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Genomic therapy for the treatment of Cancer: A review

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Abstract

Gene therapy plays significant role in the cancer management .It has experienced considerable advancements. Multiple mutations in the cancer cell cause uncontrolled proliferation. Gene therapy selectively targets and destroys tumor cells for example Insertion of tumor suppressor genes and blocking the overexpression of oncogenes, which have been identified in cancer cells. Approximately two-thirds of the clinical trials in gene therapy have been aimed at the treatment of various types of cancers. Past and current scientific advances have facilitated development of selectively targeted vectors that are efficient in gene transfer and reduce off-target effects.

Key words: Oncogenes, Gene therapy, mutations

Introduction

Changes can trigger drug resistance and metastasis. Increasing evidence suggests that these processes are deliberate, with a finite number of distinct mechanisms.[1] 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.[1,2,3] 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.[3] Among all these alterations are a select few that drive the 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.[4,5] 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.[5] Real progress in cancer research will come through the measurement and integrated analysis of all these interdependent processes. The key characteristic of next-generation sequencing technologies is that billions of independent sequence reads are generated in parallel, with each read derived from a single molecule of DNA.[6]

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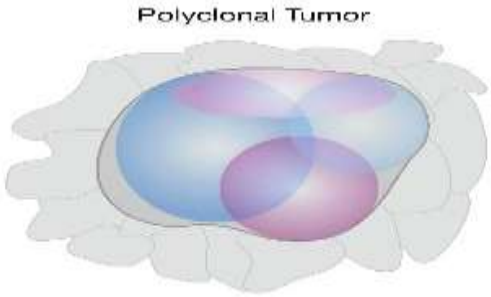
The resultant data approximate a random sample of DNA molecules which, in turn, represents the genomes of individual cells contained in the tumor sample.[6,7] This provides us with a powerful toolbox to untangle the causes and mechanisms of cancer.

Cancer Biology

Tumor Heterogeneity

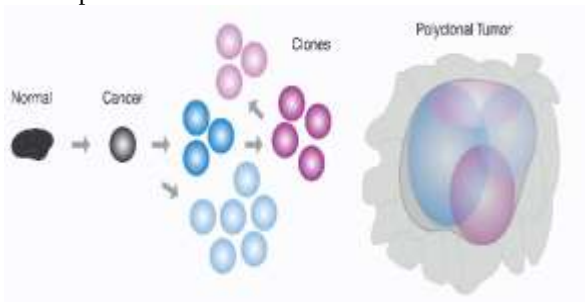
Every individual carries a unique set of inherited germline mutations. As cancer progresses, additional somatic mutations and genomic rearrangements accumulate.[6] These longitudinal experiments, where samples are collected over the course of the disease, are useful to elucidate the mechanism of disease progression. These samples are commonly used to understand the causes of relapse and drug resistance.[7,8]



A polyclonal tumor in a background of normal tissue. Most tumor samples contain a mixture of tumor and normal cells. The tumor itself may contain several different clonal types, each with a different response to therapy and potential for recurrence.

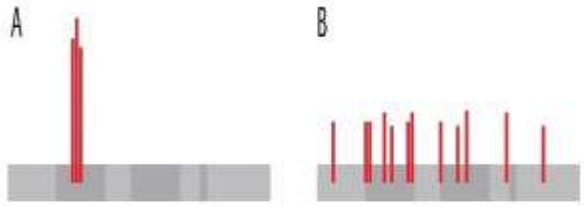
Tumor samples typically include normal cells, such as stromal cells, blood vessels, and immune cells.[9] Based

on conventional pathology estimates, most studies focus on tumors with >60% tumor nuclei present. To determine which mutations are unique to the tumor, a reference normal tissue sample from the same individual is usually included in the analysis. The tumor itself may be heterogeneous.[9,10,11] During cancer progression new mutations may occur in individual cells and these newly mutated cells can go on to proliferate and form clones. As a result latest age cancers often consist of polyclonal tumors, where each clone has a unique set of mutations, unique pathology, and unique drug responses. Deep sequencing has the sensitivity to detect clones comprising as little as 1% of the sample.[12]



Intratumor heterogeneity. The progressive accumulation of somatic mutations results in a heterogeneous polyclonal tumor in which different clones may respond differently to treatment.

