Review Article

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Changing Nature of Diagnosis and Treatment of Cancer

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Abstract

Traditionally, cancer has been diagnosed / classified by pathologist under the microscope. Different types of cancers have been identified in relation to the location where they are first observed. Also, treatment and prognosis of cancer has been in relation to its histopathology and pathology analysis. Misdiagnosis and mistreatment have resulted from this approach which has increased the suffering and death of patients. Newer diagnosis and treatment methods are based on the molecular analysis of the tumor genes and identification of mutations which are directly related to the tumors. Under the new system, tumors are classified and treated according to their mutation type and not based on their location. Among the treatment options, immunotherapy relies on such approach.

Introduction

The immune system is in charge of body's protection against internal and external maladies. As we age, the immune system undergoes changes that are brought about through signals produced within the body itself. These changes affect the immune system's ability to protect the body against the diseases. On occasions, the signals (sent through alterations in the genes to the cells in various body organs) weaken or get misinterpreted, directing the cells to become diseased including cancerous. The alterations in the genes may include addition or deletion of DNA pieces or changes in the number of DNA copies. The tumors that result from such alterations the additional certain segments of DNA, or multiple copies of the whole gene. Alternatively, a single base in the DNA may be chemically modified via methylation or other reactions. At the end, in a single tumor, an average of 50 different mutations may be created through various such processes which compared to the total number of genes in the body is very few. Our body has 3 billion bases in its genes of which only a few may be modified, replaced, or deleted due to such mutations. Throughout our life, many spontaneous mutations also occur in our genes. All and all, only a few of the all the mutations may lead to serious conditions like cancer [1].

Each tumor type carries specific mutations, some with higher number of mutations and some with lower number [2]. In a series of high-throughput sequencing (HTS) studies, four genes were found to be altered in over 20% of the tumors [3,4]. Of course, all mutations do not lead to cancer. Cancer results only when

mutated cells can circumvent the normal defensive mechanisms of the body. These defensive mechanisms catch and correct most replication mistakes, leaving only some mutations to lead to cancer. Some common defensive mechanisms that prevent formation of cancer include: TP53 tumor suppressor gene, DNA damage gene, and checkpoint genes, but other genes including anti-oncogenes, and caretaker genes may also participate. Most often, mutations are corrected by specific enzymes controlled by tumor suppressor genes [5] but occasionally, they are not corrected, and the alterations will carry on for many generations until they take over the whole cellular machinery. In the process of becoming cancerous, the cells first go through the pre-cancerous stage and then to the cancerous stage characterized with uncontrolled growth. Once they have passed through the pre-cancerous stage, cancer cells display enormous genomic instability [5], changing their genome more and more as they grow. The mechanism of passage from precancerous to cancerous stage may involve changes in the caretaker genes (mostly observed in hereditary cancers) and production of new proteins through translation and transcription that are responsible for changing the normal cellular pathways.

The initial mutations may also be hereditary, or may be caused by environment, lifestyle, genetic, food, or other factors called pathogenic variants. Thanks to advancements in genetic techniques such as CRISPR, today we have gained the ability to detect and avoid genetic diseases by artificially editing the mutated parts of the genes even in the embryo, during pregnancy, or right after birth. But this

and other techniques despite their great potential, are still in their infancy and are being rapidly developed in many parts of the world. Knowing how cancer develops, we can see why cancer is not just one disease but a family of hundreds of diseases with huge genetic variability. The variability of cancer necessitates the generation of huge amount of genetic data, and this by itself adds to the difficulty of managing the cancer. Finding one damaged DNA among the 3 billion DNA bases in the human genome is time consuming and costly. However, today, with the help of fast computers, the large number of data can be managed in a matter of few days at a reasonable cost. Of course, when a mutated gene is discovered in a tumor, effective treatment may or may not be available for that tumor because effectiveness of the treatments are case specific. A treatment that works in one case, may not work in another case, or it may have to be modified to make it work in another case. Even variations exist among the people who have the same cancer.

