Notch-ing glucose into place

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A novel gene called rumi regulates Notch signaling by adding a glucose molecule to the part of the Notch protein that extends outside a cell, said researchers from Baylor College of Medicine in Houston and Stony Brook University in New York in a report that appears today in the journal *Cell*.

Cellular signaling governed by the Notch protein determines cell fate determination and differentiation.

The complete loss of rumi causes a temperature-dependent defect in Notch signaling, an unusual phenomenon said Dr. Hugo Bellen, professor of molecular and human genetics at BCM and director of the program in developmental biology. He is also a Howard Hughes Medical Institute investigator.

Bellen and his colleagues discovered the gene's effect on bristles in the fruit fly. These bristles are external sensory organs that can be easily screened for changes involved in Notch signaling. Indeed, loss of Notch signaling causes loss of these external sensory organs. Fruit flies that lack the rumi protein have a higher than normal density of bristles on the thorax, indicating a subtle loss of Notch activity. However, at 25 degrees C, the bristles are lost, which suggests a severe loss of Notch signaling.

"The activity of the Notch receptor needs to be inactivated in one cell to allow it to become different from the other daughter cell, and this process is used reiteratively in many consecutive cell divisions. For example, if Notch is activated inappropriately in cells of the blood lineage, it will cause leukemia in humans," said Bellen.

"It is also a key gene to specify neurons in the peripheral and central nervous system," said Bellen. When embryos lack a functional Notch protein, they have far too many neurons. The same phenomenon can be observed in rumi mutant embryos.

In animals with mutated rumi, the Notch protein accumulates in the membrane and fails to become activated. Similarities between rumi and some sugar-modifying enzymes involved in a particular process in the yeast Cryptococcus neoformans prompted Bellen to ask if loss of rumi affects the manner in which glucose molecules are added to the Notch protein.

He and his colleagues found that some sugars are not added to the Notch protein in rumi-mutant animals. This finding led to further experiments that demonstrated that the protein associated with rumi is a type of enzyme called an O-glycosyltransferase.

The Notch protein crosses the cellular membrane, with part inside the cell and part outside. The outer portion of Notch contains amino acid repeats that are similar to epidermal growth factor. Rumi is involved in adding a sugar to certain areas of these repeats.

Bellen said, "The sugars play a crucial role to ensure that Notch is folded properly and that it can be cleaved at the cell membrane. If cleavage does not occur, there is no Notch signaling. Rumi is the first protein identified that can transfer glucose to proteins directly."

Source: Baylor College of Medicine