SIGNAL TRANSDUCTION

Predicting the future of signaling for 2018

Chief Scientific Editor, *Science Signaling*, American Association for the Advancement of Science, Washington, DC 20005, USA. David H. Koch Institute for Integrative Cancer Research, The Broad Institute, and the Departments of Biology and Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA. Email: myaffe@mit.edu

As the famous baseball philosopher Yogi Berra once said, "It's tough to make predictions, especially about the future." That being said, I have been asked by the editorial staff to offer my predictions of what the future might hold for our field. As you might expect, I believe that the horizon for signaling research is endless and that we are about to enter a particularly exciting time, despite the increasing challenges in the funding of biomedical research. As the focus on genomic sequencing as the key to new discovery finally begins to ebb (though not the demand for sequencing), it is leaving behind a host of useful data and experimental tools that should help take signaling research to the next level, particularly when combined with CRISPR/Cas9-based approaches and high-quality mass spectrometry. Although I expect rapid growth to continue in many areas, including those we have touched upon in previous editorials and perspectives, I have chosen to emphasize four research areas where I think we may see dramatic signaling breakthroughs over the next year.

First is the emerging field of immune signaling after host cell stress and tissue damage, an area that my colleagues Tim Billiar and Yoram Vodovotz refer to as "trauma immunology." The concepts on which the edifice of immunology was built were largely derived from observations related to infectious disease and vaccines, and later extended to organ transplantation and oncology, and focused on the concept of distinguishing self from nonself. However, the idea that aspects of self could themselves activate or modulate the immune system was elegantly elucidated more than 25 years ago by Polly Matzinger in her "danger model" hypothesis and subsequently gained molecular traction with the later discovery of Toll-like receptors, pathogen-associated molecular patterns, and damage-associated molecular patterns. Many details of the signaling mechanisms downstream from these events are emerging, and this is an area that I believe is ripe for new discoveries. I suspect that the new findings in this area are likely to be relevant to immuno-oncology, as well as to evolutionary ancient aspects of innate immunity, including blood clotting and the complement system.

Second, the links between epigenetics and signaling are poised for rapid scientific advancement. Here, the refinement and dissemination of sequencing technologies and mass spectrometry approaches that better facilitate the simultaneous mapping of multiple epigenetic marks on chromatin, combined with potential improvements in signaling measurements, even at the single-cell level, should enable new connections between the signaling state and the epigenetic state of a cell to be unraveled.

Third, control of signaling pathways through redox regulation remains on the cusp of major advances. Whereas it is now well recognized that tyrosine phosphatases are regulated, at least in part, through the oxidation state of their catalytic cysteine residues, there are an increasing number of papers that demonstrate, or at least hint at, the idea that redox state may be a key regulator of many other signaling pathway components. The difficulty in this field is largely a technical one—most probes and tools for studying redox control are either too insensitive or too unwieldy for routine use. I expect huge growth in this area from both a technological and a scientific perspective.

Finally, I predict that we will see the emergence of several new types of posttranslational modifications (PTMs) that have hitherto not been recognized for their importance in signaling. The discovery that histone citrullination (once considered an obscure PTM) plays an important role as a mechanism for chromatin decompaction in the innate immune system is one example. I would even go so far as to predict that at least one of these PTMs will directly couple metabolism to signaling, with pathway metabolites serving a second signaling function through direct protein modification. The relatively recent discovery of widespread lysine succinylation and its potential role as a regulator of metabolic flux provides a glimpse of the types of things that might lie ahead.

– Michael B. Yaffe

10.1126/scisignal.aar7429

Citation: M. B. Yaffe, Predicting the future of signaling for 2018. *Sci. Signal.* **11**, eaar7429 (2018).

Predicting the future of signaling for 2018

Michael B. Yaffe

Sci. Signal. **11** (511), eaar7429.
DOI: 10.1126/scisignal.aar7429