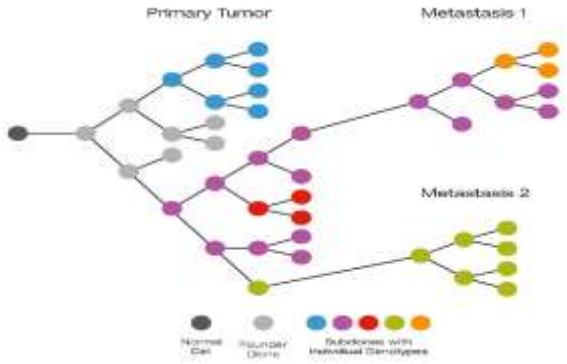
In some genes mutations frequently occur in the same location, which may indicate a specific mechanism at work.[13] However, in the majority of genes mutations can appear apparently randomly throughout the gene, which may reflect the failure of replication and repair mechanisms. Sequencing can detect mutations from both scenarios with equal facility.



Two hypothetical genes with two different mutation models. The dark boxes indicate exomes and the red bars indicate locations where mutations occur. Panel A: Recurrent mutations in a specific location may indicate the involvement of a biological mechanism to generate the mutations. Panel B: Scattered mutations occurring throughout the gene, such as P53, may be due to the failure of the replication and repair mechanisms. Sequencing can detect mutations generated in both scenarios.

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. At new sites, the cells continue to multiply and eventually form additional tumors comprised of cells that reflect the tissue of origin.[14,15] The ability of tumors, such as pancreatic cancer and uveal cancers, to metastasize contributes greatly to their lethality.[15] 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.[16,17]



Metastases can originate from either a major clone in the primary tumor (metastasis 1), or from minor clones (metastasis 2). Metastases can also undergo clonal evolution (as shown in metastasis 1).

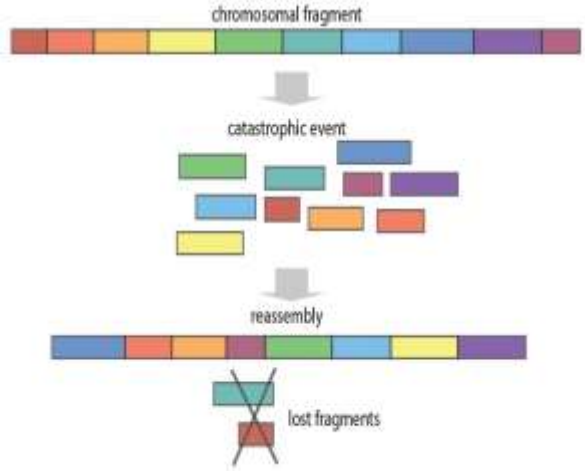
Genomic Mutations

All tumors accumulate somatic mutations during their development. Most common cancers are associated with diverse cancer genes that are mutated at a low frequency.[18] 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.[19,20] Comprehensive catalogs of somatic mutations are being compiled for various cancer types to better understand the mechanisms that underlie this disease.[21]

Chromothripsis

Chromothripsis is a one-off cellular crisis during which tens to hundreds of genomic rearrangements occur in a single event.[22] The consequences of this catastrophic event are complex local rearrangements and copy number variants where a limited range of two (or occasionally three) copynumber states are detectable along the chromosome.[23] This model of a single

catastrophic event is different from the typical model of cancer progression through the progressive accumulation of mutations. In a cancer progression model where mutations accumulate, there is no upper limit to the copy numbers, so it is common to see a wide range. It is estimated that chromothripsis occurs in 2%–3% of all cancers, across many subtypes, and in ~25% of bone cancers.[23,24,25]



