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The Potential of Cancer Driver Gene Mutation

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Abstract*—NGS technology shows which genes are involved in cancer cells. Driver genes are becoming a new target for cancer treatment. In the age of the 4th information revolution, AI (artificial intelligence) analyzes the therapeutic data of many cancer patients and finds bad mutations that drive cancer. However, finding a driver gene does not mean that cancer is overcome. Shortly, cancer cells activate another driver gene. It need a deeper mechanistic investigation of the link between protein structure and cancer driver gene. Driver genes have high protein-protein connectivity. Protein map coding driver genes may offer insight for overcoming cancer*.

***Keywords*—** *Next Generation Sequencing(NGS), Gene Aberrations, Human Protein Atlas (HPA) Driver Gene*.

I. INTRODUCTION

The completion of the human genome map in 2001 opened the era of cancer therapy through genetic analysis[1]. It is becoming a medical rule that individual cancers begin with gene aberrations. At present, the cost of genome analysis is getting lower by the Next Generation Sequencing (NGS) technology. Precision medicine is not a new concept but the availability of large-scale human genome databases, the advent of powerful methods such as next-generation sequencing (NGS) and advancement of computational tools have created an opportunity for significant progres[2]. Precision medicine is particularly important in oncology because along-standing problem is the variability of treatment response, especially in early stage clinical trials[2].

Next-generation sequencing (NGS), also known as massively parallel sequencing, represents an effective way to capture a large amount of genomic information about a cancer[3]. Cancers are classified in two ways: by the type of tissue in which the cancer originates (histological type) and by primary site, or the location in the body where the cancer first developed[4]. For example, let's consider a lung cancer treatment strategy through gene analysis. First, the task of finding gene aberrations should be done first. If a gene abnormality is found, it is assumed that it is the direct cause of lung cancer, and a molecular target therapeutic agent is administered as a therapeutic target of a misfolding protein with abnormal gene. Compared to normal cells, cancer cells are always activated in their proliferation pathways. For the transition from normal cell to cancer cells, many proteins are involved from the growth receptor of the cell membrane to the primer in the nuclear membrane. The gene aberration that directly causes cancer appears as a modification of the steric-structure protein. Many proteins are produced and ubiquitinated in the cytoplasm of cancer cells. In normal cells, there is no protein activity of the proliferation pathway. However, protein activity of the proliferation pathway is observed in cancer cells. Proteins involved in cell proliferation are called adapter proteins[5]. Gene aberrations induces the activity of the adapter protein. It is now important to sort out which of the adapter proteins might actually be involved in signal transmission from various mitogenic stimuli in vivo. It is now apparent that signal transduction is often mediated by specific protein-protein complexes. In many cases, the formation of such complexes is controlled by small modular domains. The domains bind specifically and with high affinity to tyrosine-phosphorylated proteins and mediate the association of signaling proteins in response to tyrosine phosphorylation. The cytoplasmic domain of the tyrosine kinase receptor is called the docking protein. When the phosphate group is attached to the docking protein, the proliferation signal is transferred to the leader protein. The adapter proteins transfer the propagated signal in turn into the nuclear membrane. In conclusion, modifications of the docking and adapter proteins make cancer cells[7]. The cause of the transformation is a gene aberrations. This study aims to investigate the pathway in which one gene or two or more genes induce cancer cell growth, and to identify the process by which a gene leads the proliferation signal.

Gene Aberrations

Next-generation sequencing (NGS) technology has expanded in the last decades with significant improvements in genetic analysis on cancer cells[4]. Gene aberrations are not simply a mutation. There are constant patterns in gene aberrations, a gene amplification in which gene sequences are repeatedly present, a gene deletion without a gene sequence to be present, a gene shift that is not present in the original place, a gene transfer in another. Normal cells do not become cancer cells even if gene aberrations occur[8]. When a gene aberration occurs in normal cells, p53 is activated, the cell cycle is stopped, the apoptosis pathway is activated, and the cells die. Therefore, a tumor suppressing gene aberrations is also a cancer-causing factor[9]. p53, a tumor suppressor gene, inhibits tumor formation, acting as a brake on the process. P53 has to be inactivated in or deleted from the genome of the cancer cell in order to release the brake, allowing cancer to develop. The process that inactivates p53 often involves deletion of both copies of the gene in the cancer (one copy originally inherited from the mother and one from the father)[10]. However, even if the tumor suppressor gene is normal, It is more likely to become cancer cells. Cancer cells are resistant to immune cell attack through immune evasion but show strong resistance to apoptosis[11]. In other words, Cancer cells synthesize proteins that block the activity of the p53 to avoid apoptosis. There are more cases of normal p53 in the gene mutation test of tumor tissue. The abnormal p53 gene is not directly linked to cancer cells, nor does the normal p53 gene guarantee anti-cancer.

