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Cancer Genomics and P3 Medicine

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Editorial

Cancer is a disease of the genome. The first evidence for the role of genetics in cancer causation was identification of Philadelphia chromosome in chronic myeloid leukaemia [1] and now we are in such a state that we can create neoplastic cells in the laboratory through genetic manipulation of normal cells. Normal cells can be transformed into cancer cells by introducing few genes (hTERT, Ras, large T oncoprotein of simian virus 40, etc.) in embryonic cells or telomerase negative cells [2]. De novo neoplastic transformation is initiated by a genetic lesion due to an error occurring during normal cell division. This initial event provides a platform for other genetic lesions to develop in due course of time. When the proper combination of genetic lesions accumulates in cell, it becomes malignant. Neoplastic cells possess numerous chromosomal (aneuploidy, polyploidy, rearrangements, deletions, amplifications, etc.) and/or genomic (mutations, small deletions and small insertions) and/or epigenomic (promoter/euchromatin hypermethylation, heterochromatin deacetylation, miRNA, etc.) alterations. This genomic changes are multi steps process and mainly due to failure in check points of cell cycle regulation. Genomic and epigenomic abnormalities are more with malignant and metastatic tumors than benign tumors. The hallmark of cancer cells are genetic instability, self-maintained replication, neo-angiogenesis, invasion and metastasis and longer survival. Furthermore, every cancer patient is different, every tumor is different, every tumor cells with 100s of genomic/epigenomic abnormalities (more with lung cancers, melanomas, etc. and few with medulloblastoma, testicular germ cell tumour, acute leukaemia, carcinoids, etc.) and every tumor cell is different as their genetic alterations are unstable i.e., dynamic in nature. Hence, there is a need to know phenotype/genotype correlation to find out genetic prognostic markers individually in a given point of time (will alter in due course of time). Recurring chromosome abnormality of cancers can assist in diagnosis, sub-classification and selecting appropriate treatment (including targeted therapy viz., tyrosine kinase inhibitor for ABR/BCL fusion positive chronic myeloid leukaemia, Her2/neu receptor blocker/ trastuzumab in Her2/neu positive breast cancers, etc.) besides as an independent prognostic factor. Certain chromosome abnormalities/ genetic changes are associated with a good prognosis, whereas others with poor outcome. Cancer cytogenomics provides disease-specific information to the attending physician and enables to design patient-specific protocols for disease intervention. Now, in many protocols, treatment decisions are based to some extent on molecular analysis of malignant cells. Genomic changes should disappear (normal newer cells with death/disappearance of neoplastic cells) following completion of successful treatment. Hence, genomic markers should be looked upon during treatment as well as during follow-up period to declare complete remission or relapse [3]. Second line of treatment can be instituted much earlier than present approach in case of persisting genomic changes after therapy. Despite extensive information on cancer; very little is progressed in cancer survival in last few decades. Increase in survival mostly related to early detection (down staging) and preventive measures.

Retrospection on previous techniques (conventional FISH/PCR based) reveals that these methods provided either focused information and/or with limited resolution on cancer cells. Present thrust is for global approach (i.e., whole genome high resolution) through genomics, epigenomics, proteomics, etc., platforms. The present decade is observing breath-taking advances in the characterization of point mutations and structural alterations including copy number variations, loss of heterozygosity, etc. in a wide range of cancers; all thanks to the aCGH (array comparative genomic hybridization/DNA array) and NGS (next generation sequencing) technologies. Increasingly, the complete genome sequences of a large number of cancer types are being obtained (through cancer genome project), providing us with a comprehensive view of cancer development pathways. Soon we can construct genomic profiles of cancer and in near future we will know where to target and how to target different cancer in different patient (individualized targeted therapy including targeting cancer stem cells and principal/driver pathways). Cancer genome analysis is expected to have a far-reaching impact on our understanding of cancer biology and will likely prompt newer medical approaches viz., P3 medicine i.e., predictive (early detection of susceptibility: critical information for optimizing wellness through identifying factors responsible for disease, sending alerts early and suggesting preventive measures), preventive (reducing the likelihood of disease: identify at-risk individuals long before the development of disease so that preventive treatments/early detection can be planned) and personalized (targeted therapy: medicine must focus on each individual uniquely, including drug toxicity). Soon genetic profile of tumors will be characterized as well as rationalize personalized cancer therapy. However, we also realize that the high genomic variability and dynamic nature of tumor cells, difficulties in distinguishing driver mutations (confer growth advantage, allowing cells to expand more than normal cells from the same tissue and metastasize) from passenger mutations (remaining large majority of alterations resulting from mutational exposures, genome instability, or simply the larger number of cell doublings that occur during progression from a single transformed cell to a clinically detectable cancer and do not confer growth advantage) or protective/beneficial mutations from destructive/ harmful mutations, etc are serious obstacles for success in war against cancer. Targeting the driver mutations will impact on tumor growth, while targeting passengers will have very little effect. It is therefore crucial to differentiate driver from the passenger mutations in order to clearly identify the targets of interest, to avoid the administration of unnecessary, costly and potentially toxic treatment. In addition, some of so called passenger mutations are deleterious to cancer cells (a barrier to cancer progression by a critical population size) and hence targeting them will result deleterious effect. Furthermore, inherited/ acquired mutations in non-coding regions of the genome also

contribute to cancer development and progression and likely to create additional complexity [4].

In fact, presently we do not know either our enemy (cancer) or our capability (modalities of cancer management) fully/completely and hence it is unexpected to win all battles without a single loss against cancers. We need more knowledge and integration of information to reach in stage so that we win all battles against cancer in near future. World is expecting massive generation of data/information on most cancers at genomic, epigenomic, proteomic, pharmacogenomics, metabolomics, etc. levels. To integrate these data into meaningful manners (i.e., identifying pathways/pathophysiology) will require massive work in coming years. For this we need convergence of system biology approaches, new technologies and new computational and mathematical tools [5] to find out cosmos from chaos. This will allow our current, reactive medicine, where we wait until the patient is sick, to be replaced by P3 medicine (predictive, preventive and personalized) that will be cost effective and increasingly focused on wellness through prediction, prevention, down staging and early treatment.

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