The New Paradigm

So far, cancer has been diagnosed and attacked as a disease of the specific organ where it is first detected, e.g., cancer of the lung, cancer of the liver, cancer on the head and neck, etc. In the new paradigm, cancer is looked at not as an organ specific disease but as a genetic malfunction that may appear at any part of the body. Under this new system, cancer cells are not classified or categorized by a pathologist under the microscope but studied and diagnosed by a geneticist and/or pathologist trained in the genetics. Treatment too will be based on the type of genetic mutations in the cancer. This approach to diagnosis and treatment for cancer will eventually be applied to many diseases that result from genetic malfunctions and mutations. Accordingly, it is expected that the diagnosis and treatment of cancerous and many non-cancerous [6] genetic maladies will be organized and performed based on specific genetic profiles of those diseases (Figure 1). Such profiles are obtained through massive parallel sequencing (MPS) of their genomes. Both RNA and DNA will be assayed and targeted for treatment [7].

In the case of cancer, recent studies have established a correlation between the sequence of the tumor genes, the prognosis for the cancer, and survival of the patients [8]. Among the 3281 tumors that were studied, according to TCGA, 93% had at least one mutation [9]. The relation between the molecular profile of tumors and the clinical manifestation of the tumors have been described for several tumors including localized prostate cancer [10]. Also, a relationship between the metastatic behavior [11,12] of cancers and the tumor genetic profile has been established [13]. In the diagnosis of cancer based on its tumor gene profile, one looks at the genetic makeup of the tumor and classifies the tumor accordingly. In this approach, "driver mutations", mutations that are responsible for the cancer development are identified. Then, tumors are targeted with specific drugs that have been designed to attack those specific mutations. Using this approach, for both diagnosis and treatment of cancer, we look at the molecular makeup of the basic cell constituents, DNA, thus gradually moving away from the current practice of diagnosis and treatment based on morphology and histopathology.

Of course, some cancer cells become resistant to treatments,To overcome the resistance, we again must resort to molecular changes that are responsible for the resistance and design treatments which only target those molecular changes. In resistance, initial "driver genes" may become dormant and new "driver genes "take over their role. Sometimes, it is not the genes, but the way genes are expressed that leads to the appearance of cancer or resistance to treatment [14]. Biology at the molecular level is chemistry but diversity among the molecules and their roles in the biological systems makes understanding the relationship between the two challenging. These challenges stem from the high number and the variety of different diseases that are associated with cancer. Also, they stem from the heterogeneity of the mutations amongst the various tumors and within each tumor type. Furthermore, the enormous amount of data the enormous amount of data that must be generated and the cost involved may prove challenging. Unfortunately, a higher level of mutagenic heterogeneity is associated with a worse prognosis [15]. Advantages of diagnosis and treatment based on genetic profiling include avoiding misdiagnosis, requirement for smaller samples, and the possibility of using skin or blood samples for diagnosis Figure 1.
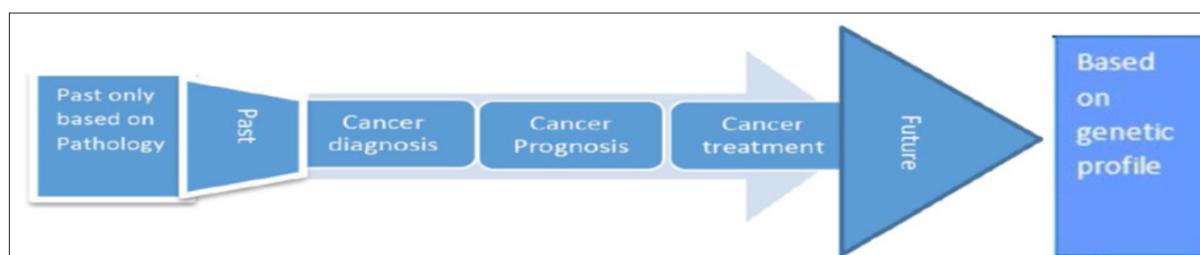

Figure 1.

