Cancer a Golden Age in New Treatments?

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Abstract

This paper involves a way to characterize cancer, its complex interactions with immunity, its genetics, involvement in transcription, the proteins or metabolites formed, gut microorganisms, and cancers influence on certain organelles for example, mitochondria.

Keywords: Cancer; Immunity; Transcription; Proteins; Gut Microorganisms

Cancer treatments

Have we reached the golden age of immunology, and treatments by immunotherapy? What about fighting cancer, are we on the brink of tremendous break throws, and successes in treatment? We can begin by looking at the way cancer can breakdown the illusive protective barriers, that protect cancer from the immune system [1]. Part of the story may lie in whether by immune cells that are capable of sending many message signals, that can prevent the activation of tumor cells. Important cells are for example, the so called myeloid-derived suppressor cells or MSCS. They occur in children suffering from cancer. With this form of cancer, it has been found that CD33 a particular protein occurs on the surface of MSCS cells. These particular cells have the ability to prevent CAR-T cells from working. Researchers have developed an antibody like drug called gemtuzumab ozogamicin, in order to target human MDSCs, after reprogramming of T cells, in order to make them more effective at destroying cancer cells. An antibody was also used in order to boost, the efficiency of CAR-T cells. Other avenues for treating are on the arisen, with the use of golden nanotubes, called nanoshells. They can destroy tumor cells when heated by a "near-infrared laser, which can be used to kill the cancer, without the problems that other form of treatments can result in side-affects [2].

Other forms of cancer treatment that are on the fore-front, are the use of what that has been termed as "gold-based molecules. These "metal based drugs" are more effective than currently used therapy, and can help to increase survival rates, but are limited due to side-affects from these gold based molecules. This therapy seems to be particularly toxic to prostrate, breast, cervical, melanoma, and color cancers, that targets the enzyme thioredoxin reductase, which is linked to inhibit tumor growth, compared to cisplatin [3]. The drug called Cetuximab has had some success with the diagnosis of colorectal cancer. This is significant since 40% of patients with colorectal cancer have a mutated KRAS gene in cells tumors. As a rule colorectal cancer does not respond to cetuximab. However, patients with a KRAS G13D mutation do respond to cetuximab. In the case of normal healthy cells, the tumor suppressor neurofibromin keeps the KRAS gene in check. The drug cetuximab in essence works by preventing the KRAS gene from being overactive, by making neurofibromin available [4].

In the case of Prostate cancer, researchers are tuning in on aggressive cancers by turning to a protein called AMACR. This particular protein has been found to occur in large amounts in those types of cancers. So, their discovery should lead to better ways to target this particular cancer protein, that is associated with aggressive types of prostate cancer [5]. Other important discoveries in cancer, are related to the interaction between the two proteins mitoNEET and voltage-dependent anion channels (VDACs). VDACs are associated on the
Cancer a Golden Age in New Treatments?

Surface of mitochondria and serves as a channel for the movement of metabolites in and out of mitochondria. In a recent discovery by Rice University, they learned that a cancer-linked version of mitoNEET can regulate the opening and closing of the VDACs channel. This regulation is based on a oxidation potential between the two proteins. In the authors words, cancer is a progressive entity, which can alter metabolism. This new research opens up the possibility to regulate cellular metabolism, as well as the development of new drugs, that can regulate VDAC and with new "weapons" to battle multiple cancers [6].

With Glioblastoma (GBM) a cancer of the brain, a old pharmaceutical drug may provide new ideas for treating an aggressive cancer, that is a difficult inoperatively. The drug is called surfen and has been used as a delivery drug for insulin. It initially was described in 1938, and this drug is highly positively charged. It has an affinity for negatively charged molecules, which is excellent, since GBM is negatively charged [7]. Other forms of brain cancer found in children, another aggressive and incurable cancer, is called Diffuse Intrinsic Pontine Gliomas (DIPG). This cancer is due to the silencing of a gene called NAPRT, a gene responsible for the metabolite NAD (nicotinamide adenine dinucleotide). PPM1D is "critical" to cell growth, and a mutation of PPM1D, cells must seek an alternate pathway for NAD production. By using a drug that can inhibit NAPRT, researchers have found a way to starve the cancer cells [8]. In breast cancer, the protein E-cadherin helps cancer cells to be able to “survive.” E-cadherin helps cancer cells to survive as they travel in the various parts of the body during their travel from the primary foci. It does this by allowing cancer cells to be able to stick together [9].