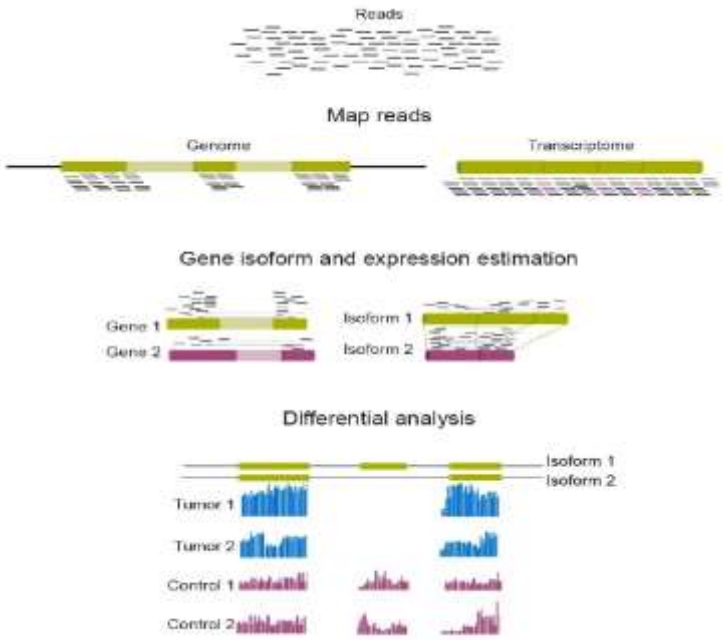
A pictorial representation of chromothripsis. Tubio JM (2011) Cancer: When catastrophe strikes a cell. Nature 470:476-7.

Gene Expression

Gene expression analysis measures the product of gene transcription, RNA processing, and epigenetic control.[26] 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.[27] Microarray-based mRNA analysis has been used extensively to study gene expression in cancer research,[27,28] 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.[29] The ability of mRNA-Seq to detect modified RNAs24 and RNAs expressed at very low levels makes it uniquely suited to cancer research.[30] Methods based on mRNA-Seq can also detect very rapid changes in transcription,25 splice variants, fusion genes, and the use of alternative polyadenylation sites.[31]

RNA Editing

In humans, differences between the sequences of DNA and RNA—also called RNA editing—are widespread.[32,33,34] The most frequent type of RNA editing is conversion of adenosine to inosine by adenosine deaminases acting on RNA (ADARs).[35] The splicing and translational machineries subsequently recognize the inosine as a guanosine.[36] Some tumor genomes have a higher percentage of RNA-DNA differences than their matched normal genomes.[37]



A typical bioinformatics pipeline for studying gene expression and alternative splicing in cancers using RNA-Seq. Short reads are first mapped to a reference genome or transcriptome. After mapping, the expression and splicing of the annotated genes and transcripts can be estimated. Feng H., Qin Z. and Zhang X. (2012) Opportunities and methods for studying alternative splicing in cancer with RNA-Seq. Cancer Lett in press

MicroRNA and Noncoding RNAs

MicroRNAs (miRNAs) range in size from 17 to 25 bp and are members of the noncoding RNA (ncRNA) family.[38] They regulate a variety of biological functions, including development, cell proliferation, cell differentiation, signal transduction, apoptosis, metabolism, and life span.36-37 miRNAs suppress the gene's post-transcriptional expression through the interaction of the RNA-induced silencing complex (RISC) with its target recognition sites in the 3'-untranslated region (3'-UTR) or the coding regions of the transcript.[39] 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.[40] Editing sites have also been observed in miRNAs, suggesting a potential link between RNA editing and miRNAmediated regulation.[41] The ease of measurement, relative stability, and role in the control of large numbers of

mRNAs make miRNAs attractive markers for the detection and staging of cancer during diagnosis and treatment.42 miRNA preparation and detection have become routine and users can expect very high sensitivity and specificity from the manufacturers' protocols.[42,43,44]

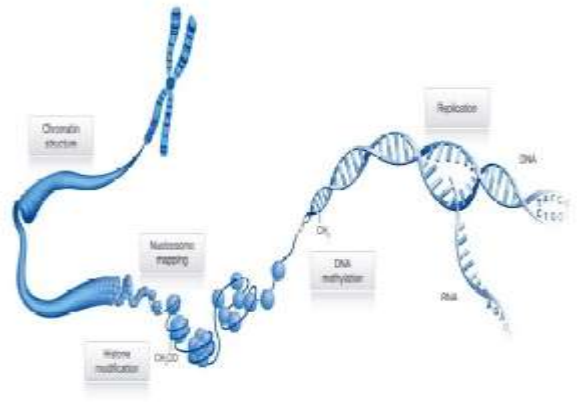
RNA-Protein Binding (CLIP-Seq)

