An Insider’s View

THE COVER OF THIS SPECIAL ISSUE DEPICTS A VANTAGE POINT NEAR THE surface of the cell as molecules carrying cellular signals veer down from the membrane and through the cytoplasm, some diving deep to the nucleus below. The image is apropos of the unusual and inspiring point of view of the field of cell signaling provided by an eclectic selection of topics chosen to reflect the nature of current signaling research and the viewpoints of authorities who have recently contributed detailed descriptions of cellular regulatory pathways to the Database of Cell Signaling at Science’s STKE (see www.sciencemag.org/sciext/cellsignaling07/). These pathways describe mechanisms that underlie leading causes of life-threatening diseases (such as heart disease and cancer), control excessive stimulation of the immune system (like that in patients suffering from arthritis), and regulate development and a range of environmental responses in plants.

Oxygen is necessary for life as we know it, but either too much or too little oxygen can lead to trouble. Semenza (p. 62) describes how cells sense hypoxia through a mechanism that leads to activation of the transcription factor HIF-1α (hypoxia-inducible factor 1α), which in turn regulates the expression of hundreds of genes. Promoting such a signaling mechanism could provide a useful strategy to combat diseases such as atherosclerosis, in which circulation and resultant oxygenation are disrupted. Inhibition of HIF-1α–mediated acclimation of cancer cells might provide a strategy for combating invasion and metastasis.

Hedgehog is an unusual proteinaceous signaling molecule with key roles in developmental patterning. As Jacob and Lum explain (p. 66), not all the components of Hedgehog signaling are known. Nor do we fully understand why in mammalian cells Hedgehog signaling components are localized at the primary cilium. However, disruption of this pathway clearly leads to developmental defects in humans, and excessive Hedgehog signaling contributes to certain cancers.

Hawkins and Stephens (p. 64) describe signaling through the γ subtype of phosphoinositide 3-kinases, which link G protein–coupled receptors to the generation of phosphorylated lipid signaling molecules. The resistance of mice lacking functional PI3Kγ to inflammatory disease has focused efforts on exploiting PI3Kγ inhibitors to control diseases such as rheumatoid arthritis. Other indications suggest roles for this pathway in cardiovascular disease.

Müller and Sheen (p. 68) describe how plants use a two-component signaling mechanism, well known from prokaryotic organisms, to respond to cytokinin, a hormone derived from adenine. Examples of cytokinin-regulated processes include development and growth, stress tolerance, and leaf senescence, and the list continues to grow.

The new Connections Maps in the Database of Cell Signaling provide expertly curated information on these complex signaling mechanisms and may enable new insights into the pathways and help decipher the clues they offer to advance new therapies. A participating authority recently proclaimed, “I am excited just thinking about what might be possible in a few years’ time.” We hope you will be, too, and that you’ll share your “wish list” with us at sigtrans-feedback@highwire.stanford.edu.

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