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Evolution of cancer genomics and its clinical implications

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Muhammad Tawfique
Pediatrics and Pediatric Hematology and Oncology, Bangladesh Specialized Hospital, Bangladesh

Correspondence: Muhammad Tawfique, Pediatrics and Pediatric Hematology and Oncology, Bangladesh Specialized Hospital, 21 Shyamoly, Mirpur Road, Dhaka 1207, Bangladesh, Email mtawfiqe@gmail.com

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Introduction

Genomics is defined as the study of genes and their functions, and related techniques while genetics is the study of heredity.[1,2] The main difference between genomics and genetics is that genetics scrutinizes the function and composition of the single gene whereas genomics addresses all genes and their inter-relationships in order to identify their combined influence on the growth and development of the organism. Thus, genomics is an interdisciplinary field of biology that focus on the structure, function, evolution, mapping, and editing of genomes. A genome is an organism's complete set of DNA, including all of its genes. It refers to the study of individual genes and their roles in inheritance. Objectives of genomics are collective characterization and quantification of all of an organism's genes as well as their interrelationship and influence on the organism.[3] Genes may direct the production of proteins with the assistance of enzymes and messenger molecules. In turn, proteins make up body structures such as organs and tissues as well as control chemical reactions and carry signals between cells. Genomics also involves the sequencing and analysis of genomes through uses of high throughput DNA sequencing and bioinformatics to assemble and analyze the function and structure of entire genomes.[4]

First human genome project

The human genome project was an international scientific research project with the goal of determining the base pairs that make up human DNA and of identifying and mapping all of the genes of the human genome from both a physical and a functional standpoint. After the idea was picked up by in 1984 by the US government when the planning started, the project formally launched in 1990 and was declared complete on April 14, 2003. A parallel project was conducted outside the government by the Celera Corporation, or Celera Genomics which was launched in 1998.[5] Omic technologies adopt a holistic view of the molecules that make up a cell, tissue or organism. They are aimed primarily at the universal detection of genes (genomics), mRNA (transcriptomics), proteins (Proteiomics), and metabolites (Metabolomics) in a specific biological sample in a non-targeted and non-biased manner. Genomics is the systemic study of an organism's genome. The genomic is the total DNA of a cell or organism. The human genome contains 3.2 billion bases. The transcriptome is the total mRNA in a cell or organism and the template for protein synthesis in a process called translation. The transcriptome reflects the genes that are actively expressed at any given moment. The proteome is defined as the set of all expressed protein in a cell, tissue or organism. Metabolomics can generally be defined as the study of global metabolite profile in a system (Cell, tissue or organism) under a given set of conditions.[6]

Cancer genomics or Oncogenomics is the part of genomics that characterizes cancer-associated genes taking into account genomic, epigenomic (define possibly earlier near genomics definition), and transcript alterations in cancer. Cancer is a genetic disease caused by accumulation of DNA mutations and epigenetic alterations leading to unrestrained cell proliferation and neoplasm formation.[7] The goal of oncogenomics is to identify new oncogenes or tumor suppressor genes that may provide new insights into cancer diagnosis, predicting clinical outcome of cancers and new targets for cancer therapies. The success of targeted cancer therapies such as Gleevec, Herceptin and Avastin raised the hope for oncogenomics to elucidate new targets for cancer treatment.[8]

In addition to developing an understanding of the underlying genetic mechanisms that initiate or drive cancer progression, oncogenomics targets personalized cancer treatment. Cancer develops due to DNA mutations and epigenetic alterations that accumulate randomly. Identifying and targeting the mutations in an individual patient may lead to increased treatment efficacy.

The completion of the Human Genome Project facilitated the field of oncogenomics and increased the abilities of researchers to find oncogenes. Sequencing technologies and global methylation profiling techniques have been applied to the study of oncogenomics also.

Evolution of cancer genomics

The first real stride towards understanding of cancer genomics occurred in 1985 when the concept that knowing cancer cell function requires the untangling of the whole of cellular complexity was realized. Evidence that mutation of normal genes could lead to cancer led researchers to appreciate the value of knowing the sequence of whole human chromosomes as the basis of understanding of cancer.[9]

The journey progressed through its initial stage in 1986 when merely knowing a single gene sequence of 1 kb was remarkable and knowing the whole human genome was a far-fetched possibility. The completion of human reference genome became the reality in 20037 when a finished human genome reference was available to assist in unravelling the basis of genetic derangement that lead to cancer. During the period from 1990 to 2003 cancer researchers used variety of cloning strategies, improved their sequencing abilities, and as a result identified the most of the potent oncogenes and tumor suppressor genes. Since then through this process, an inventory of 291 cancer genes have discovered by the researchers.[10] With the base resolution of the human reference genome, the large scale study of mutation has progressed and the promise of identification of all the cancer genes peculiar to each and every cancer has become very much within

possibility.[11,12] As yet using the whole genome sequence (WGS) is not a routine practice for diagnostic, therapeutic and prognostic purposes.

