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Cancer a Multi-Mutation Disease

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Abstract

Cancer is a mutational disease, involving the control of DNA, transcription, translation, Mitochondrial DNA and genes, that may be involved in immunity, cancer proteins, and cell division.

Keywords: *Cancer; Multi-Mutation Disease*

Cancer's simple definition

What is cancer? Is it just a cell gone wrong? W.C. Shiel explains that cancer is an "abnormal growth of cells," in which growth occurs, in ways that are out of control of normal replication [1]. According to Research at Cornell University, cells become cancerous, when they express two or more mutations, in their genes [2]. However diseases often arise due to multiple genetic changes, in order for a cell to become cancerous [2]. How do these mutations occur? These changes can occur during DNA replication, during protein synthesis, the presence of oxygen radicals, and or exposure to ionizing radiation [3].

How cells protect their DNA

Current research has shed light on how the cells protect their DNA, as well as aging, and neurological disease. It is by a membrane-less organelle known as a "biological condensate," and is important in DNA repair. This organelle has only recently been discovered, and it appears that their dysfunction, may be related to neurological diseases, such as Amyotrophic lateral sclerosis, or ALA [4]. However, cells do protect themselves from damaged DNA. They do this, by what are called nucleosomes, which block the cyclic protein GMP-AMP synthase (cGAS). cGAS functions for the detection of damaged DNA. cGas synthesis is a "second messenger," that activates the cGAS-STING signaling pathway. This pathway operates in "fighting infections, inflammatory disease, and cancer". cGas therefore is important, in the recognition of healthy cell DNA, from "pathogenic DNA". However, it is unknown how it is able to differentiate from our "healthy DNA" [5]. In the case of viral infections, due to Covid-19, blood clotting and coagulation, may in part be linked to mutations of the complement system, resulting in severe infections [6].

Along with changes in the DNA, cells also experience cytoplasmic changes that occur in the movement of metabolites in, and out of the cell. These changes are linked to a cancer-linked version of the protein mitoNEET, and voltage-dependent anion channels (VDACs). The VDACs are responsible for regulating the movement of metabolites and molecules, between mitochondria, and the rest of the cell [7]. Exosomes which are "extremely small vesicles can play a part in genetic changes, by releasing microRNAs (miRNA), which can bind

to messenger RNA, and rendering it inactive. Macrophage secreted miRNA can also inhibit the production of a protein, when it binds to messenger RNA in tissues [8]. Therefore, exosomes are important in the intercellular communication, and the release of microRNAs, and their various metabolites, depending on the cell environment, in which they are, released [9].

Microbiome Influence on cancer and Immune system

What about the influence the microbiome has on the immune system, and cancer. There are approximately 38 trillion microbes, that make up our gut microbiome. Microbes not only do they influence our physiology, metabolism, but also how affective our immune system functions. They do this by either reacting with our immune cells, or by releasing metabolites, such as short-chain fatty acids (SCFAS), polyamines, and secretions, which may help maintain a balance of the intestinal tract. Microbes can do this by releasing a large variety of metabolites, and products (acetate, butyrate and SCRAS), which directly interact with metabolic pathways, and molecular signals, that can promote the release of anti-tumor immunity [10,11]. Certain microbes such as, *Bifidobacteria*, *Akkermansia muciniphila* and *Bacteroides* species, have been shown, to improve anti-tumor immunity [11]. Scientists also believe that microbes may also shape our mental state. Research conducted at the University College Cork, John Cryan discovered that rats, with irritable bowed syndrome (IBS), displayed both irritable bowel syndrome, and mood disorder. He also noticed from patients displaying "digestive symptoms, also displayed problems with their mental health. He in addition, recognized that stressed patients, also exhibited a loss of a more "diverse gut flora. Indicating the type, and diversity of flora can affect ones mood, the generation of metabolites like butyrate, which can improve the release of mood-boosting dopamine, and serotonin. Thus, it appears in test mice, changing the intestinal flora, can act to reduce stress, and improve behavior. In a small study with human trials in 2017, by a Belgium team, at the Belgium VIB-KU Leuven Center for microbiology, researchers found that individuals with the genera of *Faecalibacterium* and *Coprococcus*, tend to have a better "life quality". Whereas, those individuals having lesser gut levels of the genus *Coprococcus*, are more likely to be depressed [11]. Thus, implying that beneficial bacteria, can improve mental health, for some common "mental health disorders". Certain Gut microbes, thus produce serotonin in the intestinal tract, and in so doing, influence the enterochromatin cells, certain immune cells, and neurons in the intestinal tract. In the intestinal tract, they produce up to 90% of the peripheral serotonin, where the level of serotonin has been linked to such diseases as "irritable bowel syndrome, cardiovascular disease, and osteoporosis [10-13].