Molecular methods

Research in the area of molecular biology, researchers at the University of Delaware have discovered a new form of RNA, which they describe as a new circular RNA (ribonucleic acid). Although scientists knew of circular RNA, this new discovery is important, in that it makes aware that this type of RNA can perform in two roles. One RNA can function as a cancer suppressor, and secondly as a cancer promoter. This particular role occurs based on the RNA-level. Although circular RNA and linear RNA have the same sequence, Linear RNA makes a tumor-suppressing protein, whereas circRNA can independently work a tumor to be more active. Scientist believe that studying circRNAs, could provide a better understanding how these RNAs are able to "turn off the cancer-suppressing effect in the body” [10].

Noncoding DNA regions

Another new tool in the use of gene editing is SATI. The Salk Institute researchers have developed a new gene editing tool, that can target noncoding regions of DNA. SATI (intercellular linearized Single homology Arm donor mediated intron-Targeting Integration), works by inserting a “normal copy” of a gene into noncoding region of DNA. SATI is a new technology and can characterize mutations that occur in noncoding regions of DNA. It thus represents a mechanism that beam in on select regions of noncoding DNA [11]. At the cellular level, Scientists at the Institute of Cancer Research have unveiled the existence of a key molecule, in the process of transcription and translation. The molecule is called DHX8, and is a key member in the DHX8 complex, and is important during alternate splicing, that can occur during transcription. During the transcription process, as RNA is copied from DNA, certain pieces are removed, and stuck together to be translated into protein. The DHX8 protein is important in its binding of the RNA during transcription, and acts to "unravel RNA during the rest of the “spliced material.” The DHXi complex therefore helps in the release of finished RNA into the cell, so it can be translated into protein [12].

Metabolic channels

Very recently researchers at Oregon Health and Science University, have been able to visualize the 3-D structure of the P2X7 protein receptor, by cryoelectron microscopy. This receptor has been associated with inflammation, artery plaque buildup, cancer metastasis, and neurological conditions. It serves as a subtype of "ligand-gated ion channel P2X family. Its significance is that once the channel is opened, it can remain opened. Thus, allowing charged particles to enter, and may signal for pathways of inflammation, and ultimately leading to cell death. Researchers believe their discovery could lead to better understandings of ligand-gated ion channels, which can be modified by
Cancer a Golden Age in New Treatments?

palmitoyl groups, and possible treatments for health conditions associated with ion channels [13].

Germinal centers, T-cells and signaling factors

With the development of T follicular helper cells and germinal centers, there is interplay between IL-6 and IL-2, with T follicular cells and germinal centers, both in competition for immune responses and autoimmune disease. This is due to a loop whereby IL-2 is important in "fine-tuning the level at which IL-2 may respond to infection or maintain a blind eye thru surveillance. In order that T-cells and germinal centers can be maintained, there is a need for continuous T-cell receptor stimulation. This is in order to overcome the T-cell receptor/IL-2 inhibitory feedback loop, which can hinder T-cell development. The relative levels of both IL-2 and IL-6 therefore can help to determine the destiny of T-th cells [14]. Other regulations of T-cells can occur by the signaling from sphingosine 1-phosphate (S1P), which can affect their fate. Some T-cells due to immunotherapy may lead to the production of cytokine interleukin-15 (IL-15). This can promote a central memory-like T cell (Tcm) phenotype, capable of killing unwanted cells. A second factor transforming growth factor beta (TGF-β), can propel T cells to differentiate into T regulatory cells, which as a third factor peroxisome proliferator-activated receptor gamma (PPARγ) regulates lipid metabolism. Ultimately the path of T cell differentiation depends on IL-15 for leading to a Tcm phenotype, occurs by inhibiting the SphK1 (sphingosine kinase) and S1P, whereas TGF-β leans T-cells towards the Treg phenotype by activating Sphk1. Most importantly note is the fact when S1P is inhibited, T cells are more active at killing tumors. Also, these metabolic pathways can influence each other, "intricately" controlling T-cell fate [15].

