Neural stem cell differentiation factor discovered

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Neural stem cells represent the cellular backup of our brain. These cells are capable of self-renewal to form new stem cells or differentiate into neurons, astrocytes or oligodendrocytes. Astrocytes have supportive functions in the environment of neurons, while oligodendrocytes form the myelin layer around axons in order to accelerate neuronal signal transmission. But how does a neural stem cell "know" which way it is supposed to develop?

On the molecular level receptors of the Notch family play a significant role in this process. So far, only stimulating extracellular ligands of Notch receptors had been described. Biochemists of Goethe University Medical School now describe a long time assumed but not yet identified soluble Notch inhibitor.

Franfurt scientists led by Mirko Schmidt and Ivan Dikic reported in the renowned journal *Nature Cell Biology* that the secreted protein EGFL7 (Epidermal Growth Factor-like domain 7) is such an inhibitory factor. EGFL7 had already been known from its involvement in the development of blood vessels.

"It was a surprise when we discovered that EGFL7 bound the extracellular domains of Notch receptors and competed with known Notch ligands," explains Ivan Dikic from the Institute of Biochemistry and CEF Institute in Frankfurt. Researchers analyzed the antagonistic effects of EGFL7 in adult neural stem cells. The self-renewal potential of these cells depends on an intact interaction of the ligand Jagged1 and

its receptor Notch1. Addition of EGFL7 blocked the essential interaction and reduced the division of neural stem cells. At the same time, EGFL7 stimulated the differentiation of neural stem cells into neurons.

"It has been well defined that Notch signaling drives the formation of astrocytes from neural stem cells while it suppresses the formation of neurons and the maturation of oligodendrocytes," explains Mirko Schmidt at the Institute of Neurology. Inhibition of Notch signaling reverses the situation and more neural stem cells differentiate into neurons. This is exactly what happened upon the addition of EGFL7. In order to verify their findings in vivo, the researchers analyzed mouse brains and identified mature neurons as a source of EGFL7 in the adult brain. The distribution of these cells in the brain was biologically significant, as EGFL7 was absent from regions with high amounts of neural stem cells, e.g. the subventricular zone. "This way EGFL7 may promote the formation of new neurons," suggests Schmidt.

The findings of Schmidt and Dikic offer a plethora of medical applications. Maturation of adult stem or precursor cells is significant for the development of multiple tissues, e.g. in the central nerve system or in the heart. Moreover, cancer stem cells have been described, which are important for the formation of tumors, especially in the human brain. EGFL7 might also be applied as a neuronal differentiation factor in ischemic insults or neurodegenerative diseases such as Alzheimer or Parkinson predict both researchers. Future work will unravel in which diseases EGFL7 can unfold its therapeutic potential.

More information:

Nature Cell Biology:
www.nature.com/ncb/journal/vao … ent/abs/ncb1896.html

Nature Reports Stem Cells
www.nature.com/stemcells/2009/ … emcells.2009.84.html

Nature Signaling Gateway:
www.signaling-gateway.org/update/featured/

Source: Goethe University Frankfurt