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Precision medicine is the main anticancer-therapy in clinical hospital. It is necessary to first search for gene aberrations and analyze the effects of the gene aberrations on cancer cells to establish treatment strategies[5]. Gene aberrations affect protein conformation in some form. Gene aberrations change the sequence of amino acids in ribosomes according to central dogma. The order of the altered amino acids ultimately determines the nature of the finished protein. If the protein made before the gene aberrations is hydrophilic, the protein made after the gene aberrations can have a hydrophobic. Cancer cells can be produced even though there is no abnormality in the gene base sequence. In normal cells, proteins involved in cell proliferation remain inactive, proteins necessary for maintenance of inactivity are always produced. However, when a methyl group is bonded to a promoter of a gene that synthesizes a protein necessary for maintaining inactivity, the gap between DNA and histone is narrowed, making it difficult to access the RNA polymerase[12,13]. This is another cause of cancer. The next is miRNA intervention. Cancer cells synthesize too few miRNAs, and some cancer cells synthesize too many miRNAs[14]. MicroRNAs (miRNAs) are small physiological non-coding RNAs that regulate gene expression through an RNA interference (RNAi) mechanism[14]. The expression of miRNAs is tightly controlled both spatially and temporally. Aberrant miRNA expression has been correlated with various cancers[15]. miRNAs are also the result of gene translation. Studies have shown that miRNA affects cancer cells. Subsequently, the roles of miRNAs in various cancers have been investigated. Some investigators have found a global down-regulation of miRNA levels in tumor cells[16]. This down-regulation is partially explained by the fact that some tumor suppressors and oncogenes can modulate the miRNA-promoters' activity. Indeed, tumor suppressors and oncogenes, including p53 and c-Myc which are transcriptional activators, have been shown experimentally to modulate the activities of miRNA promoters[17].

Exploring Driver Gene

Next-generation sequencing (NGS), also known as massively parallel sequencing, represents an effective way to capture a large amount of genomic information about a cancer[18]. Cancer sequencing using next-generation sequencing (NGS) methods provides more information in less time compared to traditional single-gene and array-based approaches[18]. Using NGS an entire human genome can be sequenced within a single day. With NGS, researchers can perform whole-genome studies, targeted gene profiling, tumor-normal comparisons, it also offers the sensitivity to detect rare somatic variants, tumor subclones, and circulating DNA fragments[19]. At Memorial Sloan Kettering (MSK), lung cancer patients now routinely receive genomic testing of their tumors as a part of diagnosis and staging[20]. For certain mutations, drugs already approved by the US Food and Drug Administration are available as treatments. For others, experimental treatments being tested in clinical trials may be the best option. MSK-IMPACT is based on next-generation sequencing, cutting-edge technology that allows cancer genomes to be profiled very quickly and with great sensitivity[20]. For example, the test can tell if a gene has been mutated or deleted, or if there are additional copies of it. MSK-IMPACT allows clinicians to look for alterations that, while less common than EGFR, KRAS, and ALK mutations, still have important implications for choosing treatments[21]. On testing for gene aberrations in tumor tissue, the cases in which a gene aberration is confirmed is rare. In most cases, more than two gene aberrations are observed. For example, it is assumed that three or more genes A, B, and C are observed as a result of genetic test. All three genes are involved in carcinogenesis, and two of the three genes are involved in carcinogenesis. Sometimes, one of the three genes is involved in cancer. Among many genes, genes involved in carcinogenesis are called the driver genes[22]. Genes that are not involved in carcinogenesis are called the passenger gene[22]. In cancer genomes, it have to distinguish the driver gene that push cells towards cancer from the passenger gene. The majority of gene aberrations are likely to be passenger genes that don't contribute to the development of cancer but have occurred during the growth of the cancer, while a minority are the driver genes. The challenge of efficiently picking out the driver genes in a cancer genome is yet to be fully answered. It is essential to distinguish the drivers from the passengers because knowing the driver mutations leads to understanding of the cellular processes that have been subverted in cancers and hence to new drug[23]. Finding driver gene is the most critical for effective anti-cancer therapy[24]. However, even with the development of gene analysis techniques, it is difficult to find all the driver genes for a specific cancer. In cancer cells, the process of finding the protein involved in the proliferation pathway should be preceded. Currently, the Human Protein Atlas (HPA) Project is on a global scale, but it is still incomplete[25]. The correct spatial distribution of proteins is vital for their function and often mis-localization or ectopic expression leads to cancer[26]. For more than a decade, the Human Protein Atlas (HPA) has constituted a valuable tool for researchers studying protein localization and expression in tumor tissues[25]. The centerpiece of the HPA is its unique antibody collection for mapping the entire human proteome by immunohistochemistry and immunocytochemistry[26]. By these approaches, more than 10 million images showing protein expression patterns at a single-cell level were generated. The antibody-based approach is combined with transcriptomics data for an overview of global expression profiles[22,27]. To date, about 470 cancer genes have been identified[28]. This is due to the understanding of the function and location of the proteins corresponding to 470 genes. In most cancer patient tissues, some genes in to 470 gene groups are observed. However, in some cancer patients, no mutation has been detected in tumor tissue. As mentioned above, methylation or miRNA should be presumed to be involved in carcinogenesis. Cancer cells start from the growth receptors, and the proliferation signal is sequentially transmitted through the docking protein and the adapter protein sequence, and the cell cycle is reversed. In normal cells, all proteins involved in proliferation are inactive. In cancer cells, the proliferation-related proteins are off. However, it is crucial to know which protein's activity is the direct cause of cancer cells. When the Cancer-related Protein