In human cells most mRNAs (or pre-mRNAs) are associated with heterogeneous nuclear ribonucleoparticle (hnRNP) proteins, forming large hnRNP-RNA complexes.44 hnRNP proteins play a role in all crucial aspects of RNA processing, including pre-mRNA splicing, and mRNA export, localization, translation, and stability.[45-46] The hnRNP proteins of dozens of other RNA-binding proteins (RBPs) and genes are associated with cancer.[47]

RNA-protein interactions can be measured with cross-linked immunoprecipitation sequencing (CLIP-Seq). In CLIP-Seq, cells are treated with ultraviolet light to covalently cross-link RBP-RNA complexes. The cells are then lysed, the RBP-RNA complexes are immunoprecipitated, and the RNA sequenced.[48]

Epigenetics and Methylation

Epigenetic changes during cancer progression are associated with aberrant gene expression. Recent evidence indicates that epigenetic changes may play a role in cancer initiation. Epigenetic control is mediated thorough multiple processes, including DNA modification via methylation or acetylation, histone modification, and nucleosome remodeling.[49] Mutations in genes that control the epigenome are surprisingly common in human cancers.[50] Next-generation sequencing provides an extensive set of tools to map mutations and measure their impact on cancer progression.[51]



Genetic mutations in epigenetic modifiers in cancer. Mutations in the three classes of epigenetic modifiers are frequently observed in various types of cancers, which highlight the crosstalk between genetics and epigenetics. Mutations of epigenetic modifiers have the potential to cause genome-wide epigenetic alterations in cancer. Understanding the relationship of genetic and the epigenetic changes will offer novel insights for cancer therapies.

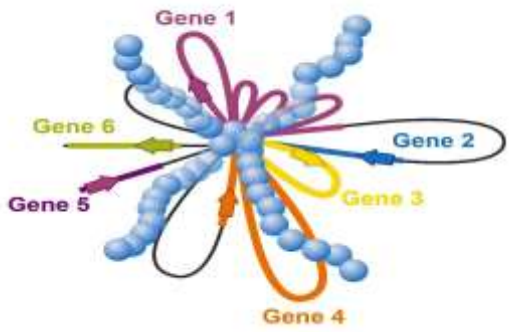
DNA Modifications

DNA modifications can be readily determined via a variety of techniques. The choice of technique depends on the throughput and resolution required.

Technique	Characteristics
Whole-genome bisulfate sequencing (BS-Seq or WGBS)	In bisulfite-treated DNA, unmethylated cytosines are converted into thymidines.[50] Nextgeneration sequencing provides a complete overview of CpG methylation level at base pair resolution.
Reduced-representation bisulfite sequencing (RRBS) or restriction enzyme-enriched sequencing (rrBS-Seq)	RRBS involves digesting DNA with a methylation-insensitive enzyme to enrich the sample for CpG islands. The CpG-enriched sample is then bisulfite-treated and sequenced. RRBS is an efficient technique that is suitable for obtaining information from most CpG islands and information about sequences outside CpG-rich regions.[51-52]
Affinity-enrichment-based sequencing techniques (MBD-Seq or MeDIP-Seq)	MBD-Seq and MeDIP-seq combine the advantages of next-generation sequencing and enrichment of methylated regions by immunoprecipitation.[53,54]
DNA methylation arrays	CpG-specific array technology is an alternative option for determining a genome-wide DNA methylation profile. The Human Methylation 450 beadchip assay (Illumina) covers 99% of all human RefSeq55 genes and approximately 450,000 CpGs overall.[56]
Locus-specific DNA methylation analysis	In addition to genome-wide technologies, locus-specific identification of the DNA methylation level is a cost-effective strategy, especially if single genes are already established as biomarkers for diagnosis or prognosis.[57]

Chromatin Structure and Rearrangements

Chromosomal rearrangements require formation and joining of DNA double-strand breaks. These events disrupt the integrity of the genome and are frequently observed in leukemias, lymphomas, and sarcomas.[58,59] The recurrence of gene fusions between specific genes in multiple individuals indicates that those genes must be physically close at some stage in the cell cycle.[60,61]



A hypothetical three-dimensional, transcriptionally active complex containing dense looping positions. This schematic diagram is based on the looping events detected, assuming that all looping events can occur in a single cell. In this model, all small loops converge onto a common core base (blue spheres). Loops reduce the physical size of the active transcriptional complex to enhance the accessibility of transcription factors to specific genomic sites. Kohwi-Shigematsu T., Kohwi Y., Takahashi K., Richards H. W., Ayers S. D., et al. (2012) SATB1-mediated functional packaging of chromatin into loops. Methods 58: 243-254

