Review Article

Novel approaches to treat cancer by target therapy

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ABSTRACT

Cancer is a multifactorial disease and is one of the leading causes of death worldwide. Emerging evidence indicates that impaired cellular energy metabolism is the defining characteristic of nearly all cancers regardless of cellular or tissue origin. In contrast to normal cells, which derive most of their usable energy from oxidative phosphorylation, most cancer cells become heavily dependent on substrate level phosphorylation to meet energy demands. Evidence is reviewed supporting a general hypothesis that genomic instability and essentially all hallmarks of cancer, including aerobic glycolysis (Warburg effect), can be linked to impaired mitochondrial function and energy metabolism. A view of cancer as primarily a metabolic disease will impact approaches to cancer management and prevention. The contributing factors include specific genetic background, chronic exposure to various environmental stresses, and improper diet. All these risk factors lead to the accumulation of molecular changes or mutations in some important proteins in cells which contributes to the initiation of carcinogenesis. Chemotherapy is an effective treatment against cancer but undesirable chemotherapy reactions and the development of resistance to drugs which result in multidrug resistance are the major obstacles in cancer chemotherapy.

Keywords: Multidrug resistance, genes mutations, microarray-based MRNA, non-coding RNAs, targeted delivery

INTRODUCTION

Cancer is the second leading cause of deaths all over the world. Globally, 7.6 million deaths are caused by cancer which represents 13% of all global deaths.[1] Surgery, chemotherapy, and irradiation are the mainstream therapeutic approaches for cancer, chemotherapy being an important component of treatment for cancer patients. However, its success is limited due to lack of selectivity for tumor cells over normal cells resulting in insufficient drug concentrations in tumors, systemic toxicity, and the appearance of drug-resistant tumor cells.[2] Several strategies have been proposed which include alternative formulations, for example, liposomes,[3] resistance modulation, for example, PSC833,[4] and antidotes/toxicity modifiers, for example, ICRF-187[5] and gene therapy. Recently, targeted therapy is gaining importance due to its specificity toward cancer cells while sparing toxicity to off-target cells. Targeted therapy aims at delivering drugs to particular genes or proteins that are specific to cancer cells or the tissue environment that promotes cancer growth. Effectiveness of the therapy lies in targeted release of therapeutics at the disease site while minimizing the off-target side effects caused to normal tissues. It is often used in conjunction with chemotherapy and other cancer treatments. Targeted therapy involves developing drugs that block cancer cell proliferation, promote cell cycle regulation, or induce apoptosis or autophagy and targeted delivery of toxic substances specifically to cancer cells to destroy them. Targeted therapy involves the use of monoclonal antibodies or oral small drugs.[6]

In a landmark review, Hanahan and Weinberg suggested that six essential alterations in cell physiology could underlie malignant cell growth.[7] These six alterations were described as the hallmarks of nearly all cancers and included, (1) self-sufficiency in growth signals, (2) insensitivity to growth inhibitory (antigrowth) signals, (3) evasion of programmed cell death (apoptosis), (4) limitless replicative potential, (5) sustained vascularity (angiogenesis), and (6) tissue invasion and metastasis. Genome instability, leading to increased

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mutability, was considered the essential enabling characteristic for manifesting the six hallmarks.[6] However, the mutation rate for most genes is low making it unlikely that the numerous pathogenic mutations found in cancer cells would occur sporadically within a normal human lifespan.[8] This then created another paradox. If mutations are such rare events, then how is it possible that cancer cells express so many different types and kinds of mutations? The loss of genomic "caretakers" or "guardians," involved in sensing and repairing DNA damage, was proposed to explain the increased mutability of tumor cells.[9,10] The loss of these caretaker systems would allow genomic instability, thus enabling pre-malignant cells to reach the six essential hallmarks of cancer.[6] It has been difficult, however, to define with certainty the origin of pre-malignancy and the mechanisms by which the caretaker/guardian systems themselves are lost during the emergent malignant state.[5] In addition to the six recognized hallmarks of cancer, aerobic glycolysis or the Warburg effect is also a robust metabolic hallmark of most tumors.[11-15]

In cancer research, each cancer sample presents the researcher with an altered genome that contains a unique and unpredictable number of point mutations, indels, translocations, fusions, and other aberrations. Since many of these alterations might never have been observed before and might not necessarily reside in coding regions of the genome, whole-genome sequencing is increasingly seen as the only rigorous approach that can find all the variants in a cancer genome. Among all these alterations only few showed progression of the disease. Based on the assumption that changes in gene expression levels impact disease progression, RNA-Seq is increasingly employed as a useful technique to determine if these genetic alterations impact disease progression. Genetic alterations have the potential to impact all cellular processes, including chromatin structure, DNA methylation, RNA splice variants, RNA editing, and microRNA (miRNA) to name but a few. Real progress in cancer research will come through the measurement and integrated analysis of all these interdependent processes.[16-19]

