Researcher investigates how cells tune in to important information

January 25 2013

(Phys.org)—Every minute of its existence, a living cell must assess and analyze myriad bits of information—everything from the temperature of its environment to the chemical makeup of its surroundings. Sometimes, these inputs cause a cell to change how it functions, but other times, the information may not lead to a measurable change in the cell's activity. Now, Howard Hughes Medical Institute researchers have discovered how a single molecule in a cell can tune its response to different strengths of an input, an important advance in understanding how a whole cell varies its behavior in different situations.

"This signal processing ability is something that's normally associated with collections of molecules or manmade devices," says HHMI investigator Erin K. O'Shea of Harvard University, who led the new research, published January 25, 2013, in the journal *Science*. "Here, the surprise is that we have one molecule that has evolved to do it." O'Shea was recently named HHMI vice president and chief scientific officer, a position that she will begin full-time in July.

O'Shea studies transcription factors, which control when genes in a cell are turned on or off. Scientists know that cells manage transcription factors by moving them in and out of the cell's nucleus, where genes are located. When the transcription factors are inside the nucleus, they can act on their associated genes—either as an on or off switch. O'Shea has previously discovered that shuttling of some transcription factors in and out of the nucleus is controlled by phosphorylation and dephosphorylation—the addition or subtraction of phosphates to the

transcription factors.

O'Shea's lab group was studying Msn2, a transcription factor in yeast cells that helps the cell respond appropriately to stress. In order to study Msn2's response to stresses such as heat, UV light, or toxic chemicals, the researchers selectively controlled PKA, the protein that adds phosphates to Msn2. The response of transcription factors to phosphorylation and dephosphorylation is normally strength-dependent: if a stronger signal is delivered, this usually means a stronger response by the cell. Consistent with that observation, when they delivered a strong, oscillating signal that completely inactivated PKA, Msn2 activity followed or "tracked" the PKA signal.

"But when we applied a periodic weaker signal, it was pretty much entirely filtered out; the cell just didn't respond," says O'Shea. "We wanted to know how the cell could respond to a strong, periodic signal but not to a weaker, periodic signal."

The team began studying the differences between the Msn2 molecules in each case. They found that there are two different sites where the protein can have phosphates added or subtracted—one that slows the import of Msn2 into the nucleus, and another that stimulates export. But the sites aren't phosphorylated equally. When the signal is weak, the import sites are phosphorylated preferentially to the export sites and Msn2 enters the nucleus only very slowly. As a result, during the time the weak pulse is being applied, not much Msn2 enters the nucleus, effectively filtering out the weak signal. It is only when a stronger signal is delivered that PKA is completely inactivated, Msn2 is not phosphorylated at all, and it enters the nucleus rapidly, accumulates there and turns on genes.

"What this does is create a situation where depending on the strength of the input, it can create different patterns of gene activation," says

O'Shea.

Some genes are activated when Msn2 spends a short period of time in the nucleus—which could happen by a weak pulse of PKA. Other genes, however, are only activated when Msn2 bursts into the nucleus in stronger pulses, requiring more inactivation of PKA. If the mechanism of signal filtering is shared by other transcription factors, O'Shea says, it explains how a limited number of transcription factors can create incredibly complex patterns of genes.

Now that the scientists understand how the two distinct phosphorylation sites on Msn2 function to control the nuclear import and export signals, they can use the information to design artificial transcription factors and have control over how fast they move in and out of the nucleus, effectively controlling how they respond to signals and control gene expression. "These sites are very modular," says O'Shea, "so it's really not hard to imagine cutting them out of one protein and adding them to another."

Her lab next plans to understand how widespread the filtering mechanism is among other transcription factors and how other pathways feed information into the system—when the lab is under higher stress, for example, it could tune the system to filter out even greater levels of input than usual or, conversely, to react more strongly.

Provided by Howard Hughes Medical Institute