Microbiome metabolite versus pathogens

It is significant that our intestinal floral not only generates important metabolites like butyrate, short chain fatty acids, and may also release indole, as well. Indole formation is also important, since it can influence the presence of pathogens, either in a positive or negative fashion [14]. Intestinal microbes can in addition, increase the multitude of receptors, found on B cells, as well as, increase the diversity of antigens, that can be recognized, an increased number of antibodies as well. Microbes can also be directly involved in the development of antibodies, prior to the incidence of a serious infection. Recent evidence has shown that in the gut wall, some B cells do not need to be primed by T-cells. These B cells are able to be activated without the help of T-cells [14-16].

Microbiome, its role and cancer influence

Certain gut bacteria according to experts produce the molecule called inosine. This molecule is important, since has the ability to "interact directly with T-cells," and can help to improve immune therapy, and in the treatment of colorectal cancer [17]. Other bacteria such as *Faecalibacterium prausnitzii*, are able to affect metabolic pathways, such as the NF kappa B. The molecule inosine can have a calming effect, on inflammation. Thus this recent research information, could be a significant mechanism for cases, involving Crohn's disease. This could occur particularly, where patients are experiencing overactive inflammation, due to Crohn's disease [18]. Other research by MIT technology, has shown that the production of butyrate by these bacteria, can influence the level of inflammation, by a reduction in the activity of the pathway called NF kappa B [18].

Immunotherapy and cancer

One of the problems with the effectiveness of immunotherapy, where "traditional therapy" has failed, is in part due to the immune systems, inability to recognize a specific antigen. This can occur because of a poor immune response, as a result of the presence of tolerant t-cells [19]. Another concern, occurs with the recognition of "regulatory t-lymphocytes (Tregs), which can suppress the immune response to cancer. Sophie Lucas (University of Louvain de Duve) has discovered the presence a molecule called GARP, which is found on the surface of Tregs. Her research has shown that tolerance by Tregs, can be overcome by the neutralizing affects that of GARP antibodies, when combined with the anti-PD1 antibodies, can improve the effectiveness of the immune response, and subsequent "effectiveness of cancer treatment" [19,20].

Cancers strategies

One of cancers strategies in a way is to avoid detection, from the immune system, by encircling themselves by a cellular member, inside the nucleus. This helps to make cancer appear invisible to the immune system [21]. Cancer also has the ability to "attract nearby blood vessels," to gain access to available nutrients, and oxygen supply. This appears to signal the tumor to begin to migrate, and metastasize [22]. In addition, by "coaxing" a signaling protein called Slit2, cancer can stimulate signaling protein just enough, to help cancer cells to migrate. Cells usually with "silenced DNA," are now activated to produce double-stranded RNA, signaling a "trigger for the movement of the tumor, from the primary site to enter the blood stream, and the spread to other organs [22].

