Researchers find key to keeping cells in shape

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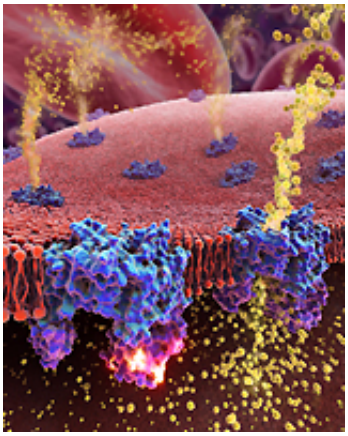

Ion transporter in blue within the red blood cell membrane. When phosphorylated or inactivated (white flash) the transporter shuts down. When dephosphorylated it is active, allowing potassium and chloride to leave the cell. Photo: Yale University

(PhysOrg.com) -- Yale University researchers have discovered how a protein within most cell membranes helps maintain normal cell size, a breakthrough in basic biology that has implications for a variety of diseases such as sickle cell anemia and disorders of the nervous system.

Cell size is regulated by the balance of positively and negatively charged ions and other solutes in the fluid inside and outside cells, which in turn prevents water from moving across cell membranes and changing cell size. Changes in chemical composition of extracellular fluid can disrupt this balance, sometimes with damaging consequences to health.

"If you eat a bag of salty potato chips or a jug of water, the cells lining your stomach will be under pressure to shrink or expand," explains Richard Lifton, senior author of the paper and Sterling Professor of Genetics and Internal Medicine. "Cells need to rapidly change their ionic composition to compensate and avoid blowing up like balloons or shrinking like raisins, and they do this by almost instantly changing their chloride levels."

In the Aug. 7 issue of the journal *Cell,* a team of Yale scientists led by Jesse Rinehart, associate research scientist in genetics and Lifton, an investigator of the Howard Hughes Medical Institute, report they used innovative new quantitative proteomics technologies to identify two key regulatory transporter sites that control the exit of potassium and chloride out of cells.

The proteomics technologies allow scientists to observe specific sites on proteins that undergo phosphorylation. Phosphorylation is a common and reversible modification made to a protein after it is synthesized and can turn a protein's function on or off. The Yale scientists show that the regulatory sites they identified are almost completely phosphorylated under normal conditions, when the transporter is inactive. When confronted with changes in the environment that challenge the cell, the proteins are rapidly dephosphorylated and dramatically increase transport activity.

"These transporters are overactive in sickle cell anemia and play a role in the dehydration of sickle cells," said Patrick Gallagher, professor of pediatrics at the Yale School of Medicine and a co-author of the study. "With this new information, we may be able to find new strategies to manipulate this activity and identify new treatments that are so urgently needed."

Gallagher's lab is already studying genetic variations in the potassium-

chloride pathway in a search of new drug targets.

This same system also helps regulate how brain cells respond to the neurotransmitter GABA, which governs wakefulness and has been implicated in anxiety and other disorders, Lifton said. The investigators found that phosphorylation of the regulatory sites worked the same way in the brain.

Looking to the future, Rinehart speculated that application of these new technologies will prove to be relevant to understanding many other biological regulatory systems.

Source: Yale University (news : web)