Microbial influence on cancer and metabolic pathways

In regards to the health of the colon, the so called clock genes help to maintain stability of the colon through such cells, known as type 3 innate lymphoid cells (cells). These cells line the intestinal tract and produce molecules that provide a barrier from overacting "harmless microbes," and other disease causing microorganisms [16]. In the article by Researchers from George Washington University, in their research they found a correlation between the interactions of proteins, from carcinoembryonic antigen related cell adhesion molecular (CAECAM) family, when those antigens were able to make contact with microbes. It was found this contact affected the growth factor beta (TGFβ) pathway. CEACM thus affects the expression of TGFβ pathway genes, in a manner that can increase cell proliferation [17]. In an article by the National institute of Allergy and Infectious Diseases, they do believe that alternating the human gut microbiome can hinder the immune system, after oral antibiotics, and could affect the quality of vaccination as well [18].

Reprograming immune cells, microbiome’s influence, and chemotherapeutic agents

The reprogramming of mouse and human skin cells may provide a new method for improving the ability of immune cells to be able to search and destroy antigens and their pieces. This approach could be particularly helpful in which there is a lose in the number of immune cells, including dendritic cells. In this article the team from Lund University has “reprogrammed mouse and human skin cells” into dendritic immune cells. They were able utilize three proteins called PU.1, IRF8, and BATF3, in order to change these two cell types into functional dendritic cells. This represents a direct cell reprogramming, a direct way to convert human, and mouse cells into dendritic cells [19]. Another powerful tool is the use of protein mapping thru proteomics for immunotherapy, allowing for the “global mapping” of thousands of proteins. This methodology can be very helpful particularly in metastatic melanoma cancer. These patients may not respond to immunotherapy readily [20]. One cannot overlook the influence of the microbiome. With approximately 24 million oral and 22 million gut microorganisms, that have been found from these areas, being linked to a variety of dental caries, gut infections, and other serious infections, such as chronic inflammatory bowel disease, diabetes, and multiple sclerosis [21]. Patients that are triple-negative breast cancer, that do not respond to paclitaxel alone, may respond when in combination with BOS172722, if some tumor cells can escape to give rise to new tumor cells. BOS172722like paclitaxel also affects proper chromosome distribution during cell division [22]. These drugs not only affect proper chromosome distribution, by blocking the molecule called MPS1. They do this by speeding up cell division, which can result in the “gross chromosomal aberrations, chromosome errors, and ultimately tumor death cell death [22]. With lung cancer, during
Cancer a Golden Age in New Treatments?

Injury or sepsis, there can be an on-going battle between infection and inflammation, when white cells try to clean up the inflammation. In these cases, when "drug-like molecules bind white blood cells, this can allow them to pass from the blood stream and enter tissues and cause severe damage. The University of Calgary's team has discovered two drug-like molecules which can bind not only white blood cells, but also can bind cancer cells [23].

Alternate chemotherapy methods

Other methods that can target cancer cells, an article by the Society for General Microbiology has suggested by their research, that anaerobic bacteria such as Clostridia, could provide treatments other than radiotherapy, and or chemotherapy. This could eliminate suffering side effects, as a result of these types of cancer treatments. They insist that clostridia are capable of being affective against oxygen starved tumor areas. Their point is that endospores from Clostridia are well equipped to spread throughout the body, germinate and become active to attack tumors, where they occur. Clostridia may also be genetically engineered to attack tumors, in combination to conventional therapies [24].

