Wnt signaling pathway plays key role in adult nerve cell generation: study

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Researchers from the University of Utah have gained new insight into the regulation of adult nerve cell generation in the hypothalamus, the part of the brain that regulates many aspects of behavior, mood, and metabolism. In the Sept. 10, 2012, issue of *Developmental Cell* they report that a cell-to-cell communication network known as the Wnt signaling pathway plays an important role in both the production and specialization of nerve cell precursors in the hypothalamus.

The hypothalamus is a highly complex region of the brain that controls hunger, thirst, fatigue, body temperature, and sleep. It also links the central nervous system to the body system that regulates hormone levels. Recent studies have shown that the hypothalamus is one of the parts of the brain in which neurogenesis, the birth of new nerve cells, continues throughout adulthood.

"In our earlier work, we discovered that Wnt signaling was required for neurogenesis in the embryonic zebrafish hypothalamus," says Richard Dorsky, Ph.D., associate professor of neurobiology and anatomy at the University of Utah School of Medicine and senior author on the study. "We also found that, in zebrafish, both Wnt signaling and hypothalamic neurogenesis continue into adulthood. The goal of this study was to define specific roles for Wnt signaling in neurogenesis."

The Wnt signaling pathway is a network of proteins that transmits signals from the cell surface to DNA in the cell nucleus to regulate gene expression, and it is known to play a critical role in cell-to-cell

communication in both embryos and adults. In this study, Dorsky and his colleagues demonstrated that in zebrafish embryos Wnt signaling is present in progenitor cells that are actively multiplying in the hypothalamus. Progenitor cells have the potential to divide and differentiate into a variety of specialized cell types. Dorsky and his colleagues also found that Wnt signaling continues to be required for hypothalamic neurogenesis throughout life.

Neural progenitor cells arise from neural stem cells, and retain the capacity to develop into more specialized types of nerve cells. After the embryo is formed, some neural stem cells lie dormant in the brain and spinal cord until they are activated to serve as a repair system. When tissue damage or death occurs, chemical substances trigger these neural stem cells to make neural progenitor cells that assist in tissue recovery. Recent research suggests that other neural progenitor cells continue to make new nerve cells in the uninjured brain and contribute to the plasticity of the brain in response to changes in the environment.

"From a functional standpoint, it is not yet clear why the ability to continuously produce hypothalamic nerve cells is important in adult zebrafish," says Dorsky. "However, in adult mice, hypothalamic neurogenesis seems to be significant in the regulation of feeding behaviors due to environmental changes."

Dorsky and his colleagues discovered that the role of the Wnt signaling pathway differs between embryos and adults. In zebrafish embryos, activation of Wnt signaling is required for proliferation of progenitor cells contributing to growth of brain structures. However, at later stages of development including adulthood, Wnt signaling must be active for neural progenitor cells to commit to becoming nerve cells, but then must be inhibited for these cells to complete the differentiation process. Significantly, Dorsky and his colleagues also found that mice displayed a similar pattern of Wnt activity.

"Compared to other regions of the brain, the hypothalamus is relatively unstudied as a model of post-embryonic neurogenesis," says Dorsky. "Our research represents a significant contribution to the field because it establishes the vertebrate hypothalamus as a model of Wnt-regulated neural progenitor differentiation that can be used to shed light on the plasticity of the adult brain."

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