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EDITORIAL

Systems biology in human health and disease

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Understanding the factors that influence human health and cause diseases has always been one of the major driving forces of biological research. With the spectacular progresses in quantitative techniques, large-scale measurement methods and with the intimate integration between experimental and computational approaches, Biology has recently acquired new technological and conceptual tools to investigate, model and understand living organisms at the system level. While the still young discipline of Systems Biology has been most widely devoted to the study of well-characterized model organisms, it has been clear since the early days of the human genome project that applications of system-wide approaches to human biology would open up tremendous opportunities in medicine.

Recent lessons learned from Systems Biology, when applied to simple organisms like bacteria or yeast, prefigure the kind of insights that will benefit both basic medical research and clinical applications: deeper understanding of the genotype–phenotype relationship; impact of the interactions between environmental conditions and genotype; novel mechanistic and functional insights based on global unbiased approaches; elaboration of powerful predictive models capturing the intricacies of physiological states. Advances on these various fronts obviously depend on different types of research, ranging from investigations on fundamental aspects of human biology to the more clinically oriented applications. Significantly, as techniques and concepts mature, a new discipline is emerging at the interface between Medicine and Systems Biology. To provide a snapshot of this evolving field of Systems Medicine and to illustrate new insights gained by applying Systems Biology approaches within the context of human health and disease, *Molecular Systems Biology* releases this month, in print, a collection of articles recently published in the journal.

In many fields relevant to medical research, including cancer biology, deciphering the mechanisms of disease requires a deep knowledge of how signaling transduction pathways operate. Quantitative proteomics has made possible the simultaneous monitoring of the concurrent activity of multiple signaling molecules, enabling a broader and unbiased view of cellular signaling events. The work by White and co-workers (Wolf-Yadlin *et al*, 2006) illustrates how this type of high-throughput data can be correlated to biological response (e.g., proliferation and cell migration) to further our understanding of one of the major pathways known to be deregulated in cancer. These global approaches also reveal the inescapable fact that biological pathways are highly interconnected, which represents one of the major motivations for adopting a system-level approach in biology. In the study by Lehár *et al* (2007), the impact of connectivity on biological outcome is analyzed to explain synergies and other non-intuitive interactions observed between simultaneously applied drugs, with important consequences for drug design and pharmacology. In fact, the classical concept of linear pathways is being increasingly challenged by network representations, which emphasize the importance of interactions between components of a biological system. Loscalzo *et al* (2007) discuss how this network-based conceptual framework may transform current paradigms in disease classification and treatment. However, a major practical challenge is how to deduce the structure of complex networks that underlie biological processes and how to characterize their state when perturbed by disease. New computational strategies combined with the now well-established genome-wide expression profiling techniques provide completely new tools to reverse-engineer network structure and to identify and track mediators associated with a disease as illustrated by the work of Jim Collins' team on prostate cancer (Ergün *et al*, 2007).

Since the completion of the human genome sequence, research in human genetics has been progressing at a rapid pace. With major achievements including realization of the HapMap project facilitating the analysis of human genetic variability, the recent flurry of genome-wide associated studies providing a host of potential genetic determinants for major common diseases and the advent of the first personalized human genome sequences, the power of genetics and genomics to explore the human disease landscape does not need to be demonstrated any more. But it is important to realize that beyond genetic determinants, diseases are characterized by a perturbed physiology, and methods providing a wider and deeper window into physiological states will be instrumental to acquire an integrated view of human disease. By their proximity to physiological output, metabolite measurements provide such a window, and advances in the associated techniques have led to the development of the field of metabonomics, pioneered by Jeremy Nicholson. His study (Martin *et al*, 2007) reveals the profound influence exerted by gut bacterial flora on the metabolic equilibrium of the host and, as a consequence, on its health status. This work also demonstrates that the genotype–phenotype relationship is far from being the entire story when dealing with disease, and it highlights the crucial importance of integrating all facets of physiology, including contributions from the microbiome and environment, thus adopting an even wider scope than the genome-wide paradigm.

One of the great hopes generated by the application of high-throughput technologies to human samples is that the increased amount of information gathered can lead to more powerful models able to predict susceptibility to disease, response to treatment and, perhaps even more challenging, help in the prognosis of disease outcome. It is the latter question of prognosis that is addressed in the study by MacBeath and co-workers (Knickerbocker *et al*, 2007), where

integration of clinical parameters with protein microarray measurements of blood samples allows improved prediction of early mortality of patients initiating a kidney dialysis treatment. Wider application of these technologies is likely to be instrumental in opening the door to the era of personalized medicine with tailored strategies encompassing all dimensions of clinical practice, including prevention, diagnosis, treatment and prognosis.

Translating the Systems Biology framework to the human 'system' will represent a formidable challenge, not only because of the daunting complexity of human physiology, but also because the human condition implies serious consideration of ethical, legal, safety, individual and epidemiological issues. Revolutionary technologies, novel insights, massive digitalization of information will call for clear thinking and innovation in the formulation of governance policies. It is thus also our hope that by providing an excerpt of some of the recent concrete contribution to the field, we can stimulate, already at this early stage, reflections and debates, extending beyond the Systems Biology community, so that the full potential and promises of Systems Medicine can be realized in harmony with societal standards.

References

Ergün A, Lawrence CA, Kohanski MA, Brennan TA, Collins JJ (2007) A network biology approach to prostate cancer. *Mol Syst Biol* **3:** 82

Knickerbocker T, Chen JR, Thadhani R, MacBeath G (2007) An integrated approach to prognosis using protein microarrays and nonparametric methods. *Mol Syst Biol* **3:** 123

Lehár J, Zimmermann GR, Krueger AS, Molnar RA, Ledell JT, Heilbut AM, Short GF, Giusti LC, Nolan GP, Magid OA, Lee MS, Borisy AA, Stockwell BR, Keith CT (2007) Chemical combination effects predict connectivity in biological systems. *Mol Syst Biol* **3:** 80

Loscalzo J, Isaac Kohane I, Barabasi AL (2007) Human disease classification in the postgenomic era: a complex systems approach to human pathobiology. *Mol Syst Biol* **3:** 124

Martin FP, Dumas ME, Wang Y, Legido-Quigley C, Yap IK, Tang H, Zirah S, Murphy GM, Cloarec O, Lindon JC, Sprenger N, Fay LB, Kochhar S, van Bladeren P, Holmes E, Nicholson JK (2007) A top-down systems biology view of microbiome–mammalian metabolic interactions in a mouse model. *Mol Syst Biol* **3:** 112

Wolf-Yadlin A, Kumar N, Zhang Y, Hautaniemi S, Zaman M, Kim HD, Grantcharova V, Lauffenburger DA, White FM (2006) Effects of HER2 overexpression on cell signaling networks governing proliferation and migration. *Mol Syst Biol* **2:** 54

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