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Atlas project is completed, a revolution in cancer therapy is expected to begin. Until then, genetic mutation tests must be performed to identify gene aberrations. After finding a number of gene aberrations, the treatment target should be determined based on the function, location, and properties of the proteins that each gene synthesizes. It is important to distinguish between a driver gene directly involved in malignant tumor and a passenger gene independent of malignant tumor. Therapeutic strategies targeting passenger genes are likely to fail.

Same Cancer, Different Driver Gene, and Different Cancer, Same Driver Gene

Even the same lung cancer does not have the same driver gene. Epidermal growth factor receptor (EGFR) mutations account for a large proportion of lung cancer[29]. The gene to code the receptor protein is likely to be a driver gene. However, the receptor is normal, but the abnormality of the domain protein linked to the receptor is sometimes causes lung cancer. Alternatively, adaptor protein abnormalities may be the cause of lung cancer. Cell growth receptors are not only EGFR but also HER receptors[30]. There are three types of HER receptors: HER1, HER2, and HER3. HER mutations among breast cancer patients are observed. However, HER mutations are also observed in lung cancer. Mutations, gene amplification and protein overexpression of HER family members are all linked to carcinogenesis[31]. Overexpression of EGFR and HER2 is well-documented in a variety of tumor types. If the receptor mutation is the cause of cancer, it is presumed that the gene to code the receptor functions as a driver. The adaptor proteins associated with the EGFR receptor is RAS-RAF-MEK-MAPK. The genes to code adaptor proteins function as drivers. Assuming that there are six lung cancer patients (No.1 to No.6) as shown in table 1 below, it could be deduced that different driver genes cause lung cancer.

TABLE 1.

EGFR	HER	RAS	RAF	MEK	MAPK
No.1	No.2	No.3	No.4	No.5	No.6

Conversely, assuming six cancer patients with different cancers, there may be a number of cases in which the same driver gene causes cancer even though the cancer type is different (Table 2).

TABLE 2.

No.1 (,Lung)	No.2 (Gastric)	No.3 (Breast)	No.4 (Colorectal)	No.5 (Pancreatic)	No.6 (Ovarian)
RAS	RAS	RAS	RAS	RAS	RAS

Targeted Therapy Oncogenic Driver Mmutations

In recent years, molecular targeted therapies play a central role in chemotherapy. There is a driver gene in all cancer. The target treatment based on driver gene mutation is precision medicine. Driver gene mutation is linked to a modification of the protein conformation that is involved in the proliferation pathway[32]. Inhibiting the activity of proteins involved in the proliferative pathway is central to the therapeutic strategy. Recently developed molecular target therapy drugs combine with modified proliferation proteins to block their activity in advance. If the modification of the receptor protein is the cause of cancer, the target therapeutic drug binds to the receptor protein and blocks the activity of the receptor. If the adapter protein is the cause of cancer, the target therapeutic drug binds to the adapter protein and blocks the activity of the adapter protein. Genetic aberrations can be detected by extracting tumor tissues from cancer patients and performing genetic mutation tests. The discovery of gene aberrations does not mean that driver genes can be found. Proteins involved in the proliferation pathway should be considered driver genes, therapeutic strategies should be developed. Even if a molecule-targeting drug is administered to a driver gene mutation, the probability of disrupting cancer cell growth is about 70%. It boasts considerably higher efficacy than conventional chemical drugs. However, molecular targeted therapies also have limitations that can't interfere with 30% cancer[33]. Cancer without any response to a molecular target therapy drug has another driver gene. the other driver genes are unknown yet. Driver genes are defined as genes containing driver mutations. Although genes can be confidently identified as drivers because mutations are observed in many tumors, the identification of driver genes that are infrequently mutated is more difficult. One of the major goals of cancer genomics is the identification of the driver genes responsible for tumor initiation and progression. It is generally thought that a larger number of driver gene mutations is required. As more sequencing and epidemiologic data are gathered on cancers of various types, it will be of interest to find driver genes. Recently, technology for analyzing gene aberrations is progressing according to the development of artificial intelligence. In the case of the same cancer, it will be also experienced a case where what you know as a past passenger gene is converted into a driver gene by Big Data analysis. All of that big data is being collated and connected in order to find driver genes. Data driven medicine has the ability to not only improve the speed and accuracy of diagnosis for cancer, but also unlock the possibility of personalized medical treatments for targeting driver gene. By the way, when the Protein Atlas project is completed, Protein corresponding to driver gene can be identified[25]. In other words, you the time will come to discover proteins that directly participate in the proliferation of all cancers. A new drug to inactivate the causative protein of cancer will be a pioneer in the age of 150-year-old human longevity

