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News

NORTH CAROLINA AGRICULTURAL AND TECHNICAL STATE UNIVERSITY

Cells Never Rest: Kudos to Cellular Signaling Pathways

Greensboro, NC – January, 2019 – The human body is composed of trillions of cells, the basic building blocks of all living things. Our cells perform many diverse functions, including converting nutrients from food into usable energy, promoting growth, and preventing infection and disease. Each of these cellular functions involves a series of coordinated biochemical reactions and, in order for cells to function efficiently, they must "know" which reactions to "turn on" and which ones to "turn off" in the face of an everchanging environment. Importantly, failure to properly coordinate these activities underlies many pervasive diseases, including cancer, diabetes, cardiovascular disease and Alzheimer's disease.

How do cells know what to do and when to do it?

This is the subject of Dr. Robert Newman's research. Newman, an associate professor in the Department of Biology at North Carolina Agricultural and Technical State University, is interested in understanding the organization and regulation of cellular signaling pathways, with a particular emphasis on phosphorylation-dependent signaling pathways mediated by protein kinases and phosphatases.

What?!

A cellular signaling pathway is exactly what it sounds like. A typical cellular signaling pathway is composed of an array of signaling molecules, including small molecule second messengers (such as calcium ions or cyclic AMP) and various types of signaling enzymes (such as protein kinases and small G-proteins), acting in a coordinated fashion to process information about the cellular environment. However, these signaling pathways do not operate in isolation. In fact, hundreds of intersecting signaling pathways are operating simultaneously to process information about both the cell's external environment and its internal state. Moreover, the same signaling molecule(s) are often involved in multiple cellular signaling pathways. For instance, a given signaling enzyme, such as one of the 518 protein kinases encoded in the human genome, might play a role in regulating diverse cellular processes, such as cell proliferation and programmed cell death. A major question in the signaling field is how cells are able to selectively activate one signaling pathway (e.g., a pathway leading to cell proliferation) while not activating another (e.g., a pathway leading to cell death) even though key signaling molecules are shared between the two pathways.

Dr. Newman's group is exploring the hypothesis that, by modulating the substrate selectivity of protein kinases, the cell is able to control which "arm" of a branched pathway is activated in response to a given signal.

Protein kinases, which are key components of nearly all cellular signaling pathways, catalyze the transfer of a phosphate group from a high-energy, phosphate-donating ATP molecule to specific substrates (a substrate is the material upon which an enzyme acts). As you might recall from biology class, this process is known as "phosphorylation"; the substrate gains a phosphate group while the high-energy ATP molecule donates a phosphate group. Inside the cell, phosphorylation can impact a protein's cellular function in several related ways. For instance, phosphorylation can alter a protein's stability, protein-protein interactions, enzymatic activity and/or sub-cellular localization. Thus, by regulating the phosphorylation status of cellular proteins, protein kinases play a critical role in the regulation of nearly all cellular processes, including replication, cell growth, metabolism, and cell death.

Dr. Newman was recently awarded a $1.4M grant from the NIH National Institute of General Medicine Sciences to better understand how redox modification (i.e., modulation of a protein's oxidation state) of select protein kinases alters their substrate selectivity. The four-year project, entitled "Analysis of Redox Modification on Kinase Substrate Selection: Molecular Mechanisms and Cellular Consequences", plans to investigate the biochemical mechanisms underlying oxidation-induced shifts in protein kinase substrate selection and to begin to explore the functional consequences of redox modification on kinase-dependent signaling processes inside cells.

Newman's research, which has the potential to answer fundamental questions about the regulation of cellular signaling pathways, will identify points of signal integration between redox- and phosphorylation-dependent cellular signaling pathways. This information can be used to develop computational models of cellular signaling pathways to predict dynamic changes in pathway properties following exposure to various physiological, pharmacological and toxicological stimuli, both in isolation and in combination. His team also hopes to complement existing models of pathological oxidative stress and provide new opportunities for targeted therapies for many diseases, such as cancer, diabetes and cardiovascular disease.