Using PCR and dye-terminator sequencing, each coding exon of 18000 genes defined by human genome sequence, eleven oncogenes? for breast and colorectal cancer have been disclosed.[13] This has allowed for the first time in history to have a comprehensive view of entire cancer gene for a particular cancer in a cohort and was made possible by Whole Exome Sequencing (WES). WES today has additional advantages over WGS in that the average depth of coverage is fivefold greater, with the cost of sequencing, data processing, and storage were much less. As a result, the period from 2004 to 2013 resulted in many tumor types being analyzed in large cohorts (100 to 500 patients). Both WGS and WES have given a great deal of insight into genetic basis of cancerogenesis. In this regard it was found that by using WGS, genetic alterations observed in the DNA of the cancer cells span from single-base point mutation to chromosome-scale amplification.[14] With these tools in hand, the Cancer Genome Atlas (TCGA), the Cancer Genome Project, the International Cancer Genome Consortium (ICGC) Therapeutically Applicable Research to Generate Effect Treatments and other privately funded large scale projects[15] began to catalog all the mutations in a wide variety of cancers in both the adult and pediatric oncology.[16] Today, WGS and WES sequencing technology have been augmented by cDNA sequencing (referred to as RNA sequencing). These are now able to explore transcriptome. Besides gene expression levels RNA-seq allows aberrant splicing, chimeric gene fusion transcripts characteristic of cancer cells and expressed mutations.[17–23] Analysis of chromatin frequency has just been started and this Microarray and next-generation sequencing techniques which allow whole genome analysis of chromatin structure and sequence-specific protein binding are revolutionizing our view of chromosome architecture and function.[24]

Implications of cancer genomics

Three fundamental categories of cancer genomic aberrations—base mutation, copy number alteration (gain or loss), and translocation/rearrangement—had been discovered by the mid-1980s. Epigenetic modifications of genomic DNA or histones by methylation, acetylation, and other mechanisms also became recognized as key mediators of the cancer phenotype. Knowledge of cancer genes perturbed by hallmark structural genomic changes continues to accumulate steadily. However, genome-scale approaches to identify recurrently mutated cancer genes required a revolution in technology and analytic capacity that began during the 1990s and has continued unabated to the present day.[25] The human genome era heralded a fundamental shift toward global views of genomes and transcriptomes in human biology and disease; the shift was made possible by increasingly powerful experimental and analytic methodologies (Figure 1). By the late 1990s, oligonucleotide microarrays and high-throughput DNA sequencing began to provide unprecedented insights across entire cancer genomes and their compendia of expressed genes. These advances, coupled with integrative computational approaches, enabled a massive acceleration of discoveries that linked each major class of tumor genomic alteration to critical functional roles in many cancer types.[26]

Genomic alterations that give rise to cancers occur at both the RNA and DNA level. Interrogation of the many types of changes and consequent pathway dysregulation has been restricted to date, in part as a result of limiting technologies. Massively parallel sequencing is one emerging technology that enables the myriad cancer-causing alterations to be interrogated on a tumor-by-tumor basis. FISH, fluorescent in situ hybridization; PCR, polymerase chain reaction.

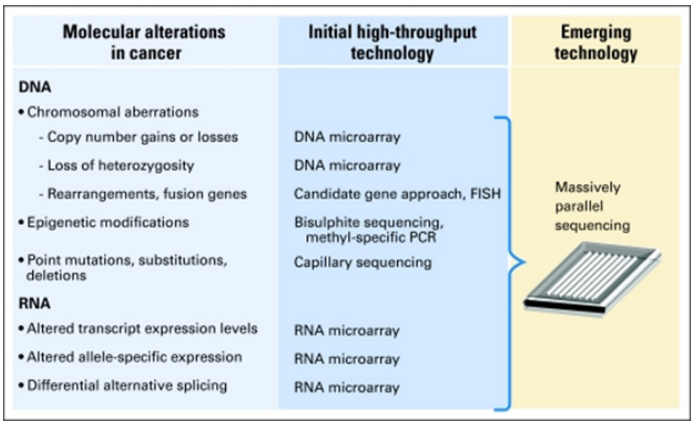

Figure 1 Interrogating molecular alterations in cancer.