Cancers influence on autonomic neural system

As with any operation that occurs within the body, all functions must start with a beginning. This is even true with the brain during stem cell proliferation. The autonomic neural system (ANS), along with its importance brain activities, also has a connection with the proliferation of stem cells. Stem cells have been found to have the presence of receptors for the ANS neurotransmitters (can change cell behavior). Therefore, it is apparent that stem cell proliferation is under the certain control of the Autonomic Nervous system [25]. Mitochondria are also important in cancer; since these organelles influence the regulation of cell death by genetic restraints by the MFF (mitochondrial fission factor). In prostate cancer for example, where the MFF gene can interact with VDA1, shutting down its function, can allow tumor cells to continue alive. The MFF has in role in control of cancer cell survival. The disruption of the MFF-VDAC complex can activate “multiple cell death mechanisms” of mitochondrial cell death, and a reduction in tumor growth. Therefore, the MFF-VDAC1 complex should offer a new strategy for treating a variety of cancers [26].

Cancer's neurological affects on Parkinson's disease, and Alzheimer's

Microorganisms and bacteria do affect the immune system. This can be recognized in the immune response during pancreatic cancer, where there can be an increase in the number of T-cells, and presence of CD-8 types [27]. Bacteria may also interfere in the performance of chemotherapy during the treatment of pancreatic cancer as well. They can do this by those that have an operating CDD gene, which displays chemotherapeutic resistance [28]. Neurodegenerative diseases such as Parkinson disease, activated microglia are “abundant” in the substantia nigra, and the brain structure is damaged in this disease. In Alzheimer's disease, there is believed to be a mutation of SOD1 gene, and can be initially protective, but may be “neurotoxic later. There is also evidence of the dysregulation of the Trem2, and programed pathway [29]. With recent new information on Parkinson’s disease, researchers from Stanford Medicine have discovered a compound that can affect Miro molecules, that are important in mitochondrial clearance of defective mitochondria. This research should help to make apparent the importance in the Miro defect in Parkinson’s disease [30]. In a related treatment on Alzheimer’s disease, the discovered drug called BPN14770 (Tetra Therapeutics) has been found to increase the level of cyclic AMP signaling in the brain, and has been shown to improve memory, nerve damage and symptoms of the disease [31]. In the case of Multiple Sclerosis, it was found that a 40-nucleotide myelin-binding DNA aptamer, can improve myelin binding. This could be a “refinement” in the treatment of disease [32].

Bacterial drug delivery

Recent research in a method for a bacteria-based drug delivery system, scientists in collaboration with University tech, are retrying an old idea of bacteria, in an effort to tract various forms of cancer. In their research methods, they are using nanoparticles with targeted Salmonella enteric serova Typhimurium VNP20009. This method provides a way to transport anti-cancer drugs into the desired tissues, with more drugs reaching cancer cells. These researchers estimated a 100 fold increase improvement in the “distribution” and retention

