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Guest Editorial

PHYSIOLOGICAL GENOMICS

Understanding the ‘functioning’ of the living organisms has been central to the quest of biological sciences since the very beginning. This realization reached a critical mass sometime in the 17th century and Physiology as a disciple was institutionalized. It was an idea whose time had come.

If god is in details, then physiologists are most religious. The elegance of physiology is in details and in the fundamental principles that govern the interactions between them. It is this quest that has reduced an organism to conglomeration of organ systems, an organ to assembly of cells and a cell to a cluster of organelles over the last two millennia. Last few decades have seen further reduction to the level of protein and genes. Today no physiological explanation is ‘adequate’ without the details of the genes and proteins involved. Rene Descarte would have been ecstatic at this development and but he would have soon realized that even with whole genome sequences in hand we are still unable to ‘truly’ explain the ‘how’ and ‘why’ of physiological phenomenon. Despite the enormous factual information about genes, protein, translation and transcription processes, the picture of physiology far from complete. The reductionist approach aimed at identifying the molecular and cellular events, studied in purified form or isolated systems can only be extrapolated to a discrete molecular or cellular phenomenon. We have reached a stage ‘loosely’ analogous to the Heisenberg’s uncertainty principle in quantum physics. The more we attempt to understand the whole in terms of its units, more difficult it becomes to understand the whole. The lower we go in the level of organization more difficult it is becoming to see the complete picture. A strictly reductionist approach is not giving the answers to questions we started with. Is there a way out? Physiological genomics is perhaps the answer or at least a way towards that answer.

The genome project was stared in 1991. Today we have full genome of many organisms across the animal kingdom. Developments in genomics have spawned newer technologies that allow identification, quantification and comparison of multiple genes. The current workhorse of the genomics is DNA microarray. It allows rapid and high throughput method of analyzing the transcripts in given cell, tissue or organism. It is not uncommon to see publications with thousands of genes being simultaneously studied in different experimental setups to give the ‘snapshot’ of genetic machinery of a cell. The enormity of the genomic and proteomic data has resulted in evolution of methods of analyses hitherto not considered by the biologists. Computation and algorithms are integral to these techniques. Physiologists, in general,

have tended to keep the cellular and molecular realm away from the so called 'classical physiology' or the systemic physiology. In doing so, we have strayed away from the very essence of physiology. The understanding the 'functioning' of living organism is the domain of physiologists and the level of analysis viz. organism, organ, tissue, cellular, molecular and even submolecular is immaterial. In this milieu genomics is implicit in physiology. However, naming ceremonies are often useful to re-emphasize, so the term Physiological Genomics. It is an idea whose time has come.

Physiological genomics is the study of the functioning of gene products in the context of the whole organism and its environment. It is an emerging field that brings together the disciplines of genomics and cell, organ and whole animal systems integrative physiology in an effort to attach function to the DNA sequences of complex living systems. It is an attempt to bring together the familiar approaches of biochemistry, molecular and cellular biology, genetics and classical physiology and pair them with recent technologies. Terminologies are created for ease of communication but more often than not they endup being confusing. At this point subtle differences in the connotation of various terminologies must be explicitly emphasized. Genomics deals with determination of sequences of the genome of the organism, identification of the regulatory and the expressed components. Proteomics deals with identification and characterization of proteins of the cell in a given functional state. Function genomics goes a step further and deals with understanding the biological function of the genes, mechanisms of regulation and interaction between the genes. The physiological genomics provides the 'gestalt' to the genes and proteins.

Every level of organization finds its mechanism at lower levels of organization and its significance at higher levels of organization. The Physiological genomics is an approach to look at the significance of genes and proteins at higher level of organization i.e. the organism in the context of its environment. A thorough knowledge of complex interaction between genotype and phenotype is required to have greatest impact on medicine and disease prevention.