Exosomes their influence on cancer growth

"Exosomes which are important in the recovery of reusable cell materials, can also be involved in the ability of cancer cells, to adapt to changing needs of nutrients for growth. Exosomes can improve cancers adaptability, by providing a mixture of proteins, RNAs and other molecules, which can reprogram surrounding cells. Therefore, exosomes are thought to be important in the several processes such as immunity, and reproduction. However, exosomes may also drive "pathological changes" such as tumor growth, and metastasis. It is important to note, that as inner tumor cells continue to grow within infected cells, they can become starved, for key nutrients, such as amino acids. Exosomes can allow cancer cells to be more adaptive, by giving other cells around them, a "growth-promoting boost, which can select for more aggressive cell types, and worsen the presence of cancer. If there is the presence of certain Rab 11a exosome types, which can carry a variety of molecules, these exosomes can help cancer to adapt, and grow even in the influence of "current treatments" [23].

What is the proteosome and its function in the cell

The proteasome is a "multi-enzyme complex," that is important in the breakdown of target proteins, for destruction. The Proteasome along with its importance in the destruction of unwanted proteins, is in addition important in the process of cell apoptosis [24]. Current research by Scripps Research Institute, indicates that information on proteasomes, could help to understand how an antifungal agent can be used for the treatment of cancer. The agent cepafungin l which is approved by the FDA for against fungi, also has been found to also act as a "anti-cancer agent. It functions by acting, or blocking the function of the proteasome, and so doing, can result in the death of infected cells, due to the accumulation of waste [25]. It works in a similar fashion as the FDA-approved chemotherapy drug bortezomib, but should have fewer "unwanted side effects for patients" [25].

How do lysosomes act as the driving force, that allow the endoplasmic reticulum to travel where ever is needed in the cell

How does endoplasmic reticulum perform its function, for taking care of the building blocks, repair and construction of new and old cellular proteins. The ER does this by "constantly changing its shape," and extending to where ever it is needed in the cell. How is it

possible for it to travel where at an instant, its needed to go? Well, according to researchers from Cambridge's Department of Chemical Engineering and Biotechnology (CEB), the "driving force" resides within the lysosome, for ER to be able to move throughout the cell. The lysosome makes it possible the ER to travel to distant parts of the cell, by the lysosome's ability, to pull the ER, like a number of box cars of trains. Even though the lysosome is much smaller than the endoplasmic reticulum, it still can carry the load. What relationship does this uncanny ability tells us, according to researchers at the University of Cambridge, these driving forces by lysosomes, have an even more importance. This ability of the lysosome to cause the ER to change shape, also has an even more importance, for nerve transmission in the brain. If for some reason the ER is unable to change shape, this could impede nerve transmission in the brain, and subsequently lead to neurodegenerative diseases, if this situation continues [27].

How cancer regulates growth and cell division

The KRAS-gene regulates growth and cell division, by producing a K-Ras protein. This protein provides instructions for cells to divide. In addition, it also plays a significant role in an immune response, via the NLRP3 protein complex (NLRP3 inflammasome). This can lead to the release of two "inflammatory promoting messenger substances," like interleukin-1?, and interleukin-18. It would appear that cancer causing mutations can influence the production of messenger substances, such as "interleukin-1?, and interleukin-18, and may lead to the presence of cancer [26].

According to the research by University of Freiburg (Dr. Zeisr, and colleagues), the presence of the KRAS gene, regulates the release of the K-ras protein, and when this protein is "excessively active," cells can divide unchecked and result in cancer. It therefore it seems logical, that if one can block the KRAS-gene, it should be possible to disrupt cancer substances, since the KRAS-gene is also responsible for regulating growth, and cell division [26].

The study shows that cancer causing mutations of the KRAS-gene, influence the production of interleukin messengers, as the Zeiser study shows. This disruption of the signaling pathways may lead to the development of cancer, and is related "directly related" to the signaling processes of the immune response" [26].

How and why do cancers become aggressive?

One way cancer cells or tumors are able to become more aggressive, is by solving the problem of overcrowding, from other cells. They do this by changing their shape. Changing their shape to a more roundness, allows them to better adapt to their cell environment [27]. This ability to change shape, allows cancer to better compete with other tumor cells, or unaffected cells, as well. This ability to overcome over crowdedness, is the "hallmark of cancer progression and metastasis, as described according to Technishche Universitat Dresden, a "epithelial-mesenchymal transition" (EMT) [28,29].

