PHYSIOLOGY

Leveraging signaling research to understand and treat disease

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This Editorial Guide describes an area of active signaling research. A challenge signaling researchers face is understanding how the information gained by analysis at the cellular and molecular levels can be translated to understanding higher-order organismal physiology and pathophysiology.

Research in cell signaling has now reached a particularly exciting point. After many years of successfully using focused reductionist approaches—studying how cells respond to stimuli in culture, biochemical analysis of the dynamic changes of small numbers of signaling molecules, and analysis of genetically tractable model organisms—we now have a wealth of knowledge of cellular regulatory networks. The challenge that remains before us is translating this knowledge into the context of higher-order structures that constitute the basis of multicellular life—namely, tissues and organs where cells function within a complex community. In this regard, studies in model organisms that have been so successful in the past—the fruit fly *Drosophila melanogaster*, the yeast *Saccharomyces cerevisiae*, and the worm *Caenorhabditis elegans*, to name a few—will continue to be instrumental in unraveling these complex connections. However, molecular understanding of human disease and physiology is likely to require experimentation in organisms that are evolutionarily closer to us, including vertebrates and mammals. Studies that test cellular networks and regulatory events, which were defined in vitro, in the context of a complex multicellular system under both normal and pathological conditions are of particular interest for *Science Signaling*.

The challenge of translating information about signaling pathways into the more complex system of a mouse or a person is evident from the exciting, yet discouraging, results of taking rationally designed cancer therapies from molecule to cell to mouse to human patient. Although knowledge of the molecular target and the ability to target the dysregulated kinase—for example, by small molecules—has worked superbly in culture and in xenograft tumor models in immunocompromised mice, the results in patients have been less than ideal. The underlying reason for this is that the systems used to test the drugs fail to capture all of the complexity of the human patient. Although many patients exhibit a dramatic initial response to signaling-targeted drugs, the cancers tend to return with a vengeance. Why? The heterogeneous nature of most cancers, the effects of an intact immune system on cancer elimination, and the ability of cancer cells to rewire their signaling pathways all contribute to therapeutic failure, and were all underappreciated. In effect, these drugs killed the most sensitive cancer cells and left behind ones with either intrinsic resistance or those that could rewire their signaling networks to avoid death, resulting in a very aggressive subsequent relapse that was most often not responsive to subsequent treatment. As signaling-interested scientists, we should have known better. Our field is fundamentally based on the concept that intrinsic signaling pathway activation or inhibition is what cells use to change their phenotypic state. Why should extrinsic pathway activation or suppression be any different?

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This particular biomedical example illustrates the complexity that researchers face in translating reductionist signaling knowledge into clinically useful therapeutic strategies. Signaling researchers have come to the rescue, however, by investigating these regulatory rewiring events, exploring how the immune system needs to be reeducated to attack the tumors, and learning how the cancer cells signal to their surrounding cells in the tumor microenvironment to promote survival and metastasis. Articles featured in the Related Resources provide recent examples published in this journal.

Turning knowledge of cellular regulation into an understanding of organismal physiology requires experiments with sophisticated animal models. Globally deficient genetic knockouts may not be sufficient for several reasons. Knockouts that cause embryonic or perinatal lethality are informative but can be difficult to use for testing therapeutic treatment strategies, and obviously are not useful for diseases associated with dysregulation of that gene product in the juvenile or adult animal. Global knockouts can also result in adaptive changes—network rewiring—that enables or optimizes survival without this gene, which can make the model inaccurate for the question under investigation. It may be necessary to develop tissue- or cell-specific knockouts or inducible knockouts to generate a physiological and testable representation of the disease or pathological condition.

Finding or generating an appropriate model system for a human disease may not be easy even when using mammalian models. As an example, the human and mouse immune systems are different. Identifying these differences to predict how they affect the use of mice as a model for a particular disease or to test a particular therapeutic strategy is an area of important investigation. Studies of knockout animals may suggest one therapeutic strategy, but subsequent testing in an appropriate disease model may reveal unanticipated and unwanted effects. This is exemplified by a study evaluating the use of inhibitors of the enzyme ITK, a critical kinase in adaptive immune function, to treat asthma. This strategy was identified on the basis of knockout mouse studies, but failed to show benefit, and even exacerbated the disease, in a murine asthma model.

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Thus, as with all experimental research, data from multiple approaches and experimental systems are required to truly test a hypothesis and build a convincing well-vetted model. Competitive Research Articles at *Science Signaling* typically test a hypothesis or prediction, rather than just provide supporting or correlative evidence for a model. A few examples of recent research that uses tissue-specific or inducible genetic mouse models to understand physiology and pathophysiology are included in the Related Resources.

Understanding complex, dynamic physiological systems sometimes requires methods to acquire and analyze large and sometimes diverse data sets through so-called "systems biology" approaches. This is true whether the "system" is the interconnected molecular regulatory networks within a normal or diseased cell, the behavior of individual cells within a population or tissue, the inflammatory response to infection or injury, the chronic inflammation associated with metabolic disease and cancer pathology, or the regulatory interactions between commensal microbes and their hosts. These studies might involve single-cell analysis, high-throughput technologies, analysis of the responses of multiple cell types, and computational analyses to explore the dynamics of these complex systems and how they respond to stimuli, stress, or changing environmental conditions. *Science Signaling* is particularly excited to consider such studies that use systems biology approaches to explore physiological questions related to regulatory biology in animals and plants, and the interactions between microbes and their hosts. Depending on the types of studies, their aims, and how the research community will likely use the results, these studies will be evaluated either as Research Articles or Research Resources. We encourage authors to read about these two types of research content to see which section is most appropriate for their study (http://stke.sciencemag.org/about/help/research and http://stke.sciencemag.org/about/help/research-resources).

With this Editorial Guide, we outline just one of the emerging areas that we see as important for signaling research. Stay tuned for upcoming Editorial Guides about other areas of particular interest as signal transduction research provides the critical clues and basic information needed for translational researchers and clinicians to take the next steps in improving human health and well-being.

Related Resources

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