholesterol, and inserting itself into the target membrane, and resulting in transmembrane pores. In a way, this allows for repairs of the host cell membrane [58]. Listeriolysin O thus is able to overcome any membrane obstacles, and may be taken up by a cellular vacuole, without the fusion of the lysosome. LLO is able to exit the vacuole by the formation of pores for its escape. LLO also is involved in calcium channeling, causing an increase in the calcium levels, and also reduces the proliferation of CD4T cells, which are responsible for T cell activation. Internalin also creates pores which can allow for the rapid movement of ions and macromolecules into the cell [58-60].

Brucella are very unique that they are able to grow as intracellular parasites, particularly of the reticuloendothelial system, and within phagocytic cells (macrophages and dendritic cells) of the immune system, and other nonphagocytic cells as well. They also are able to invade vacuoles of lysosomes, and the endoplasmic reticulum of macrophages, where “intracellular replication can take place. Brucella cells also have a preference, for their multiplication in dendritic cells, as compared to macrophage multiplication. They are able to attach to macrophages due to cell membrane receptors on the surface. The organism can produce “molecules” that can be important in its cell adhesion, use of actin filaments, and as well as cause reshaping of cell membrane [61].

In terms of the ability of Brucella to “establish” an intestinal infection, it seems that both lipopolysaccharide endotoxin (LPS), and type IV secretion system (T4SS) both are important. T4SS helps to limit an inflammatory response, which allows the microorganism to invade, to be established, and be able to grow throughout the host. LPS itself also allows the organism to be unseen by Toll-like receptors (TLR) of the innate immune system [61]. Therefore, Brucella are able to be “endocytosed” both by mucosal macrophages and Dendritic cells (DC) and are able to circumvent the both innate and adaptive immunity. They evade intracellular elimination (transient lysosome fusion) by redirecting type IV secretion system-dependent Brucella-containing vacuole (BCV) to endoplasmic reticulum where the organism is capable of reproducing [61,62].

Pathogenic microorganisms can vary in their host specificity, and this can be seen at the molecular level, for example *Neisseria meningitidis*, and *N. gonorrhoeae* both have an affinity for the human host. This affinity and or specificity can be seen in the fact that they display many surface proteins, which include immunoglobulin A1 (IgA1) protease, type IV pili, complement factor H binding proteins, gonococcal porin, transferrin-binding proteins (FHBP), gonococcal porin, transferrin-binding proteins, and lactoferrin-binding proteins. Whereas “host specificity determinates”, would include IgA1, cell surface complement regulator CD46, complement regulator factor H (FH), complement regulator C4b-binding protein (C4BP), transferrin, and lactoferrin. In the case of *N. gonorrhoeae* and *N. meningitidis* both release a “extracellular serine-type protease, which allows to be able to cleave IgA at the hinge region of IgA1. Both “*Streptococcus pneumoniae*” and “*H. influenzae*” are also able to cleave the IgA at the hinge. It is interesting to note that other nonhuman species are unable to cleave IgA1, since they produce only IgA2. *Neisseria* are also able to adhere to the cell membrane proteins of cell membranes of human membrane cofactor protein (MCP or CD46), and disrupting an alternate complement pathway, which protects the cell from inadvertent cell damage. CD46 in itself, allows for the attachment, and subsequent entrance into cell cultures. In other studies, CD46, can serve as a receptor, for a number of bacterial and viral microorganisms. For example, measles virus, herpes virus 6, adenovirus and *S. pyogenes* [63]. FH which is in great quantities in the blood, can be also on the cell surface where it can be used by an invading microorganism, for interfering also with complement by preventing the binding of factor B to C3b. Various microorganisms such as, *Neisseria*, *Candida albicans*, *Borrelia burgdorferi*, *H. influenzae*, *S. pneumoniae*, all of which can reside in the upper respiratory tract [63].

Streptococcus pneumoniae produces a protease that is also capable of cleaving the hinge are of IgA called “methallo-type IgA protease”, of which enhances the bacterial adherence to epithelial cells. M protein and CD46, both specifically bind to keratinocytes (keratin producing epithelial cell), as well as, invasion of epithelial cells. In mice models, there is been shown increasing levels of bacteremia, arthritis and mortality [63]. Pili of *Neisseria* and *Escherichia coli* display colonization and bacterial adherence to mucosal epithelia, whereas the surface proteins of *S. pneumoniae* (ChpA) and *S. pyogenes* (M protein), bind to human receptors on mucosal cells. This promotes the widespread “dissemination” of the invading bacterial cells [63]. In many cases of immunological interactions, disruption of the complement, and IgA1 immunity seems to be a common mechanism in which pathogens are able colonize human cells, as well as interfering with C4BP, which is an alternate complement pathway CD46. Pathogenic microorganisms by overcoming IgA1 mediated immunity and complement, are able to overcome an important immune mechanism, and specifically establish themselves by colonizing mucosal surfaces [63].

