Researchers identify 2 key pathways in adaptive response

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UCSF researchers have identified the two key circuits that control a cell's ability to adapt to changes in its environment, a finding that could have applications ranging from diabetes and autoimmune research to targeted drug development for complex diseases.

The new findings are featured as the cover story in the August 21, 2009 issue of the journal "*Cell*" and are available online at http://www.cell.com.

The limited number of circuits that can achieve adaptation represents a fundamental shift in our understanding of this important biological behavior, which previously had been thought to be affected by hundreds of different circuits, according to Chao Tang, PhD, who was co-senior author on the paper with Wendell Lim, PhD.

Both Lim and Tang are faculty members in the UCSF departments of Bioengineering and Therapeutic Sciences and of Biochemistry and Biophysics, and are affiliated with the California Institute for Quantitative Biosciences (QB3) at UCSF.

Adaptation is a fundamental property of many cellular sensing systems, allowing the cell to automatically reset itself after responding to a stimulus, Lim said. These adaptive circuits are what enable eyes to adjust to changes in light, white blood cells to move toward bacteria, or insulin levels to adjust to sugar loads. They are involved in heat adaptation, movement, sight and smell, among others. They also are

often the mechanisms that go wrong at a molecular level in some of the most difficult diseases to treat.

"Many diseases are diseases of homeostasis," explained Lim, who is also affiliated with the Howard Hughes Medical Institute. "Diabetes or autoimmune diseases, for example, are based on a disruption in the circuitry that prevents the body from readjusting itself."

Until now, however, the millions of circuits involved in that adaptive response were impenetrably complex.

For this research, the team used a computational method to analyze 160 million circuits that come into play when a cell adapts to environmental stimuli and monitored them for the circuit's sensitivity to a stimulus and the precision of its adaptation.

The result was an exhaustive circuit-function map of enzymatic regulatory networks that identified two core structures that are common to every adaptive response, however simple or complex: a negative feedback loop with a buffering node, and a feed-forward loop that adjusts the proportion of response. Furthermore, the researchers said, they established that the most robust adaptive responses rely heavily on at least one of these two minimal motifs.

"This is a new way of looking at biology and disease," Lim said. "We've sequenced the genome, we know the genes involved and have started to understand how they're connected together. But it's like opening your computer and looking at the chips and circuits inside - how do you begin to understand it?"

Unlike chemistry, in which the core elements were understood 100 years ago, there is no equivalent of the periodic table in the field of biology. The field of systems biology, in which both Lim and Tang focus, aims to

create that same systematic approach to understanding how cells and biological systems work.

The goal is to break down the overwhelming amount of information that has been generated by advances over the last decade in genetic sequencing, into recognizable modules that can then be further studied, understood and ultimately used to create drug therapies for complex diseases such as cancer and diabetes that involve multiple genes.

Thus, beyond the specific advance in this particular research, the team's ability to reduce millions of cellular responses to two common circuits lays the groundwork for similar analyses in other biological systems. Despite the diversity of possible biochemical networks, the team said, it may be common to find that only a finite set of core structures can execute a particular function.

"From a scientific standpoint, this is about one thing: Are there universal principles in biology, and if so, what are they," Tang said.

The potential applications from these studies could be tremendous: in medicine, an understanding of what causes a system to shift from one behavior to another could greatly aid in developing more targeted therapeutics for treatments of complex diseases like cancer, the researchers said.

Fundamentally, the complex network of homeostatic response is what makes these diseases so difficult to tackle therapeutically, according to the research team. If the entire network is out of balance, a drug that blocks a single receptor won't work. Identifying the core structures behind adaptive response, however, makes it possible to someday create a therapy that could readjust that network.

It also could have applications in the emerging field of synthetic biology,

by serving as a manual for how to engineer robust biological circuits that carry out a target function.

Source: University of California - San Francisco