Tumor cells can be more aggressive by their influence of the "dangerous protein" called SNA2. The protein SNA2 helps protect cancer from both the immune system, as well as chemotherapy. It does this, by preventing the molecule ubiquitin from reaching high enough levels, that cancer proteins are not tagged for destruction. Some cancer cells are thus, able to continue to grow, since the SNA2 proteins, make cancer cells invisible to the immune system, and resistant to chemotherapy [30].

Other ways cancers progress

An example, of reoccurring cancer, is in the case of metastatic breast cancer. This form of cancer may lead to cancer of the brain. This can be shown to occur, when the amino acid glutamate is released from "pre-synaptic neurons". A possible explanation is that breast cancer cells have a tendency to seek out, in order to spread cancer to the brain. The answer lies in the fact that when sufficient amounts

of glutamate are produced by tumor cells, this activates the "N-methyl-D-aspartate receptor (NMDAR), and allows for metastasis to occur in the brain. Cancer therefore is able to occur in the brain, when a threshold amount of glutamate, reaches the amount needed to "auto-activate the N-methyl-D-aspartate receptor (NMDAR) [31].

How do immune cells models combat cancer particular in the brain

In the case of glioblastoma (GBM), radiation can result in cancer, becoming more resistant to chemotherapy. This can occur following irradiation. If after radiation, a daily dose of the inhibitor of colony stimulating factor-1 receptor (csf-1r) is used. This can lead to the survival of the both types of tumor associated macrophages, namely the brains microglia (resident macrophages MD), and monocyte-derived macrophages (MDM). The inhibition of the colony stimulating factor-1 receptor, thus promotes and suppresses the tumor resistance, and growth of the glioblastoma cells. Irradiation alters the behavior of immune cells known as macrophages, occurring in glioblastoma tumors. This may show researchers, how these cells might be reprogramed, by blocking tumor-associated macrophages, which can improve survival, with CSF-1R inhibitor treatment, after radiotherapy [32,33].

Improving a healthy immune system

One of the common problems that affects our health, is the degree at which are immune system is overtaxed. The chronic over activity of our immune system, results in the chronic release of inflammatory substances. This constant release of inflammatory substances can lead to a number of "associated diseases," such arthritis and Alzheimer's disease. Scientists have by studying the roundworm Caenorhabditis elegans, begun to have a better understanding, on longevity by their research on this organism. They found that this organism can be more easily infected by certain bacteria, and that these infections can over time, tend to shorten this organisms life span. According to the research by Max-lanck-Gesellschaft, they concluded, that a certain gene called PUF60, which is a conservative gene, could shed lite on longevity. This gene, seems to help to strike a balance, on maintaining the immune system, and longevity". It seems at least in this organism, that the importance of this gene, is that it plays an important role, in allowing for a more flexible operation of the immune system, by "splicing out segments of RNA, in order to "generate more functional proteins" [34].

Vitamins play a prominent role in its importance in regards, to the idea of long life, and better health. Vitamin D plays hand in hand with the immune system. Vitamin D according to research by the University of Eastern Finland, has its part in creating better health, by "regulating the immune system". Vitamin D provides its influence, by exerting its influence thru the vitamin D receptor (VDR). It seems relevant the greater functioning of the VDR receptor, can improve the operation of the immune system, and provide a means for good health. Vitamin D therefore, provides better health, by its influence on the rapid regeneration of tissue, and the differentiation of blood cells during hematopoiesis. Vitamin D therefore provides a platform for better health by improving the functioning of the immune system, and by its positive influence on the prevention of cancer [35].

Vitamin C's function for better health

Vitamin C has been used in the past. It has been used in the past, in order to tackle many viral diseases, such as treating polio, diphtheria, herpes zoster (shingles), herpes simplex, chickenpox, influenza, measles, mumps, and viral pneumonia. Current research has shown that vitamin c works by acting on both double, and single stranded RNA viruses, during replication, and transcription of viruses. It is also works, by improving innate and adaptive immunity. In the case of the influenza A virus, recent studies indicate that vitamin c can serve as an antiviral agent. It also seems likely that when vitamin c reaches sufficient levels, it prevents viruses from entering the cell, by increasing the level of alpha and beta interferon [36]. It would also seem relevant that vitamin c prevents virus from entering the cell, when levels of the vitamin c are sufficient, to prevent the virus from entering the cell [36-39].