Correlation Between Pathology and HTP Gene Profiling

One major benefit of targeting (mutationally similar) tumors based on the genetic makeup of their mutations rather than their location is that during the testing of the drugs, clinical trials don't need to be repeated for each organ that share the same type of mutation. Using the current classifications based on histology and histopathology, many cancers including breast cancer have been misidentified and misdiagnosed [16]. This has led to patients suffering or dying unnecessarily. It is hoped that using the newer method of gene profiling, and designing treatments based on the

mutation profile of the tumors, misdiagnosis and inappropriate treatment will be reduced. In several studies, good correlations have been shown between the traditional methods of cancer diagnosis and prognosis, HTP [17,18], and targetable mutations [6]. Comparison of the cost and laboratory techniques between the two approach as well as sample handling have also been made [2]. To accurately correlate the traditional methods of diagnosis and treatment based on pathology and the new gene profiling, profiles of more genes must be defined using methods that may require synthesis of DNA pieces or strands. Today, in the lab, we can synthesize the whole genomes of small viruses and bacteria but synthesizing the whole human genome is way more complicated and challenging. Until the time that we can synthesize the whole genome of humans, we can provide help for patients by editing their mutated genomes [19-21]. For editing, the genetic "mistake" inherited or created by mutation, is detected and corrected as if it were a word document [22].

Immunotherapy

Immunotherapy involves using T-cells, normally in charge of the body's defense, to attack and destroy foreign bodies including cancer cells. In cases where T-cells attack non-cancerous "self" cells, the body will normally get rid of those T-cells, or else, they will cause autoimmune disease. To avoid being detected as a foreign body, the cancer cells use a variety of tricks to show themselves as "self" rather than foreign to the T-cells and thus avoid being detected and destroyed. In immunotherapy, either the T-cells or the cancer cells are modified at the molecular level so that the cancer cells can be selectively identified and destroyed by the immune cells. The modifications are necessary because without them, T-cells are not able to recognize cancer cells as foreign cells to attack them. Two methods of modifications are currently prevalent

a)   Using checkpoint inhibitors to remove or prevent the formation of the proteins or peptides that cancer cells produce to fool the T-cells into thinking that they are not foreign but "self" cells. Keytruda,a checkpoint inhibitor was tested in 49 patients who had not responded to other drugs, 40% with colon cancer and 48% with other types of cancers showed dramatic shrinkage or complete disappearance of the tumors. Keytruda and Yervoy are antibodies approved by the FDA that increase T-cell activity towards tumors by blocking proteins that prevent T-cells from being active against the tumor. Antibodies work by selectively attaching themselves to specific target proteins and taking those specific proteins out of the circulation and remove them from accessibility. It is estimated that 20% of the cancers respond to checkpoint inhibitors. However, of those that respond, some may develop resistance due to mutation or other mechanisms and make themselves invisible to the T-cells.

b)   Modifying the immune system T-cells that are not able to recognize cancer cells as foreign cells so that they are able to recognize the cancer cells as foreign and attack and destroy them. An example of that are the chimeric antigen receptor (CAR) T cells or modified CAR-T cells which can recognize and attack the cancer cells as foreign cells. In practice, through

genetic engineering, T-cells are modified so that they carry a protein (called CD19) that binds specifically to the cancer cells and capture them through antigen-antibody interaction. The genetically modified T-cells are grown outside the body before they are given to the patient for treatment. This technique which has worked for leukemia can evoke severe body reaction because it involves elevation of cytokines related to amplified immune response. In the (CAR) T cells method tested recently, T-cells were removed from a leukemia patient, were genetically modified to recognize cancer cells as foreign, and then they were given back to the patient and allowed to fight the cancer [23]. Here, the T cells were engineered to destroy any cell that has the protein CD19 on their surface, in the body of the leukemias and lymphomas patient. The altered T cells are called CAR-T cells.