DNA microarray is a high throughput technology that allows profiling of the state of a cell in terms of relative abundance of mRNA (transcriptome) or proteins (proteome). The relative ease of doing microarray comes with hidden enormity of data and consequent analysis. Initially major issues were the standardization of experiments, data management, and standardization of data representation. The analyses have been explorative and concentrated on the statistical determination of upregulated or downregulated transcripts or proteins. This, with due respect to the effort of those involved, has been the easy part. The difficult part is and will be in drawing meaning out of it, in linking the genome to physiology. These issues were debated in the 1997 Banbury conference organized by the American Physiological Society, "Genomics to physiology and beyond: how do we get there?". The 'mating' resulted in the birth of a journal, aptly named 'Physiological Genomics' in 1999, dedicated to provide a common ground.

So much for what physiological genomics is ? The next obvious question is how does one practice physiological genomics ? The work of David Woo and Ira Kurt (1) on the determination of genetic loci of hypertension is instructive. To physiologists regulation of blood pressure is staple diet. We know that blood pressure is complex trait determined by genetics and environment influences. However, the specific genetic determinants and their interaction with environment are not known completely. David Woo and Ira Kurt studied the genetic determinants of high blood pressure in mice. They crossed two inbred strains of mice, one strain that tended to have higher blood pressure (mean –132 mmHg) and one that tended to have lower blood pressure (mean ~ 105 mmHg). The F2 generation resulted in generation of litter that had mixed population of mice with pressure ranging from low to high (range = 70 to 162 mmHg, n = 1,521). The distribution of the blood pressure showed Gaussian distribution. They selected mice with blood pressure 1 Standard deviation above the mean (n = 233) and those with blood pressure 1 standard deviation below the mean (n = 232). These two groups of mice were phenotypically distinct (hypertensive vs hypotensive) but had same genetic background (F2 crosses of the same inbred strains). They then proceeded to genotype the two groups using a set of microsatellite markers. Using the tools of genomics and bioinformatics they identified four regions (‘quantitative trait loci’ to put it in genomic jargon) on the mice genome which were related to the blood pressure phenotype. This study shows how tools of genomics were utilized to understand factors determining the blood pressure. The story is not complete, what remains to be determined is what are the genes in these loci and what do they do ?

This work also illustrates the changing approach in scientific methodology. The work was explorative and not driven by hypothesis. However, once the genes in these loci are determined, hypothesis driven experiments will have to be devised to identify the significance of these genes in the determining the blood pressure.

Similar work is being done at many laboratories. The physiological genomic maps of cardiovascular function have been created for rat (2, 3). These approaches are also being utilized to understand the phenomenon of metabolic imprinting, relationship between nutrition, exercise, genes and physiological function.

Evolutionary pressures have ensured the robustness of biological systems. As a result, at all of level of organization, the system has high degree of redundancy and pleiotropy. This is especially evident at the level of genome and proteome. Thus, exclusive one physiological function-one gene approach is untenable. We have to deal with thousands of genes with overlapping functions at cellular level, hundreds of cells with overlapping function at organ level and so on. More so, these interactions are ‘non-linear’. The interplay of environmental, genetic and physiological factors that goes into controlling the complex biological process makes the processes of dissection an intimidating task. In this scenario, the traditional methods of analysis are grossly inadequate. Systems biology has emerged from this chaos. At its core, the systems biology represents renewed recognition that

a coordinated systems view is necessary to 'truly' understand biology.

Next question is who can practice physiological genomics? Given the very nature of its goal and scope, it is unlikely that it can be done by single person or even single laboratory. This will need combined efforts of mathematicians, engineers, computation biologists and above all will require physiologists with broad knowledge and experimental skills, capable of hypothesis development and testing at the cellular, organ and whole organism level. As physiologists, our responsibility is paramount. In a global world, only the laboratories without walls will survive and contribute.

Physiologists play an important role as teachers to budding scientists and physicians. However, this emerging wave has not been given adequate attention by the physiologists, in general. We will fail in our duty as teachers if do not expose our students to the concepts of physiological genomics. Take any textbook of physiology and you will recognize the chasm that has grown. Most of us are growth retarded at pre-genomic level to put it mildly. It is urgent and crucial that physiologists take up the challenge to be instep with rapidly changing times. We have to change not only our view point to these developments but also the way we teach physiology to our students. We have to incorporate newer dimension of physiological genomics, bioinformatics and systems biology in our quest to understand the 'functioning' of living organisms. Failure to do so has only one logical end: the physiology as we know today will be a footnote in textbooks of genomics if not history.

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