Harnessing “omic” tools and computational hypothesis-driven approaches to understand biocomplexity: the future of Physiological Genomics

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Physiological Genomics is currently entering its eighth year of publication. The formation of this new journal was considered a high risk venture when first discussed in 1998. The American Physiological Society was convinced that this journal would advance and consolidate the information emerging from the studies of fundamental determinants of the biological system (genes) to an ultimate understanding of the function of the whole organism. It must be recalled that at this time, the first draft of the human genome was yet 3 years in the future and only the sequencing of a few bacteria such as Escherichia coli had been completed. It was uncertain when the then costly high-throughput genomic techniques being applied in the Human Genome project could soon be widely used. Only a few laboratories were beginning to custom stamp DNA microarrays to assess changes in gene expression under various conditions, and the term “bioinformatics” had not yet been coined. Yet, the “genie was out of the bottle,” and the evolving genomic approaches would provide tremendous opportunities for physiologists to link genes to the complex functions of living systems.

No one could imagine, however, how rapidly things would progress in the course of a single decade and how commonplace the application of the many genomic technologies would become. Physiological Genomics has been at the leading edge of publishing research that has applied these advancing technologies to understand the genomic regulation of complex biological functions. We have encouraged new paradigms that have challenged the way research previously has been conducted. Unprecedented, genome-wide views of biological regulation have been presented in various forms in this journal including comprehensive analyses of genome sequence, genome expression, and phenotypes, many of which have been made possible by the development of novel experimental and bioinformatic tools.

As these areas have quickly matured, it has become apparent that although the molecular determinants of complex functions and diseases very often have their roots at the genetic level, many of them are difficult to pinpoint using the genome sequence and mRNA data alone. Moreover, complex functions and diseases are often critically mediated by events that may not be immediately obvious by looking at the genome sequence and mRNA levels. Importantly, many of these intermediate events can now be assessed on a genome-wide or near genome-wide scale. For instance, epigenetic modifications due to methylation of CpG islands in the regulatory sequence of genes and changes in chromatin structure can regulate gene expression and function. Signaling pathways are regulated by posttranslational changes through kinases and phosphatases, or modulators of protein stability mediated by acetylation, hydroxylation, or ubiquitination. Translation of certain mRNAs is not concentration dependent but involves mechanisms such as differential recruitment of existing mRNAs to polysomes. MicroRNAs represents another example of posttranscriptional regulation. Efforts are currently underway to develop and apply genomic-scale techniques to address these molecular elements including proteomics, metabolomics, and other so-called “omic” approaches. We welcome the publication in our journal of all such work that links genes or proteins to complex functional pathways.

Importantly, physiologists are making serious efforts to build upon the vast amount of molecular omic data to achieve an understanding of functional activity. The paradigm is shifting from genomic-scale molecular characterization back toward hypothesis-driven approaches. The quantitative understanding of the complex interacting mechanisms of mammalian organisms remains the most daunting challenge of modern biology. The so-called field of “systems biology” is emerging to meet this challenge. The tools of physiological genomics and other omics, when coupled with computational approaches that bring together bioinformatic and novel computational strategies, provide remarkable opportunities to advance our understanding of the integrated function of complex organisms. Various investigators are currently developing computational models of cellular organelles or signaling pathways that respond to inputs from the genome and proteome as well as extracellular signals. It is the goal to link these models to subcellular, cellular, organ, and whole animal levels using multiscale computational approaches. Information obtained from experimental regimes, both broad (genome-wide) and specific (single molecule), in vitro and in vivo, can then be connected in a meaningful way to provide predictions of human and whole animal function. Another aspect that will be critical to the success of systems biology is advanced intervention techniques that allow efficient manipulation of genes in mammalian model organisms. This may determine, more than any other factor, the ability of physiologists to determine the relevance of genes upon critical functional pathways. Such studies are of the greatest interest to this journal and may include: in vivo applications of siRNA using various viral delivery systems, induction of pluripotency and novel applications of nuclear cell transfer techniques to elucidate gene function, effective utilization of site-specific transgenic model systems to over- and underexpress DNA sequence variants within controlled genomic backgrounds, and other intervention approaches that enable physiologists to manipulate and study genes in mammalian organisms. It is hoped that such
experimental paradigms and multidisciplinary systems approaches will pave the way for a deeper understanding of physiological systems and complex diseases.

Given the rapid evolution of science, it can be argued that the name of our journal may now seem overly narrow and must be changed to encompass the scope of all that has evolved. Although this may happen sometime in the future, I would argue that to change the name of this journal so early in its development would be unwise. Launching and branding a “new journal” in a highly competitive market represents a risky and expensive project. Physiological Genomics has been well received and has seen continued growth in submitted manuscripts and in the quality of its publications. Moreover, one can also argue that all of the new advances described above are well within the domain of physiological genomics since the ultimate goal is to link genomes to physiology. However, in light of the dramatic advances in the breadth of postgenome science and to encompass this research without overly limiting the scope of journal, the Associate Editors have carefully revised the scope statement of Physiological Genomics. To reflect the changing times and the goals to which we aspire, this scope statement now reads:

“Physiological Genomics publishes the results of a wide variety of experimental and computational studies from human and model systems to link genes and pathways to physiological functions. The journal encourages the submission of research utilizing genomics, epigenomics, proteomics, metabolomics, and other systems approaches together with novel technologies linking genes to the function of complex biological pathways.”

The next decade of scientific progress will undoubtedly necessitate further changes in the scope of this evolving journal, but for now we encourage anyone working in areas that are reflected by this vision to submit original articles and reviews. For our part, we will make every effort to provide the best editorial expertise for the peer review of your work.

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