A Limitation of Targeted Anticancer Therapy

Most cancer patients are susceptible to therapeutic agents targeting the driver gene. Over time, the cancer cells begin to show resistance to the target drug. It is an inevitable intrinsic problem that cancer cells exhibit resistance to a target therapeutic drug[34]. If one receptor is blocked, another receptor may be activated to continue the proliferation. When one adapter protein is blocked, another adapter protein may be activated to continue the proliferation. Each driver gene has a markedly different susceptibility response to a molecule-targeting drug. Currently, there are also studies to treat two or

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more driver gene mutations simultaneously[35]. It is possible to prevent cancer cell proliferation more effectively by administering different kinds of molecular target treatment drugs against cancer in which EGFR mutation and HER mutation coexist. Simultaneous therapies also can't avoid the resistance of cancer cells. Cancer cells have various proliferation pathways. If one proliferation pathway is blocked by a molecular target therapy drug, it will react to other proliferation pathways. Resistant cancer cells are presumed to have very strong stem cell capabilities. Cancer cells that are resistant to the target drug can't be killed. Recent attention has been focused on cancer virus treatment and cancer immunotherapy. The former is a treatment for directly killing cancer cells using viruses, and the latter is a treatment for killing cancer cells by inducing the activation of immune cells. With these latest treatments, resistant cancer cells can be removed (Figure 1).

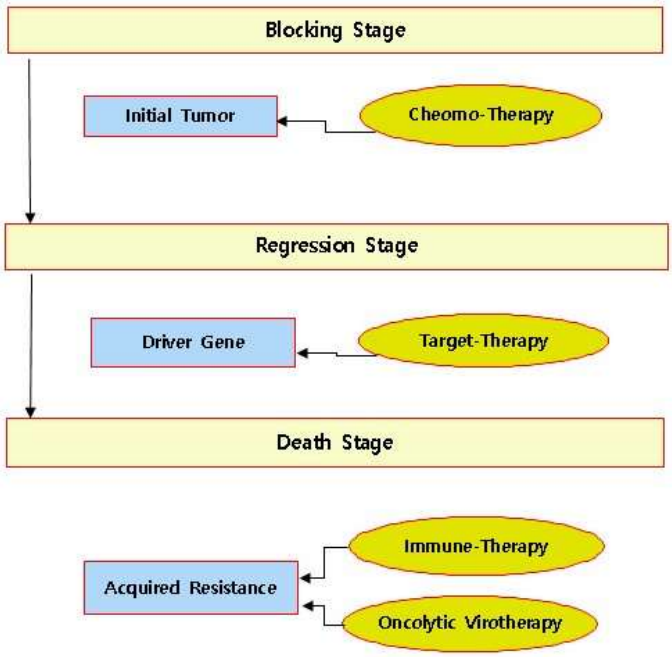

Fig. 1. Current paradigm on anticancer therapy.

II. CONCLUSION

The success of precision medicine depends on having accurate diagnostic tests that identify patients who can benefit from targeted therapies[2]. NGS technologies have revealed a more detailed molecular characterization of cancers helping to realize the great promise of precision medicine. NGS-based cancer gene panels analyze the molecular features of tumor tissues simultaneously and can provide enough depth of coverage to detect minor allele frequencies in a cost-effective manner. Signaling pathway guided cancer therapy has gained success and off-label drug use based on NGS results has been successful. NGS has brought new hopes to deliver the drug to patients at the right dose and the right time. However, the overwhelming complexity of the cancer genome suggests that we are in the earliest phases of interpreting molecular results and translating that data into knowledge that is useful to clinicians and to treat cancer patients. Many more cancer genomes need to be analyzed in order to achieve a deeper understanding of cancers and develop additional tools for molecular analysis. Additional clinical trials with molecular criteria conducted in adult and pediatric patients are needed. Optimal exploitation of all these data through integrated analyses across the different cancer types will lead to a comprehensive understanding of the genetic events that lie at the basis of tumor development and evolution[2]. As a result, a comprehensive map of cellular alterations will benefit all cancer patients[2].

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