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Researchers identify cellular distress signal

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Researchers from the University of North Carolina School of Medicine have discovered that a well-known associate of G protein-coupled receptors—a common target of FDA-approved drugs—may play a critical role in mounting a rescue effort to avert an intracellular meltdown.

Like a toddler in need of a nap or a snack, the cells of our bodies can turn a bit sour under conditions of stress or nutrient deprivation. The pH levels inside these cells – starved, perhaps by a heart attack or other injury – have been known to drop dramatically in a cry for help.

This cellular distress signal is captured by molecular "pH meters" that signal the cell to slow down its activities or look for alternative sources of nutrition. Now, researchers from the University of North Carolina School of Medicine have discovered that a well-known associate of G protein-coupled receptors—a common target of FDA-approved drugs—may play a critical role in mounting a rescue effort to avert an intracellular meltdown.

The researchers believe that understanding this process could lead to more effective interventions for illnesses that are characterized by cellular stress, such as diabetes, stroke, heart attack, trauma, and cancer.

"Proteins that sense a change in pH are rare and hard to find, but they are likely to be important in protecting the cell from pretty dramatic effects. It was a big surprise to find that G-proteins could play this completely new role, because this protein family is already so well

understood," said senior study author Henrik Dohlman, PhD, professor and vice chair of the Department of Biochemistry and Biophysics. The results of the research appear online Aug. 15, 2013, in the journal *Molecular Cell*.

G protein-coupled receptors serve as middlemen in the constant and essential communication between cells and their environment. They can detect chemical and sensory cues—familiar hormones and neurotransmitters like dopamine, histamine, and adrenaline and environmental signals like odors, taste and light—and then activate responses to those stimuli within the cell. In this study, Dohlman and his collaborator Dan Isom, PhD, decided to investigate whether G protein-coupled receptor pathways could also sense a change in pH.

Isom began by designing a computer program, which he called pHinder, to examine large numbers of protein structures for hints that they might be able to detect pH. Specifically, the program looked for patterns or spatial networks of protein building blocks that could go from a neutral to a charged status with a change in the environment.

When Isom used this computer program to screen a database of 11,890 different protein structures, he found that only 10 percent of proteins contained potential pH-sensing patterns. However, among this fraction were Ga subunits, structures that had been shown to be key in transmitting signals from G protein-coupled receptors.

The researchers then conducted a series of biochemical and biophysical experiments to confirm the pH-sensing properties of this specialized subunit. By changing the pH inside the cell, they were able to drive a change in the actual shape of the Ga subunit that mimicked the changes seen when the G protein-coupled receptor itself is turned on.

"This pH sensor appears to be part of a signaling network that can tell

when the cell is in trouble," said lead study author Dan G. Isom, research assistant professor in Dohlman's laboratory. "When a cell is starved, the pH drops, and these sensors alert the cell to go into a mode of protection. It gets reprogrammed to only do what is absolutely necessary and to start looking for alternative resources."

By further understanding this pH sensor and uncovering others like it, researchers may be able to develop new ways of treating common illnesses like heart disease and cancer. For example, a shared characteristic of nearly all cancers is a slightly elevated pH inside the cell. By identifying the pH sensors within cancer cells, researchers may be able to develop a universal strategy that could work for many different types of cancer.

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