Jigsaw a critical piece of the Notch puzzle

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The Notch signaling pathway helps determine cell fate determination, differentiation and proliferative ability of numerous cells. How it accomplishes these tasks has been a puzzle, but researchers led by those at Baylor College of Medicine and the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital have identified a key piece –a specific domain (or part of the receptor) within the Notch receptor that is critical for determining the specific ligand to which the receptor binds. The finding provides researchers with a molecular handle on which to base future studies of this critical protein. A report on their work appears online in the journal *Science*.

Misregulation of Notch signaling is seen in various types of cancers and numerous human diseases. The Notch receptor can be activated by binding to two families of ligands, Serrate and Delta. Since different ligands can have different consequences on signal activation depending on the context, understanding how Notch discriminates Serrate and Delta is crucial. Most of the Notch receptor is composed of what scientists call EGF repeats (epidermal growth factor-like repeats). Previous studies have suggested that the key lies within these repeats.

"We don't know the function of most of these EGF repeats on Notch," said Dr. Shinya Yamamoto, a former graduate student from the Program in Developmental Biology and currently a postdoctoral fellow in the laboratory of Dr. Hugo Bellen, director of the Program in Developmental Biology and professor of molecular and human genetics and neuroscience at BCM. "There are 36 of them. Some are needed to bind to both of the ligand families, while others are required to bind to

only one kind." Indeed, mutations in these repeats have been found in patients with Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), a hereditary stroke disorder; Alagille syndrome, a genetic disorder that affects the liver, heart, skeleton, eye and other organs; aortic valve disease, and squamous cell carcinoma.

In studies in fruit flies (Drosophila melanogaster), Yamamoto and his colleagues screened for mutated alleles (alternative forms of a gene) of Notch and focused on a mutation that they named Jigsaw. Flies with this mutation have normal bristles on the thorax but defects in the wing. They showed that the Notch gene exhibits defects in its ability to bind to Serrate but not Delta. They also showed that a similar mutation in mouse Notch2 fails to signal in response to Jagged, the mammalian homolog of Serrate.

"Structural biologists will now have a molecular handle with which to begin investigating the molecular basis of ligand selectivity at the atomic level," said Yamamoto. "Others may consider EGF repeat 8 as a potential drug target for small molecules and monoclonal antibodies."

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