Introducing the Systems Biology of Cell State Regulation section of Physiological Genomics

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As part of the formation of distinct sections within the Physiological Genomics journal, we are delighted to announce the launching of a new section entitled “The Systems Biology of Cell State Regulation.” While in some instances, a single marker or a few markers may be suitable for defining a molecular process or state, the development of new technologies has opened the possibility of using transcriptomes, proteomes, epigenomes, and metabolomes to gain a global view of a cellular state. In some instances, this more comprehensive analysis of cellular state will allow a more thorough understanding and testing of hypotheses about the role of cells in different cellular states in physiological processes. This new Physiological Genomics section will publish primary papers, reviews, and perspectives that use high-throughput and more directed experimentation to address questions such as “What does it mean for a cell to be in a particular cellular state?”; “What are the properties of cells in different states?”; “How can we use systems biology-based approaches to gain an overview of a cellular state, develop useful cell-state markers, and apply these to gain a greater understanding of physiology?”; “What are the key signaling pathways that control the transition between cellular states?”; and “How does a cell’s extracellular environment affect its ability to adopt a cellular state?”

The Systems Biology of Cell State Regulation Editorial Board chaired by Hilary Coller (Princeton University) consists of Nabeel Bardeesy (Massachusetts General Hospital), Edna Cukierman (Fox Chase Cancer Center), Jyostna Dhawan (InStem), Martin Flueck (University of Zurich), Andrew Gow (Rutgers University), Sushil Mahata (VA San Diego Healthcare System and University of California at San Diego), and Sharon Pine (Cancer Institute of New Jersey).

These topics have been addressed in multiple papers already published in Physiological Genomics (1, 3, 5). As an example, Alexander and colleagues (1) used genome-wide gene expression analysis to understand the states adopted by smooth muscle cells. In normal, healthy arteries, smooth muscle cells are essential for contractility and express contractile and cytoskeletal proteins. In atherosclerotic plaques, smooth muscle cells transition from a contractile state to a state characterized by increased proliferation, migration, and matrix synthesis. The authors compared the gene expression profiles induced by either PDGF or IL-1β, both of which have been implicated in this transition, and found that PDGF-treated cells exhibited changes in the expression of cell cycle-related genes, while IL-1β treatment resulted in transcriptional changes associated with the inflammatory response. Immunofluorescence with markers for the contractile, proliferative, and inflammatory states were then used to characterize the state of smooth muscle cells in nonatherosclerotic arteries, which showed the contractile phenotype, and atherosclerotic plaques, which contained cells in both proliferative and secretory states.

Building upon this foundation, we commence the Systems Biology of Cell State Regulation section with the publication of a paper in Physiological Genomics from the laboratory of Kenneth Marx (University of Massachusetts, Lowell) entitled “Keratin gene expression profiles after digit amputation in C57BL/6 vs. regenerative MRL mice implies an early regenerative keratinocyte activated-like state” (4). In response to injury, keratinocytes in the epidermis enter an “activated” state in which they exhibit properties such as migration, hyperproliferation, and secretion of signaling molecules and extracellular matrix components. These activated keratinocytes can be identified by their expression of specific types of intermediate filament proteins or keratins. In this paper, the authors used microarrays to monitor gene expression changes in tissue collected from mice after amputation of the middle digit. They compared the gene expression pattern in C57BL/6 mice with the pattern in the Murphy Roths Large (MRL) strain, which possesses an unusual capacity to perform regenerative wound healing with little scarring. They discovered two keratins that were induced in response to wounding in the C57BL/6 mice and were present at higher levels in the unwounded, basal state in the MRL strain. Because these two keratins had been previously associated with the activated keratinocyte state, they analyzed a panel of 40 genes that have served as markers of keratinocyte activation. Among these genes, seven were expressed at high levels in uninjured MRL mice and down-regulated following injury, while being expressed at low levels in uninjured B6 mice and induced following injury. Immunohistochemical analysis of the wounded and unwounded tissue sections from multiple locations in the two strains of mice demonstrated differences in the expression levels and the subcellular distribution of the two keratinocytes between the mouse strains. The authors concluded that keratinocytes in the MRL strain, but not in the C57BL/6 strain, are in an activated state prior to wounding and suggest that the presence of these activated keratinocytes in MRL skin may contribute to their superior healing capacity. Other models have been put forward to explain the MRL phenotype, including a lack of the cyclin-dependent kinase inhibitor p21 (2), and further studies will be needed assess the importance of activated keratinocytes for the improved regenerative capacity of MRL mice. We highlight the work here because the authors’ use of genome-wide analyses to gain an overview of the changes that occur with wounding, the selection of specific genes to serve as markers to define a keratinocyte-activated state, and the attempt to use information about cell state to explain physiolog-
lical processes capture the spirit of the types of questions we plan to address.

A number of articles are planned for the new section of *Physiological Genomics*. Some of these forthcoming publications focus on the characteristics of cells that can adopt one of multiple states. These include reviews comparing fibrotic fibroblasts with desmoplastic fibroblasts, different types of myeloid-derived monocytes in the lung, exercised with relaxed muscle, and cancer stem cells with noncancer stem cells. A review has also been solicited on the use of bioinformatic analyses of large datasets to define cellular states. Other planned reviews and perspectives will address the role of specific biological attributes in defining a cell state, in particular, the use of epigenetic markers as a distinguisher of stem cells, differentiated cells, and quiescent cells. The Section will also host reviews that focus on specific signaling pathways that regulate cell fate, and a forthcoming paper will address how cells interpret different levels of Wnt signaling. Another solicited piece will address the role of the microenvironment in determining cellular state and bioengineering approaches to engineer the stem cell microenvironment. *Physiological Genomics* and the Editorial Board actively encourage contributions in the form of primary papers, reviews and perspectives that address the questions and themes posed by this new section.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**

Author contributions: H.A.C. drafted manuscript.

**REFERENCES**