CANCER BIOLOGY

Every individual carries a unique set of inherited germline mutations. As cancer progresses, additional somatic mutations and genomic rearrangements accumulate.[20] These changes can trigger drug resistance and metastasis.[21] Increasing evidence suggests that these processes are deliberate, with a finite number of distinct mechanisms.[22] Longitudinal experiments, where samples are collected over the course of the disease, are useful to elucidate the mechanism of disease progression. These samples are commonly used to understand the causes of relapse[23] and drug resistance.

EROGENEITY

In some genes, mutations frequently occur in the same location, which may indicate a specific mechanism at work. However, in the majority of genes mutations can appear apparently randomly throughout the gene, which may reflect the failure of replication and repair mechanisms. Sequencing can detect mutations from both scenarios with equal facility.

METASTASIS

Metastasis is a complex process in which cancer cells break away from the primary tumor and circulate through the bloodstream or lymphatic system to other sites in the body.[24] At new sites, the cells continue to multiply and eventually form additional tumors comprised cells that reflect the tissue of origin. The ability of tumors, such as pancreatic cancer and uveal cancers, to metastasize contributes greatly to their lethality. Many fundamental questions remain about the clonal structures of metastatic tumors, phylogenetic relationships among metastases, the scale of ongoing parallel evolution in metastatic and primary sites, how the tumor disseminates, and the role that the tumor microenvironment plays in the determination of the metastatic site.[25]

GENOMIC MUTATIONS

All tumors accumulate somatic mutations during their development. Most common cancers are associated with diverse cancer genes that are mutated at a low frequency. One of the most striking observations from large cancer databases is the genetic heterogeneity among cancers and even within individual cancer types. However, it appears that a limited number of cellular pathways are central to tumor cell biology. Comprehensive catalogs of somatic mutations are being compiled for various cancer types to better understand the mechanisms that underlie this disease.[26]

MOSAICISM

Most of the mutations found in AML genomes are actually random events that occurred in hematopoietic stem/progenitor cells before they acquired the initiating mutation; the mutational history of that cell is "captured" as the clone expands. In many cases, only one or two additional, cooperating mutations are needed to generate the malignant founding clone.[27]

GENE EXPRESSION

Gene expression analysis measures the product of gene transcription, RNA processing, and epigenetic control. As a result, gene expression analysis provides an overview of the health of these processes as well as insight into molecular functions within the cell. Microarray-based mRNA analysis has been used extensively to study gene expression in cancer research, but the advent of sequencing-based mRNA analysis (mRNA-Seq) represents a quantum leap forward in the ability to measure and interpret the products of gene expression. The ability of mRNA-Seq to detect modified RNAs and RNAs expressed at very low levels makes it uniquely suited to cancer research. Methods based on mRNA-Seq can also detect very rapid changes in transcription, splice variants, fusion genes, and the use of alternative polyadenylation sites.[28]

ALTERNATIVE SPLICING

The biogenesis, development, and metastases of cancer are associated with many variations in the transcriptome. Cancer-

specific alternative splicing is a widespread phenomenon and a major post- transcriptional regulation mechanism that is involved in many types of cancer.[29]

RNA EDITING

In humans, differences between the sequences of DNA and RNA also called RNA editing – are wide spread.[30,31] The most frequent type of RNA editing is conversion of adenosine to inosine by adenosine deaminases acting on RNA. The splicing and translational machineries subsequently recognize the inosine as a guanosine. Some tumor genomes have a higher percentage of RNA-DNA differences than their matched normal genomes.[32]

miRNAs AND NON-CODING RNAS (ncRNA)

miRNAs range in size from 17 to 25 bp and are members of the ncRNA family. They regulate a variety of biological functions, including development, cell proliferation, cell differentiation, signal transduction, apoptosis, metabolism, and life span.[33-36] miRNAs suppress the gene's post-transcriptional expression through the interaction of the RNA-induced silencing complex with its target recognition sites in the 3'-untranslated region or the coding regions of the transcript.[37,38] Many miRNAs are located in genomic regions that are deleted or amplified in various cancer types, which indicate that they might play a prominent role in cancer progression. Editing sites have also been observed in miRNAs, suggesting a potential link between RNA editing and miRNA-mediated regulation.[39]

RNA-PROTEIN BINDING

In human cells, most mRNAs (or pre-mRNAs) are associated with heterogeneous nuclear ribonucleoparticle (hnRNP) proteins, forming large hnRNP-RNA complexes.[40] hnRNP proteins play a role in all crucial aspects of RNA processing, including pre-mRNA splicing, and mRNA export, localization, translation, and stability.[41-44] The hnRNP proteins of dozens of other RNA-binding proteins and genes are associated with cancer.[45]

CANCER CONSIDERATIONS

A good experimental design will optimize the performance of the technology to produce the most interpretable and robust results. This section is intended to highlight the unique characteristics of the biology and the technology that researchers should keep in mind when designing their experiments.