In one form of CAR-T-cell immunotherapy called TIL, T-cells that are naturally able to recognize and attack cancer cells but are limited in number, are collected from the surfaces of the solid tumor tissues. They are then grown ex-vivo, outside the body of the patient in huge numbers and then given back to the patient so that they attack and kill the cancerous cells. This method has been successful at least in one case of cholangiocarcinoma [24] at NIH. Cancer vaccines may also be used to trigger the action of T-cells that remain inactive against the cancer cells. Antibodies may be used to detect and capture either the cancer cells or the immune cells. Under ideal circumstances, tumor cells will have peptide or protein residues hanging off them that can act as antigens which can be recognized by T-cells as foreign bodies and attacked through the antigenic response system. Tumors develop many mutations. Some of those mutations lead to production of entities (antigens) that extend outside their cells, in the form of a peptide. For example, the EGFRvIII mutation is one such mutation that extends a peptide piece outside the cell which provides an opportunity for raising antibodies against them. Such antibodies can then be used as drugs to help kill the tumor cells. Once T-cells recognize the cancer cells with antigens, they proceed to capture, lyse and kill those cancer cells and thus destroy the tumor. Of course, there are several types of T-cells each of which have different defensive duties which they perform by utilizing different mechanisms.

Limitations

One limitation of the diagnosis and treatment of cancer based on genetic profile is that the types of mutations abound and not all mutations lead to cancer. In addition, once formed, cancer cells undergo further mutations. As a result, even diagnosis/ treatment based on tumor mutation is not so simple. So far, early immunotherapies in the Clinique Based on Cancer Genome Atlas (TCGA) [25], have shown that best outcomes may become reality if treatments are designed for each individual case (personalized medicine). Many centers have initiated such personalized trials but developing drugs for individual patients by pharmaceutical companies is not profitable and practical although the FDA has indicated that it will approve such drugs. An additional complication is that often multiple changes to the gene are necessary for the

cancer to develop. Alternatively, the changes may take 10, 20, 30, 40, 50 years, or a lifetime to develop into cancer.

Common Mutations and their Relevance to Inherited Cancers

When a patient inherits a gene mutation, the risk of hereditary cancer is higher in that patient than average population. Some hereditary cancers appear at certain designated time at one's life. Often one or more family members share the hereditary cancers. In one case, a female patient, developed cholangiocarcinoma at the age of 61, her father died of pancreatic cancer at the age of 58. But in a family of 8 children, only one of her brothers developed lymphatic cancer at age 50. Overall, the risk for hereditary cancers are way lower than the risk for non-hereditary cancers. The non-hereditary cancers which result from gene mutations caused by food, hormone changes, or environmental factors, make up the bulk of cancers today. Because about 5-10 percent of the cancers occur through inheritance. Genetic testing can be performed to identify the inherited mutations. Mutations identified in the hereditary cancers include BRCA1 and BRCA2, PTEN. These mutations increase the risk for breast and thyroid cancer, the STK11 mutation increases the risk for colon, breast, and pancreatic cancer, and the TP 53 mutation increases the risk for breast, sarcomas, and brain tumors. Lynch syndrome which is hereditary involves mutations in MLH1, MSH2, MSH6, or EPCAM genes and is associated with colon, uterine, ovarian, and gastric, CNS, and pancreatic cancers. People who have the hereditary Lynch syndrome have a 70% risk for colon cancer. They are also at risk for ovarian, and endometrial cancers. All this is due to a defect in their MMR genes. These genes are in charge of correcting mistakes that may occur in DNA replication. Cancers with MMR defects respond to immunotherapy.