Different groups had begun systematic exon resequencing in cancer by the year 2002. Initially, the aim was to prioritized gene families such as protein kinase and lipid kinases. Activating mutation within BRAF was one of the first important discoveries that emerged from systematic tumor sequencing. BRAF encodes a serine/threonine kinase oncogene which is known to transmit proliferative and survival signals downstream of RAS in the mitogen activated protein (MAP) cascade.[27] BRAF mutations (most commonly involving a valine-to-glutamic acid substitution at codon 600) are observed in more than 50% of cutaneous melanomas and are also found in colon cancer, papillary thyroid cancer, and other malignancies. Subsequent work identified the activating point mutations in PIK3C25—a catalytic subunit of PI3 kinase—in almost one third of the breast and colon cancers which was also present in endometrial and ovarian cancers, among others. The next important finding was activating point mutations and small insertions/deletions in EGFR. EGFR is an oncogene that encodes a receptor tyrosine kinase, in 10% to 15% of non–small-cell lung cancer in whites and approximately 25% of non–small-cell lung cancer in patients of East Asian descent.[28–31] It is important to note that the receptor tyrosine kinase family along with the MAP kinase and PI3 kinase cascades encompasses the most important known signal transduction mechanisms that rule over tumor cell growth and survival. This decisive genetic evidence demonstrated the results of base mutation discovery through systematic DNA sequencing. This illustrated the pathways playing crucial roles in formal of tumors and their maintenance. This also opened up new avenues for the rational deployment of targeted therapeutics.

Advances in microarray technology enabling exploration of copy gains, deletions, and loss of heterozygosity paved the ways in analyzing somatic DNA copy number variations in cancer. (Figure 1). The advance here was noteworthy as it involved the integration of high-resolution chromosomal copy number information with gene expression data which enabled the discovery of MITF as an amplified oncogene in melanoma.[32] MITF is the member of a new class of oncogenes (termed lineage survival oncogenes) that uncovered the tendency of several tumor types to co-opt developmental lineage-restricted survival mechanisms for tumor maintenance functions.[32] As analyses continued chromosomal copy number data identified NKX2-1 and SOX2 which are regarded as lineage survival oncogenes

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amplified in a significant proportion of lung adenocarcinomas[33] and lung/esophageal squamous cancers,[34] respectively. This is the way how the role of lineage dependency, as a novel tumor survival mechanism ratified by chromosomal aberrations, was beautifully demonstrated through systematic analyses of global chromosomal copy number data.[35,36]

Systematic chromosomal copy number analyses also produced findings in hematologic malignancies when using high resolution single nucleotide polymorphism arrays in a genome-scale survey of pediatric acute lymphoblastic leukemia (ALL). Samples found that PAX5 and other prominent transcriptional regulators of B lymphocyte differentiation were recurrently deleted or disrupted in this malignancy.[37] Moreover, in the BCR-ABL1 translocation–positive subset of ALL, deletions of the IKZF1 gene encoding the transcription factor Ikaros, another key B-cell developmental regulator, occurred in more than 80% of patients.[38] IKZF1 alterations were also predictive of poor outcome in pediatric patients with ALL.[39] All these findings suggested that genesis of lymphoid leukemias are the results of dysregulation of normal cellular pathways that direct B-cell lineage maturation.

The first published reports of complete cancer genome sequencing focused on individual genomes in acute myeloid leukemia,[38,39] metastatic breast cancer,[40] melanoma,[41] and small-cell lung cancer.[42] These efforts identified IDH1 gene mutations in 16% of cytogenetically normal AML samples,[38] thereby extending results of an earlier genome-scale sequencing effort that found IDH1 mutations in 12% of glioblastomas.[43] IDH1 encodes an isoform of isocitrate dehydrogenase, a key enzyme in the citric acid cycle. Although the role of IDH1 in carcinogenesis remains to be fully elucidated, the discovery of recurrent mutations in this gene highlights the increasing importance of altered cell metabolism in the regulation of tumorigenesis.[44]