of nanoparticles [33]. In other research in regards to Lyme disease, a new rapid test for *Borrelia burgdorferi*. This test is based on three proteins that are associated with the microorganism, in which antibodies have been identified with. This rapid test only requires 15 minutes for detection and runs on a Sia’s mChip-LD platform (Lyme microfluidic test) and has a high specificity. However, the researcher says this test is a multiplexed diagnostic test has much potential, but more research needs to be performed before its wide based use [34]. There is also good news of a possible vaccine for *Chlamydia trachomatis*, one of the “most” commonly cause of sexually transmitted diseases. Both form of the vaccine are based on antibody production, as well as T cells [35]. With the rotavirus, researchers at Georgia State University found what may explain why some individuals have more severe infections with the virus. They found by testing two groups of individuals and comparing those resistant to the rotavirus and those susceptible. They concluded those that were more resistant to rotavirus infections, were those individuals that to have a common flora namely "Segmented Filamentous Bacteria (SFB). They also concluded that resistance was also by the shedding of epithelial cells, and the replacing of new uninfected cells [36]. There’s new hope in the development of a vaccine for the chikungunya virus. Only recently a key protein has been discovered that is important in replication pathogenicity of the virus. The protein is called FHL1 and is a molecule that is commonly found in human muscle and fibroblast cells. FHL1 can interact with a viral protein and is key in the replication of the chikungunya virus [37]. There’s also new information for the experimental treatment for the Ebola (Ebola Zaire), as well as the Sudan virus, and Bundibugyo virus. The treatment is a combination of monoclonal antibodies and called MBP134 cocktail [38]. Other new viral news is in the development of new CRISPR enzyme, which is capable of cutting and editing RNA. It not only can serve as a cutting tool, but may also be used to detect viruses, bacteria and “other targets”. A potential diagnostic tool for some of the most pathogenic viruses, such as Ebola, Zika, and flu [39].

**Neurodegenerative disease treatments**

New research on neurodegenerative disease by Netherlands Institute, has shown the combination of surgical and gene therapy can contribute to faster nerve recovery. Nerve cells can be repaired, and muscle fiber growth can occur. Muscle stimulation can occur after neurological repair, and gene therapy. They accomplished this, by what they referred to as “regulatable gene therapy”. They found that they could utilize gene therapy, with the use of a growth factor, which could be turned on or off, with the use of a commonly used antibiotic. They also had the ability to turn the growth factor on or off, when it was not needed. Their research is an important step into the use of gene therapy, and the use of a “stealth switch” [40]. Parkinson’s disease new research has struck upon new insight into the nature of the disease. IDIBell Institute has found by using stem cell-derived astrocytes, they could follow the accumulation of α-synuclein, and the transfer of dopamine-producing neurons. They believe the advancement of new models, for studying neurological diseases through experimental models, can accelerate the greater understanding and treatment for these diseases [41].

**Gene therapy, and inhibitory metabolites**

The study of Pediatric leukemia has been highly sault after, because the very low survival rate, and particularly those children diagnosed with MLL-translocation leukemia, at only 30%. Northwestern Universities research has centered around the study of the molecular function of MLL, within the complex known as COMPASS (Complex Proteins Associated with Set1). This research has previously identified compounds that could possibly slow cancer growth by “interrupting a gene transcription process called as “Super Elongation Complex (SEC) [42]. Although current cancer treatments often result in side effects, the discovery of a process called protein-modification, may provide treatments with more limited side effects. These researchers believe that when certain modified proteins become nitrated, they acquire new functions that may control tumor growth. In the case of peroxynitrite (controls metabolic changes in tumor cells), has been found in high levels in tumors with “pathological conditions” for example, nervous system. Inhibitors like peroxynitrite may offer new strategies, for the targeting of other similar metabolites, that also do not affect other normal cells [43].

**Speech recognition and autopsy**

It seems that all cells must have a strategy to remove cellular waste, regardless of the cell type. This is an essential process that cells must undergo autopsy, in order to maintain similar cellular functionality. In the case of the nervous tissue, a protein called SARM1 is
Cancer a Golden Age in New Treatments?

essential for “brain cell breakdown” [44]. Other new developments by engineers include technology that make it possible to convert pure thought into “recognizable speech.” New innovation also includes the area of new artificial intelligence which should offer new hope as a tool for the treatment and diagnosis of neurological diseases, by a direct link to brain activity [45]. Artificial intelligence has also provided a method for detecting acute myeloid leukemia, by the analysis of gene activity of cells, found in the blood [43,46].