Mutations in the PTEN gene increases the risk for melanoma and breast, uterine, thyroid, colon, and kidney cancers. Mutation in TP53 (Li-Fraumeni syndrome) gene is associated with increased risk for colon, bone, pancreatic, liver, brain tumors and leukemia. Mutations in CDH1 gene increases stomach and lobular breast cancer. Gene panel tests are nowadays available for various types of syndromes that lead to known tumors. A Breast or ovarian cancer test panel for example will look for mutation in the BRCA1 and BRCA2 genes and other relevant genes. When multiple mutations are involved in one's cancer, to stop the cancer, inhibitors for all those mutations must be administered. For example, in colon cancer, both BRAF mutation and EGFR mutation may be involved in which case inhibitors for both mutations must be administered. Normally, EGFR mutation is found in lung cancer. About 30-45% of patients with melanoma have BRAF V600E mutations but less than 2% of them may have non-small lung cancer. Genetic testing in the past 2-5 years has opened the door for finding even rare mutations and drugs that have shown great promise and significant tumor shrinkage or complete remission. In addition to inherited mutations, in recent years, testing on somatic mutations has dramatically increased. They help identify those therapies that might work against a tumor. But because all the possible mutations have yet to be identified, each testing may identify new mutations. In terms of mechanism, similar pathways may be involved in the sporadic cancer as in hereditary cancers. For example, in the non-hereditary, sporadic breast cancer, the levels of BRCA2, a tumor suppressor, which is involved in the repair of the DNA, goes down as mutation is observed in the sporadic breast cancer. This in turn leads to proliferation and invasion [26].

Personalized Cancer Treatment

In personalized therapy, the mutational as well as transcriptional profiles of a person's tumor is first obtained. Then, therapies are designed that specifically attack that very profile of the cancer. Unfortunately, now, enough drugs are not available to target all the detected mutations. But the method of targeted therapy has been proven successful in many cases [27]. NCI-MATCH trial program sponsored by NCI started in 2015. The program has sequenced the tumors from 6000 patients. In this trial, 21 drugs alone or in combination are given to the patients based on the mutations and sequence in their genes. A similar trial is run by Novartis which started in 2013. This trial tests 15 types of cancers in 600 patients. When gene of the adenocarcinoma of the tongue was sequenced, mutation in PTEN gene as well as overexpression in RET gene was observed. Treatment with the RET inhibitor, Sunitinib, stabilized the cancer. Also, in a thyroid cancer case, mutation in mTOR was observed which prompted treatment with mTOR inhibitor. In other studies, patients were given drugs that matched the identified mutation. Of the 11 patients, 3 responded and 4 became stable. Other treatments based on mutation include:

a)   Larotrectinib is a drug that targets TRK gene fusion which causes about 5000 cancers each year including lung and colon cancers. Complete remission by treatment with this drug was observed in 17 cases.

b)   Vemurafenib which was expected to work against cancers with BRAF mutations such as melanoma, colon, and thyroid, works on melanoma, and skin cancer but not on colon cancer. However, if EGFR inhibitor (common to lung cancer) is added to it, it then works against colon cancer also.

Researchers are now testing broadness of the effectiveness of various inhibitors. For example, they test PARP inhibitors (which have shown activity against BRCA-muted ovarian cancer), against cancers related to other mutation.

Synthetic Lethality

In this method, vulnerability of the cancer cells is discovered, and those vulnerabilities exacerbated by treatments that in effect are additional attack [28] on the cancer cells. For example, cells use two repair mechanisms to repair any damage to their DNA, if one of those two repair mechanisms is hampered by becoming cancerous, and cells depend only on the second repair pathway for their survival, then blocking that only pathway will lead to their demise and thus destruction of the cancer. Mutations in BRCA genes disables one of the two pathways that the breast cancer cells need to repair their DNA. So, they are left with only one DNA repair pathway for their survival namely, Poly (ADP-ribose) polymerase (PARP) which repairs single stranded DNA. Because the cells are already vulnerable, attacking this second pathway by using inhibitors of the

PARP, will lead to the cell death [29]. Drugs that inhibit the PARP enzyme include Olaparib, rucaparib, and niraparib.