Clinical insights from cancer genome characterizations

Elaboration of the many oncogenes and tumor suppresser genes targeted by tumor genomic alterations resulted in progress regarding cancer genetics, tumor biology and drug development which opened up the way yielding three cardinal principles of immense clinical significance of cancer genomic analysis. With the discovery of cancer genomes the magnitude of its intricacy and density is being expressed. Considering the thousands of base mutations and hundreds of copy number alterations and rearrangements, there must alterations which play no significant role in genesis of tumor. These are called Passenger alterations. Driver events at the genomic levels also need to be identified. These Driver events are the keys to influence the viability and clinical behavior of a given tumor. Statistical first principles were adopted to identify the driver genes and in doing so, individual background mutation rates and regional variation in mutation rates across the genome were considered.[45]

Again this is not the whole story. There are many somatic mutations that show evidence of positive selection during evolution of tumors and these are low frequency events in genomic levels.[46,47] Therefore, epigenetic and other regulatory mechanisms contribute to the genetic mechanisms to express tumors. These low frequency events can again be identified as relatively frequent when these are judged by protein family or molecular pathway level.[48,49] Thus with the help of evolving statistical and other analytical methods the proliferation of complete genome sequencing across thousands of tumors over the next few years seems possible.

Despite the pre-existing ideas that complexity of alterations of cancer genome within a single tumor might be a hindrance therapeutically, it is now evident that many a tumors now are highly dependent on the function of even a single oncogene although there are many coexistent genomic and epigenetic alterations. This phenomenon was described in papers by Weinstein[50] and Weinstein and Joe.[51] This is the cellular context in which the signaling network is deranged to the extent that a mutated oncoprotein here that plays a more essential role in the malignant setting than that of their normal counterpart. This may provide a wider space for the targeting agents to work on the target cellular events to control the growth and survival of tumors. To cite an example, the loss of PTEN tumor suppressor gene results from dysregulation of P13 kinase activation. Yet in this case it is a little bit different in that a loss of a tumor suppressor is important here, not the presence of a mutated oncoprotein.

Tumor dependencies may coexist or induced by index driver genomic alterations. These dependencies involve molecular mechanisms from the driver events themselves. This gave rise to the notion of synthetic lethality in which such dependencies might be targeted in therapeutic interventions to control tumor growth.[52] Here two genes are synthetically considered lethal to one another if an alteration affecting one or the other gene individually is compatible with survival but alterations in both the genes cause cell death.[53] Research is currently seeking to revealing like mutated KRAS driver oncogene corresponding protein found refractory to a number of drugs but its synthetic lethal partners have now been identified.[54–56] Other examples include poly-adenosine-diphosphate-ribose polymerase (PARP) inhibitors in BRCA1 or BRCA2-mutated breast ,ovarian, and prostate cancers.[57,58]

Targeted therapies for major clinical responses in genetically defined tumor subtypes

The ultimate goal of all the knowledge on cancer genomic is to guide cancer research activities to bring about the treatment options and to predict the outcome of therapeutic responses in each of the cancers, The success with the all-trans-retinoic acid drew the early conceptions in treating acute promyelocytic leukemia (characterized by chromosomal translocations involving retinoic acid receptor alpha, the target of all-trans-retinoic acid)[59,60] and transtuzumab in ERBB2-amplified breast cancer (ERBB2 encodes HER2/new, the target of Trastuzumab).[61] The success of Imatinib Mesylate, a selective ABL tyrosine kinase inhibitor, in treating Chronic Myelocytic Leukemia carrying BCR-ABL fusion gene, looked a strong clinical evidence in favor of targeted therapy.[61–63] The ability of Imatinib to evoke the responses in the patients with GI stromal tumor (GIST that contains the oncogene mutation gene in KIT, another target of Imatinib) proved its success in an aggressive malignant tumor. The generalization of the effects of TKI was illustrated by the success of Erlotinib, a small molecule TKI, that inhibits epidermal growth factor receptor (EGFR) in patients with non-small-cell-lung cancer whose tumors contained activating EGFR mutations.[64] This provided a strong support in a genetically defined lung cancer subtype for the significance of genome based cancer treatment paradigm. Further supporting evidence of pharmacologic efficacy in multiple lineage of tumors carrying the similar mutation have been demonstrated in studies of imatinib or Nilotinib in KIT mutation containing melanoma as well as GIST.[65,66]

