disease biology in the coming decade(s)

Human diseases can be broadly classified into two distinct groups namely, Infectious diseases and Genetic disorders. Over the last few decades, we have seen tremendous advancement in our understanding of the biology of pathogenic microbes and viruses and also novel approaches to combat them, though several challenges remain due to development of drug resistant bugs and immune evasion. On the other hand, the genetic disorders which are caused by inherent defect(s) in the DNA sequence, encoding a particular function, have been addressed since the days of Sir Archibald Garrod, who first addressed the basis of inborn errors of metabolism. The causative defective genes for many of these disorders are being identified by both candidate gene and the reverse genetic approaches. Since the completion of the Human Genome Project, there is a great surge in our efforts to identify the genetic loci and alleles responsible for common multi-genetic disorders using Genome Wide Association Studies. The beneficial outcome of the human genome project has been phenomenal both in terms of the knowledge it has created and the kind of questions that can be asked today about Human Biology. Associated with the Human Genome Project is the emergence of newer technologies, particularly under the broad definition of "OMICS" technologies. These high throughput platforms are being exploited to identify new biomarkers and also potential new therapeutic targets for clinical interventions.

A case with Glioblastoma multiforme

It is becoming increasingly clear that many of the human diseases, and more particularly Cancer, are now shown to be comprised of distinct subtypes based on the transcriptome and proteome profiles. This has been very well demonstrated in several types of cancers including Glioblastoma multiforme (GBM). GBM was originally classified by WHO into 2 major subtypes namely primary GBM and secondary GBM based on the age of the onset of the disease and whether it is of *de novo* origin (Primary) or of a progressive type (Secondary).¹ Pathologically, GBM (grade IV) is very similar irrespective of whether it is from primary or secondary route. The genetic mutation spectrum associated with primary and secondary

GBM are quite distinct, although more recently it is found that there are overlapping gene mutations in these two subtypes of GBM.² There are many reports describing the genes whose expressions are perturbed in these two sub classes of GBM and also between Diffuse and anaplastic astrocytomas.³⁻⁶ Based on integrated genomic studies a more recent study has classified GBM into a) Classical, b) Mesenchymal, c) Proneural and d) Neural as determined abnormalities in PDGFRA, IDH, EGFR and NF1 and also transcriptome profile.⁷ GBM is also one of the four cancers identified by the National Cancer Institute, USA to map genetic mutations using a large numbers of tumor samples. The first set of data have recently been published.⁸ One of the major objectives of this initiative is to identify the Driver and Passenger mutations that are associated with GBM and also to understand the relationship between the mutation spectrum and perturbations in gene expression. Such an analysis and differentiation between the Driver and Passenger mutations is very critical to understand the biology of gliomagenesis. Transcriptome and proteomic studies are also identifying several molecules which can be used as biomarkers.^{9,10} In addition, efforts are underway to identify gene signatures of prognostic value.¹¹

Transcriptome studies are generating enormous amount of data. There is a general concern on the value of such catalogued gene list. It depends on the ingenuity of the scientist to ask the right intelligent question as to how they contribute to the development and progression of the disease. In this context an elegant study has shown that IGFBP 2 (Insulin Growth Factor Binding Protein 2) which is highly up regulated in GBM, actually contributes to the progression of the disease from a lower grade to a higher grade astrocytoma in a mouse model system.¹² In another study, it has been shown that AEBP1 (Adipocyte enhancer binding protein 1, whose expression is high in Primary GBM as against secondary GBM, plays an important role in supporting growth and survival of glioma cells.¹³ Down regulation of AEBP1 resulted in activation of apoptosis indicating that it may play an anti-apoptotic function in glioma. We need several such biological studies to really dissect out and understand the biol-

ogy of gliomagenesis. Over the last few years, we have also seen that regulation of gene expression not only occurs at the transcriptional level but also in the cytoplasm by miRNAs. These miRNAs also play an important role GBM.¹⁴ We hope to see active research in this area in the coming years so that we can get a comprehensive picture of glioma biology.

New Era of Disease Biology: A Systems approach

We are presently entering a new era of Disease Biology in which Systems approach will play a significant role in our understanding of human biology. For several decades biological research was driven by reductionism which has given a wealth of knowledge about various cellular components and their functions. However, it is now becoming apparent that a single biological function is not just because of one molecule. Most biological characteristics are a result of complex intracellular protein-protein interactions that drives cellular pathways. These cellular networks are modular and consist of interconnected proteins responsible for specific functions.¹⁵ In this context, cancer phenotype is a result of the inability multiple genetic functional modules to carry out their basic functions and are critical to the hallmark of cancer including self sufficiency in growth signals, evasion of apoptosis, sustained angiogenesis, tissue invasion and metastasis. Different combinations of perturbed genes can incapacitate each module. Each tumor can perturb individual genes by multiple mechanisms including sequence mutations, copy number alteration, gene fusion events and epigenetic events. The basic approach of systems biology is to systematically catalogue all molecular interactions within the cell and decipher how these molecular interactions determine the function(s) of the extreme complex network machinery. Such an approach is entirely feasible now because of the publicly available human protein-protein interaction network database and the tremendous advancements in the area of computational biology and bio-informatics tools. It is now possible to create disease specific networks. By using such an approach scientists are creating disease specific networks.¹⁶ One such effort has identified a GBM specific network within which CSK21 and PPIA,

both enzymes responsible for cell division, key central molecules connecting sub-networks. Interestingly, these enzymes are also highly up-regulated in GBM.¹⁷ It is also believed that key molecules that interconnect different sub-network modules within the diseased cell may be a much more effective therapeutic target for future drug development. Another interesting concept that is emerging is that the cellular network keeps changing during the course of progression of the disease and also during drug treatment as exemplified by a recent study on breast cancer cell lines.¹⁸ One cannot ignore the influence of environment in modulating the cellular network and we need to keep this in mind particularly in chronic diseases. This network approach is also relevant in infectious diseases since host cellular networks can also be modulated by pathogens.

Building bridge between Genetics and Physiology

The efforts of disease biology in the coming decade(s) will be centered around translating the genetic defects information to the ultimate cellular output, namely the physiological parameters that are of paramount importance to the Clinicians. It is here that the Systems approach has great promise in integrating the genetic defect(s) which in turn results in perturbation of gene expression causing abnormal protein-protein interaction networks that finally drive the disease physiology. Network biology should also include interaction between proteins, DNA, RNA and small molecules. We do hope that these approaches will create new knowledge of Disease biology in the years to come and we have to wait and see how this concept of 'Network Biology', that is intellectually stimulating to Biomedical researchers, will also be beneficial to clinicians as well. Deciphering this linkage between genetics

and physiology is going to be a challenging enterprise for geneticists, biochemists, cell biologists and computational biologists. Such an integrated approach is very essential today for understanding Human Biology in both health and disease conditions. Neuro-oncology, in particular and Neurosciences in general, will greatly benefit with this network biology approach and it is hoped that the coming years will be more challenging and rewarding than ever before.

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