CRISPR-Cas9

CRISPR-Cas9 is based on the CRISPR-Cas system. Technology is a new tool that allows scientists working in genetics to cut and paste pieces of DNA. This process which is biologically conducted by enzyme, is not too different from the cut and paste used in fixing a word document. The process allows the creation of new strands of DNA which can code for creation of new proteins with varied functions and properties. The technology can be used to modify cancer cells for ease of targeting. It can also be used to modify the T-cells in charge of body's defense so that they can recognize and target the cancers cells. In addition, the technology can be used to add or delete specific traits to plants and or animals. In plants, for example, the lost favor of the tomatoes can be revived or tomatoes with high yields can be generated through CRISPR technology. Also, using this technology, animals possessing specific characteristics can be created. In nature, the CRISPR-Cas system oversees providing immunity for bacteria against viruses and plasmids. The protein Cas9 is an endonuclease that uses a guide sequence to form base pairs within target DNA sequence. This allows for introduction of a specific double stranded break in the DNA [30,31]. The technique allows for efficient targeting, editing, and modifying of cells and organs which can influence the modification and regulation of their behaviors.
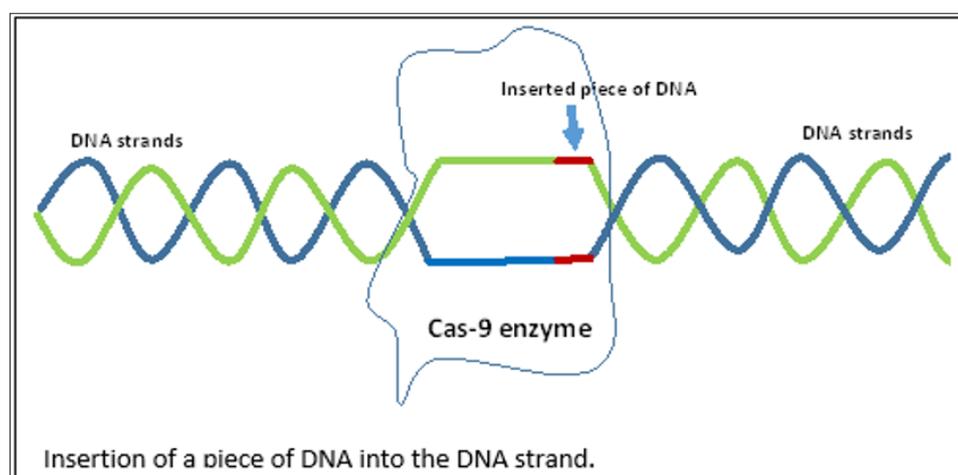

Figure 2.

The technology not only can help with correction of mutations, to prevent cancer, it can also help prevent many other inherited diseases. In addition, the technology can be utilized to design drugs, generate specifically engineered cells, organs, organisms, and animals, and plants. In research, often generation of models that contain multiple mutations are necessary [32]. To create an animal cancer model with several genes, currently, breeding is used which time is consuming. CRISPR/Cas9 on the other hand can introduce several mutations in one step in a short amount of time. For example, in ES cells, it can be used to introduce over five genes in the cells [33-36]. In practice, CRISPR uses a guide RNA to direct the Cas9 enzyme (light blue) to target DNA sequence (Figure 2). Once there, every time, Cas9 finds a protospacer-adjacent motif sequence (red) in the DNA, it will bind to and cut both strands. This process primes the gene sequence for editing [37-45]. CRISPR is only 5 years old but because of extraordinary potential value in helping patients, it is already being tested its in the clinic. In 2018, several companies are for the first time taking the technique into the clinic. Currently, the clinical studies focus on fixing mutations that lead to sickle cell disease. In this disease, red blood cells take certain shapes that prevents them from getting out of the blood vessels for delivering oxygen to the tissues. Over time, the technique and its modifications will be applied to all genetic diseases including cancer.

Acknowledgements

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