Experimental designs in cancer research offer some unique challenges. A typical tumor sample consists of two genomes: The germline inherited from the parents and the somatic mutations that accumulate during progression of the disease.[46]. The percentage of tumor cells in the sample can vary between 10% and 100%. The tumor genome is also dynamic and can accumulate *de novo* mutations rapidly. As a result, tumors can consist of several clonal types.[47] The number of samples involved in most currently published studies is very small and can be regarded as hypothesis generating. As more sequencing information becomes available, most cancer types can be divided into several subpopulations based on their molecular phenotype.[25] This severely decreases the power of the experiment and increases the number of samples required for a rigorous analysis. A partial solution is to use whole-genome sequencing in the discovery phase to find new mutations. In the second phase, whole-exome or targeted sequencing can be used to confirm the newly discovered mutations and determine their abundance in a large cohort. However, statistically rigorous whole-genome sequencing experiments in the future will likely be very large, requiring in the order of thousands of samples.[25]

SOMATIC MUTATION

There are three general approaches to detect somatic mutations in the cancer genome: Whole-genome sequencing, whole-exome sequencing, and targeted gene sequencing. The table below contains a brief summary of the advantages and disadvantages of the respective approaches.

WHOLE-GENOME SEQUENCING

Whole-genome sequencing of tumor-normal pair samples provides a comprehensive picture of all the unique mutations present in the tumor. It has become relatively inexpensive and fast to sequence complete genomes and it is an excellent choice for hypothesis-free discovery applications.[48]

EXOME SEQUENCING

Exome sequencing focuses only on 1%–2% of the genome that codes for proteins and is, therefore, less expensive to run and simpler to analyze. There have been many notable successes using this approach on Mendelian diseases. Although it produces only one-fiftieth of the whole-genome sequence, the cost saving is only half, due to the more expensive and labor-intensive processing of the genetic material. In cancer research, where gross genomic rearrangements are common, exome sequencing may miss key mutations.[49-51]

TARGETED RESEQUENCING

Targeted resequencing focuses on a restricted set of genes that were compiled based on some prior knowledge. Using only cancer relevant genes, the results are relatively easy to interpret and potentially actionable. A panel that contains the appropriate genes could be used on different cancer types to streamline laboratory processing and data interpretation. Larger studies in the future may show potential stratification of the patients according to disease progression, genetic profile, environmental exposure, or other factors. The studies to date indicate that this approach may have significant potential as a diagnostic tool.[52]

FORMALIN-FIXED, PARAFFIN-EMBEDDED (FFPE) SAMPLES

Tissue samples are commonly stored as FFPE preparations. In some cases, these may be the only samples available. FFPE samples yield relatively short DNA fragments, but they can deliver excellent results when the appropriate care is taken during collection, embedding, and storage. In addition, the method of nucleic acid isolation and sample preparation method for next-generation sequencing are also critical factors in the success of analyzing FFPE-derived samples.

CONCLUSION

Tumors commonly contain several clonal populations that reflect the ongoing accumulation of mutations. Single-cell genomic methods have the capacity to resolve these complex mixtures of cells. Molecular assays of tissues reflect an average signal of the population, or alternatively only the dominant clone, which may not be the most malignant clone present in the tumor. The clinical value of single-cell genomic methods will be in profiling scarce cancer cells, monitoring, and detecting rare clones that may be resistant to chemotherapy. These applications are likely to improve all three major themes of oncology: Detection, progression, and prediction of therapeutic efficacy. Cultured cell lines are versatile tools to study biological processes. When cell lines are cultured over a long period of time, they can be expected to accumulate mutations. Furthermore, the genetic bottlenecks that result from population reduction during the culturing process can significantly accelerate the accumulation of mutations. In a sample containing multiple clones, culturing can skew the relative abundance of the clones. Recent studies used deep sequencing to show that as many as 50% of the genomic variants that are seen in cell lines derive from low-frequency somatic genomic variants that are present in the parental fibroblasts. Next-generation sequencing provides a highly sensitive and precise tool that can help researchers distinguish between authentic biology and artifacts from the immortalization and propagation process to make these versatile models even more effective.

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