Inflammation

Inflammation can be a contribute significantly to many diseases for example in the case of Infectious Arthritis (bacterial or viral involvement), Bacterial pneumonia, Lyme Disease, various bacteria such as, *Staphylococcus aureus* (Staphylococcal infections), *Streptococcus* (strept throat), *Neisseria gonorrhoeae* (gonorrhea), *Mycobacterium tuberculosis* (cause of tuberculosis), and *Borrelia burgdorferi* (cause of Lyme Disease), all of which involve bacterial inflammation [64]. In the case of rheumatoid arthritis, in which inflammation is a major contributor, it has been found that “synovial CD4+ T cells that produce IL-21 activate synovial fibroblasts that lead to joint inflammation [65]. Inflammatory bowel disease as well as Hirschsprung-associated enterocolitis, also appear to be caused by the overgrowth of certain “inflammatory groups of bacteria, or as well as the loss of certain bacterial capable of producing anti-inflammatory factors [66]. Other research on skeletal muscle fibers, also support the idea that muscle mitochondria protein can also trigger an inflammatory response as well [67].

Summary

Microorganisms whether bacterial (toxin-antitoxin system of *Escherichia coli*), viral, fungal, and or cancer do impact the immune system either through their toxin products, manipulating either indirectly, directly or by cellular mutations, or affecting genetic mechanisms of the host cell [12,13,88]. Mutations can also occur due to disordered proteins (IDPS), which may unfold improperly, resulting in

proteins with faulty interactions of itself, or with other proteins may occur [71]. Changes in the mitochondrial organelle through mutations can lead to autoimmune diseases [68,69]. In the case of proteins, A Dr. Utpal P., *et al.* the University of Maryland has discovered a protein formed by *Borrelia burgdorferi* (Lyme Disease agent), that can combat the immune system (innate immunity), (“first wave of immune defense), and by reducing inflammation early on, can reduce the instance of inflammation and the chronic nature of the disease [70,71]. Some protozoan’s such as *Naegleria gruberi* are able to affect the function (“malfunction”) of the Golgi body, which can lead to such autoimmune diseases such as Alzheimer’s, and Parkinson’s disease [72]. It also appears that DNA mutations can also lead to human cancer, when comparing the mutation rates of *C. elegans* to human genetic patterns [73]. With the fungus *Candida albicans*, in its method of pathogenicity, competes with macrophages by consuming increasing amounts of glucose, ultimately causing the death of this immune cell, the macrophage, due to the lack of the essential metabolite glucose [74]. In the case of Cancer, viruses may gain access to promoter regions of the DNA, by “modulation of DNA methyltransferases”, (adding methyl groups), in this way are able to turn on, or off the transcription of genes, that are not normally transcribed [75]. Other viruses (influenza, Dengue fever and AIDS), naturally mutate enabling them to be able to evade the immune system [76]. In the case of tumor growth even microRNAs which are “small, noncoding RNA molecules, and regulate genes by silencing RNA”, and modulating the growth of tumors. It is possible therefore to slow the tumor by the inhibition of both microRNAs of micro RNAs miR25 and miR93.

In essence, microorganisms can manipulate the immune system either by controlling effector cells, such dendritic cells, T-cells, and or macrophages, which may drive the immune system into inflammation, or cellular repair [13,17,19,26]. This is possible because recent research has shown, that there are a “pair of receptors” one of which functions for inflammation, while another in cell repair. The release of mitochondria DNA serves functioningly as an alarm system, for the presence of foreign antigens, and is modulated by the DNA sensor of cGAS, which serves in that capacity [17]. DNA Mutations do occur either at the genetic level, or at the level of the organelle level, and with mutations of mitochondrial DNA. The release of mitochondrial DNA during stressful conditions, may indicate many other clinical conditions, resulting in pathological conditions needing treatment. In some mouse models, the cGAS is important in the treatment of cancer, since it can provide a bridge between dendritic cells, and killer T-cells, that can attack tumor cells [17]. Cancer cells also release mitochondria DNA, and can grow undetected by controlling regulatory T cells, in order to inhibit the immune system [17,19]. However, with cancer therapies involving autoimmune diseases, where effector cells are over reactive, the use of regulatory T cells could be a possible therapeutic option [19,23].

Advances in microscopy, as well as, new techniques in fluorescent microscopy, have made possible the ability to see 3-D images, and the ability to pinpoint the origin of T-cell receptors on immune cells [11,16,17,21,22,78,89]. In the case of pathogenic parasites, Trypanosomiasis, *Trypanosoma brucei*, are able to degrade messenger RNA, through the enzyme TbALPH1, whereas *Toxoplasma gondii* secretes proteins as “expressed human microRNAs”, which are similar to those found in neurodegenerative diseases such as, Alzheimer’s and Parkinson’s disease [79,80]. With the tropical disease Leishmaniasis, CD8 T cells along with Interleucin-1 contribute considerably into the inflammation of this parasitic disease [81]. Other diseases that are neurological in nature and in general, such as Parkinson’s disease, and Huntington’s disease, present a similar pathology, with either dysfunctional mitochondria, and lysosomes. In the case of Huntington’s there is an accumulation of mitochondrial iron [82,83]. However, there is greater hope on the arisen with stem cell research, with the greater understanding in the intricate interaction of the various immune cells, as they relate to the microbiome, probiotics, molecular mechanisms of pathogenicity, mitochondrial disfunctions, autoimmune disease, as it relates and affects neurological diseases, and the gamut of various microbiological diseases [13,30,84-87].

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