Although Tyrosine Kinase Inhibitors (TKI) by its ability to cause inhibition in greater breadth of molecular functionality could bring about the desired effect to control the tumor growth the other

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agents targeting the driver mechanisms lack the functional breadth of such magnitude as of TKI and failed to produce the similar clinical impact. The failure of Sorafinib to stop the growth of Melanoma has highlighted this view.[67,68]

From this discussion it becomes clear that driver genomic alterations within individual tumors can define patient categories that derive substantial result from targeted therapeutic regimen. Genomic profiling of tumors is also of benefit in defining subpopulations that are unlikely to get the result from targeted therapy. The observations that tumors resulting from KRAS mutations fail to respond to EGFR-targeted therapy clearly illustrated this view.[69] This is the foundation of concepts that constitutes the basis of the individualized cancer treatment. Table 1 here summarized the so far identified cancer genes and corresponding targeted therapeutic agents.

Table 1 Genomic alterations and corresponding cancer genes

Genomic Alterations	Cancer genes	Type of Cancer	Targeted agents
Translocations	BCR-ABL	CML	Imatinib
	PML-RAR α	APML	All-trans-retinoic acid
	EML4-ALK	Breast, Colorectal, Lung	ALK inhibitor
	ETS gene fusions	Prostate	
	Other	Leukemias, Lymphomas, Sarcomas	
Amplifications	EGFR	Lung, colorectal, glioblastoma, Pancreatic	Cetuximab, Gefitinib, erlotinib, Panitumumab
	ERBB2	Breast, Ovarian	Lapatinib Trastuzumab, Ipatinib
	KIT,PDGFR	GISTs, Glioma, HCC,RCC,CML	Imatinib, nilotinib, sunitinib, sorafenib
	MYC	Brain, colon, leukemia, lung	
	SRC	Sarcoma, CML, ALL	Dasatinib
	PIK3CA	Breast, Ovary, colorectal, endometrial	P13-kinase inhibitors
Point Mutation	EGFR	Lung,Glioblastoma	Cefuximab, Gefitinib, Erlotinib, Panitumumab, Lapatinib
	KIT, PDGFR	GISTs, Glioma, HCC,RCC,CML	Imatinib, nilotinib, sunitinib, sorafenib
	PIK3CA	Breast, Ovary, colorectal, endometrial	P13-kinase inhibitors
	BRAF	Melanoma, Pediattric Astrocytoma Colorectal, Pancreatic, GIT, Lung	RAF inhibitor
	KRAS		Resistance to erlotinib, Cetuximab(colorectal)

Vision for personalized cancer medicine

Genomic view of cancer has illustrated the need of re-evaluation of the prevailing clinical oncology status. In this new shift of paradigm diagnostic and therapeutic principles are governed by underlying genetic changes. A rigorous and vivid genomic view could elaborate the driver genetic events, identifying critical dependencies, stratify the patients with cancer for targeted therapeutic implementation. Profiling each and every patient comprehensively on the basis of clinically actionable genomic alterations gives the visionary idea of personalized cancer medicine. Response of colorectal cancers to EGFR-directed therapies targeting multiple genetic alterations is the example of benefit of profiling tumor mutations at genomic level.[70–72]

Advent of advanced diagnostic tests capable of reading various genomic information is necessary for individualized cancer treatment. These tests must be efficient and cost-effective. These should enable us to set large panel of oncogenes and tumor suppressor genes for the presence of driver alterations and they should detect all major category of tumor genomic alterations. It should also be able to detect mutation in DNA levels.[72–74] Although this profiling has been done in small fraction of informative cancer genes in a limited number of tumors the advancement is likely to progress in phases to detect the whole genome profile of all the individual cancers.

Conclusion

With the advent of new and powerful tools to unravel the human complex genome sequence, cancer genomics has started to move increasingly faster during the last half a century. So far, a limited number of genetic mechanisms have been discovered but has been limited to a few tumors including CML, APML, melanomas, breast cancers and lung cancers. The human civilization is on the verge of the ocean of the genomic data to be disclosed by the rigorous efforts through the help of newly invented sequencing methods. Methods need to be within the affordable reach of the mass people as well as

reliable and simple. The physicians and the lab personals need to be trained and skilled enough to prepare for service in the era of these newer approaches to cancer care. Similarly, mass populations need to be oriented on the beginning of a fresh system regarding diagnosis and treatment of cancer patients.

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Conflicts of interest

The authors declared there is no conflict of interest.

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