Research developments

Some recent research has centered on efforts to "target" mitochondria found in cancer cells. The interest is in using "mitophagy-inducing compounds, in an effort to treat for example, acute myeloid leukemia (AML) cells, and chronic myelogenous leukemia (CML) cells. In mouse models, one compound called PS127E, showed effectiveness for killing AML cells, in mice [40]. Other focus has been to measure the activity of living cells. This can be done by measuring light intensity produced by a rodents mitochondria, during exposure to luciferin. Thus, this new tool provides a new method for monitoring mitochondrial activity, of other aspects in regards to cancer and mitochondria, include cancers ability to increase the levels of mitochondrial protein synthesis (by mitochondrial RNA modifications), and therefore increasing the likely "invasive" spread of cancer [42]. Cancer also affects mitochondria by causing mutations of the mitochondrial DNA, which can lead to diseases, and or disorders causing energy disruption [43]. Detection methods such as genome sequencing, can improve the chance of identifying cancer cells, particularly those patients with Barrett's esophagus [44,45].

With certain diseases, inflammation can have a greater impact, for example in the case of diseases such as "asthma, allergies, chronic fibrosis, and chronic obstructive pulmonary disease COPD. The impact can be significant. Recent investigation has found that a protein called neuromedin B, can stop inflammation to occur, in diseases such as asthma, allergies, chronic fibrosis and COPD [46]. According to the University of Pennsylvania School of Medicine, the protein called histone deacetylase 3 (HDAC3) has a dual function to either "trigger or reduce inflammation. The protein serves as an enzyme, and functions to either "activate or depress inflammation" [47].

Various cancer strategies

With aggressive" forms of cancer like glioblastoma, research from Wellcome Trust Sanger Institute, have discovered that more than 200 genes are involved. They also found that the cancer gene EGFR (epidermal growth factor receptor) itself, is responsible for initiating glioblastoma, by working with mutations of tumor suppressor genes [48]. Newer methods and knowledge may help to turn the tide, in the battle against cancer. A recent experiment by investigators have found in certain types of leukemia, immunity may be improved, by "shutting the EBAG gene. This gene and its protein can "inhibit" the release of cytotoxic enzymes, and in affect retard an immune response [49]. Other researchers have discovered that immune cells are not responsible for the release of cytokines within the intestinal tract, which has been held to be the case. However, in the intestinal tract, nerve cells therein are actually responsible for the release of interleukin 18, in the intestinal tract. Interleukin 18 plays an important role in the "defense" of pathogenic microorganisms, and fighting cancer [50,51].

Various cancer types and experimental research

New cancer detecting methods based on "laser-based diamond sensing, should in the future, offer a new and more accurate portable device. This new device can offer better detection of concussion, epilepsy, dementia, techniques for brain mapping, as well as monitoring Alzheimer's, and its progress [52]. With breast cancer, a gene has been identified that allows breast cancer cells, to remain dormant. The protein kinase MSK1, also has been found to help ER +breast cancer tumors, to remain in a dormant state [53].

According to Garvan Institute of Medical Research, there are over 100 different autoimmune diseases, which attack host tissues. In new and exciting research has shown, that individual cells that attack normal tissues, may be "pinpointed" by analyzing a patient's blood, and particularly those patients suffering from cryoglobulinemic vasculitis. According to the author (Institute for Research in Biomedicine), rogue cells are the root of autoimmune disease" [54].