Common gut flora

In the research by George Washington University, they studied 157 microorganisms from a number of healthy individuals, as a reference line (baseline). Their microbial profile (Gut-Feeling KB), identified the number and variety of normal gut flora, and included Clostridia 20%, Bacteroidia 19%, Bifidobacteria 17%, Enterobacteria 14% and phylum Firmicutes, 20% Clostridia and 14% and Lactobacillales. Their research can provide a better understanding of the complex relationship between our gut flora, and its host thru their close association, and interaction [47]. A new recent algorithm has also made possible the ability of better microscopic analysis, by providing better clarity of microscopic examination by super-resolution microscopes and making diagnosis earlier and more definitive [48].

Conclusion

In summary, it is a common phenomena that various types of chemotherapy often result in side effects. However, some treatments can be useful in some forms of cancer. In the presence of cancer, some immune cells may be reprogrammed to attack cancer cells. It seems that various cancers do follow in general similar patterns, either by direct gene activity, during transcription, with intervening proteins, and or affecting different organelles such as the mitochondria, and or gut microorganism [1,2,5,6,36,42]. With some forms of cancer, such as colorectal cancer patients with the mutated KRASG13D mutation, they often do not benefit from Cetuximab, however patients with the KRAS G13D mutation are the exception and have appeared to respond to cetuximab [4].

In the case of prostate cancer, the discovery of the protein AMACR, which occurs in large amounts, should serve as substantial target in aggressive forms of this cancer [5]. The drug surfen (positively charged), which has been used as a delivery drug for insulin. It has been shown to have an affinity for Glioblastoma (brain cancer), since it is negatively charged. The protein E-cadherin is important in cancer survival, since it contributes to cancer cells as they travel to other parts of the body. This can occur as a result of breast cancer [9].

In the area of molecular biology, a new form of RNA has been described as a (biomarker for disease), which can exist as circular RNA, and a linear form. The linear RNA makes a tumor suppressing protein, whereas the new circular RNA can increase tumor activity, in soft tissue and connective tissue tumors [10]. Scientists at the Institute of Cancer Research have described a new molecule called DAX8, a key member of the DHX8 complex. This molecule is important in the process of transcription and translation. The DHX8 protein is important in its binding of RNA during transcription, binds to RNA, and “acts to unravel RNA from the rest of the splicing machinery” [12].

Gut microorganisms influence on cancer and the immune system, can contribute to various infections, associated with the intestinal tract, and may contribute to such serious disease, such as inflammatory bowel disease, diabetes, and multiple sclerosis. Such bacteria such clostridia, due to their anaerobic nature, may eliminate side affects due to chemotherapy [21,24]. Microorganisms and bacteria do affect the immune system particularly recognized in the immune response, since they can increase the number of T-cells, and the presence of CD-8 types. This could also present a problem during chemotherapy, where in some circumstances hinder its effectiveness due to the CDD gene [24,27,28].

In the case of Alzheimer’s disease, there appears to be a mutation of the SOD1 gene, initially protective, but later neurotoxic. New information on a discovered drug called BPN14770 (protects brain), can improve memory, nerve damage, and symptoms of disease, lending new hope to the treatment of Alzheimer’s patients [29,31].

There have been a new advance in vaccine therapy, for the chikungunya virus, by affecting an important protein called FHL1, which is
essential for viral replication [37]. An experimental vaccine for Ebola is also available for Ebola, and is based on monoclonal antibodies, and called a MBP134 cocktail [38]. It appears even with neurological diseases, nerve cells can be restored, by what is referred to as ‘regulated’ gene therapy. IDI BEL has found a method to follow up the accumulation of α-synuclein, by using stem-cell derived astrocytes, and creating a model for a more in depth understanding, and treatments for Parkinson’s disease [40,41]. Other treatments that focus on the identification of compounds may possibly slow down cancer. These therapies center on the protein therapies that should provide treatments with limited side effects. In conclusion, it seems cancer functions either by genetics, its involvement in transcription, affect on organelles such as mitochondria, the presence of proteins formed, and or the formation of metabolites, that can affect the growth of cancer or its activity.

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Cancer a Golden Age in New Treatments?

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