Integrative Analysis

All biological processes are interconnected, and every change in one process in the cancer cell impacts all other processes. A mutation can impact the activity of an expressed protein,[62,63] which in turn can impact the methylation of DNA, which in turn can impact the expression of many other genes and so on.[64] The vast number of mutations that are unique to every individual, when coupled with this chain of events, gives insight into the wide range of disease phenotypes that characterize many cancers. [65]An integrated analysis is a step towards reflecting the true complexity of cancer biology. Researchers now have the ability to measure most of these processes individually, but real progress in the understanding and treatment of cancer will come from an integrated analysis of all these processes.[66]

Technical Considerations

There are three general approaches to detect somatic mutations in the cancer genome: whole-genome sequencing, whole-exome sequencing, and targeted gene sequencing.[67,68] The table below contains a brief summary of the advantages and disadvantages of the espective approaches. In a comparison between whole-genome and exome sequencing in a multiple myeloma study, half of all the protein-coding mutations occurred via chromosomal aberrations such as translocations, most of which would not have been discovered by exome sequencing alone.[69,70] Targeted resequencing is a useful technique to catalog variants of known cancer-related genes in very large cohorts. In the long run, as knowledge of the genome grows and the ability to handle and interpret the large data sets improves, whole-genome sequencing will clearly be the optimal approach for molecular characterization of tumors. In the immediate future, targeted gene sequencing can map drugs already on the market to patients who can derive immediate benefit from them.[71-72]

Approach	Advantages	Disadvantages
Whole-genome sequencing	Comprehensive view of whole genome Can detect all types of mutations including structural variants Standardized processing and analysis for all patients and all tumor types Does not require any prior knowledge of the disease	More expensive Large dataset presents a challenge for data management, analysis and interpretation Findings may not be actionable Risk of incidental findings Shallow sequencing less sensitive than targeted approaches
Whole-exome sequencing	About half the cost of whole-genome sequencing Small data set is easier to manage, analyze and interpret Standardized processing and analysis for all patients and all tumor types Will detect indels, SNPs and CNVs	Only 1.5% of the genome is sequenced May miss fusion genes and oncogenes73 Findings may not be actionable Risk of incidental findings

	Does not require any prior knowledge of the disease Provides deep sequencing with good sensitivity for rare clones	
Targeted gene sequencing	Cost-effective Results are easy to interpret Findings actionable for cancer-relevant genes Very deep sequencing with very high sensitivity for rare clones	Will miss many mutations Requires a prior knowledge of the genes of interest Delays diagnosis of patients with rare tumors that are not represented on the panel

Conclusion

In the not too distant future, genomic features of every patient's cancer type will be characterized at the point of diagnosis. A list of implicated cancer genes and mutational processes will be generated, and a personalized therapeutic regimen will be chosen. One of the major challenges to this vision is how to sample the cancers to attain an accurate view of the underlying complexity and to address the fact that cancers are highly dynamic evolutionary processes. A single sample is a 'snapshot' in space and time. Multi-region sampling and sampling of distinct metastatic sites will help to reduce the problem posed by geographical heterogeneity but will have to be balanced with clinical risk and patient choice. It is necessary to acknowledge that even with the most sensitive and accurate of genomic technologies, clinically important mutations that are confined to subclones may be missed on account of inadequate sampling. The clinical approach towards sampling will therefore be guided by multi-sampling studies within all cancer types, and in particular important insights may be gained from studies that use sequential time-ordered sampling of cancers with well-defined precursor lesions, such as cervical intra-epithelial neoplasia in cervical cancer and Barrett's oesophagus in oesophageal cancer.

Understanding how the cancer genome responds to treatment and promotes metastasis presents a further challenge, requiring longitudinal sampling strategies incorporated into long-term clinical trials. Furthermore, the optimal targeted therapeutic approaches to cancers with branching evolutionary architectures remains unclear. The observation that any individual cancer may contain both clonal driver mutations (that is, mutations that occur within the phylogenetic tree trunk) and subclonal driver mutations, which are linked through epistatic interactions, indicates that cancer eradication may well demand complex combinations of drugs.

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