Neurological diseases

Aberrant changes in function of brain astrocytes, can result in the increased production levels of α-synuclein, which is considered responsible for the loss of dopaminergic neurons, a decreased level of dopamine, of which are characteristic symptoms of Parkinson disease

[55]. In the future new research may make it possible to track alpha-synuclein, by molecules, which are able to tightly bind on binding sites on alpha-synuclein. Thus, offering a screening method, as well as a means of determine the progression of Parkinson disease, may be possible by the alpha-synuclein PET tracer [56]. New key compounds such as phenylbutyric acid, and RECTAS (RECTifier of Aberrant Splicing), seem to provide treatment for Parkinson disease, by restoring the production of the DJ-1 protein, which is essential for nerve cell function [57].

The GREM-1 protein in relationship to pancreatic cancer, is responsible for regulating the incidence, and emergence of more dangerous cell types. Thus, research seems to indicate "boosting GREM1 levels, could help for dangerous cells to convert to a less hazardous form [58].

According to Scripps Research Institute during protein synthesis, sometimes protein fragments arise which are toxic, and can halt protein synthesis. These fragments are then recycled, by a "ribosomal-associated quality control system. However, it is believed that the "dysfunction" of the ribosomal quality control, can lead to neurological diseases like Lou Gehrig's disease, as a result of motor neuron death [59]. The Research by Nagoya University has shown that mutations can hamper the function of the gene MAPT, and can lead to an "unchecked level," and increase in the amount of 4-repeat tau, leading to neurological disease [60]. Neurological disease research on Alzheimer's disease, scientists from Queen Mary of London, have identified a gene, which can "suppress" signs of Alzheimer's Disease of human cells. They also found a suppressor gene (BACE2), which can help to "slow down" the progression of this disease. In addition they also believe the BACE2 gene, may offer a means (biomarker) to determine the likelihood of developing Alzheimer's disease [60,61]. In other research on Alzheimer's disease, these investigators have discovered a protein called IFTM3 that is "involved" in an immune response to pathogens, and also plays a significant role, in the accumulation of beta-amyloid plaques. This makes it clear that an "immune response" is definitely involved, in the production of beta-amyloid plaques, a common characteristic of Alzheimer's disease [62].

Summary

Cancer is a mutational disease, which can start by damaging vital pathways, which are essential to maintain DNA function, and stability. Mutations can also affect the complement system, making one more susceptible to severe infection [1,3-6].

Cancer may also regulate the movement of metabolites in an out of the cell, as well as metabolites into mitochondria. Cancer is able to make this change by the cancer-linked version of the protein mitoNEEt, and voltage dependent anion channel. Exosomes can also be involved in genetic changes, by secreting miRNA, which can bind to messenger RNA, and inhibit the production of protein synthesis [7-9]. The Microbiome can play a significant role, as well as it relates to cancer, since microorganisms can release metabolites that can improve immunity, mood, or by facilitating antibody production. Some bacteria may also work with T-cells, and in so doing, improve immune therapy [10,11,14-16].

Cancer can be metastatic by influencing signaling protein, for example Slit2, can provide help for cancer cells to migrate [22]. Various cell components such as ribosomes, and the proteasome can affect cancers ability to respond to cell changes, reclaim reusable materials, and facilitate cancer growth. Cancer may also affect the activity of the KRAS gene, and its protein, allowing cancer cells to grow unchecked during cell division. The SNA2 protein is also responsible for protecting cancer cells from the immune system, and chemotherapy [23-27,30]. With Brain cancer, and particularly glioblastoma, following radiation, the suppression of colony stimulating factor-1 receptor, can increase the survival of mouse test subjects [32,33].

Vitamins like Vitamin C and Vitamin D have been credited in the past to help in the treatment of various diseases such as polio, diphtheria, herpes zoster, and many others. Both vitamins are important in improving immunity, the immune system, and cancer [35-39]. In the future, new based methods such as 'laser-based diamond sensing, will provide for monitoring the progression, and detection of neu-

rological diseases such as, concussion, epilepsy, dementia, and Alzheimer's disease. This portable device should improve the treatment of these neurological diseases [52,53]. It seems relevant that cancer in its various forms, can control normal cells, either by its influence on mitochondria, mitochondrial DNA, DNA mutations, and or a change, which can alter the nature of gene related proteins [40-43,45].

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