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PRESS-RELEASE

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STEM CELLS AND BRAIN-ORGANOIDS ARE "HOT SPOTS" OF BRAIN RESEARCH

Stem cells give rise to the entire adult organism. After development is complete, stem cells still remain in different organs in the adult. The stem cells from which nerve cells emerge are also still active in certain regions of the adult brain. Numerous investigations are focusing on how these stem cells become highly differentiated nerve cells. In many laboratories, neuronal stem cells are cultured as three-dimensional structures, so-called organoids. These "minibrains" can be used to investigate the early phases of brain development and the development of neurological and psychiatric disorders and diseases. Stem cells and organoids are the focus of a symposium at the FENS Forum 2018 in Berlin today (10 July).

A large stem cell niche in the adult brain is the ventricular-subventricular zone (V-SVZ). Stem cells in this region have a spatial identity and, depending on their location, give rise to different subtypes of neurons that migrate to the olfactory bulb, a region in which olfactory stimuli are processed. However the signals that control the different pools of spatially distinct stem cells is unclear.

Prof. Dr. Fiona Doetsch's team at the Biocenter at the University of Basel has now discovered that long-distance cues from other brain regions can regulate the division of different pools of stem cells. "We found that the hypothalamus, which controls a variety of physiological functions, can send signals to the V-SVZ via long-distance projections and thus activate and regulate specific pools of stem cells". The scientists were also able to show that hunger and satiety play a role in this control. "Our findings reveal that physiological states can regulate the division of different pools of stem cells and generation of specific subtypes of neurons. Long-range neural circuits may therefore control distinct pools of stem cells to produce neurons "on-demand" in different physiological contexts".

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It has taken four million years for the human brain to grow from 500 to 1500 ml. In the last two million years especially there has been a dramatic increase in the size of the brain. Without the enormous multiplication of nerve cells that made the cerebrum of humans larger, the achievements of human culture would hardly be conceivable.

The team of **Prof. Dr. Pierre Vanderhaeghen** from the Flanders Institute for Biotechnology (VIB/KU Leuven) in Leuven analysed numerous gene candidates in the search for the genetic factors that cause the cerebrum to grow. they all emerged from ancestral genes through duplication. Professor Vanderhaeghen calls them ""human-specific gene duplications". The multiplication of ancestral genes by duplication that occurs only in humans could play a role in

human-specific aspects of brain development, such as the generation of a higher number of neurons that characterizes the cerebral cortex in our species. This is what the team of Vanderhaeghen tested next. Among these 35 genes, one group in particular was of interest to the scientists for their unusual ability to promote amplification of the neural stem cells of the cerebral cortex. It is called Notch2NL and comprises four members, which emerge from an ancestral gene (Notch2) which plays an important role in the signal processing of cells and thus in organ development in general.

As the team was able to show in further investigations using human pluripotent stem cells models of differentation, that the Notch2NL genes forced the proliferation of neuronal progenitor cells during embryonic development which in turn generated more neurons.

"In view of the outstanding importance of the Notch pathway in the formation of nerve cells, we assume that the NOTCH2NL genes could act as species-specific regulators of brain size," said Professor Vanderhaeghen.

Three human-specific NOTCH2NL genes are located on the first chromosome. Mutations in this area may also play a role in disorders and diseases. Research findings of a group of American researchers show that mutations in the DNA from people with microcephaly (a congenital abnormality in which the brain does not grow properly and the head is small) or macrocephaly (an enlarged head which may be linked to conditions such as autism) matched the regions of two NOTCH2NL genes.

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The research of **Prof. Dr. Arnold Kriegstein** from the University of California in San Francisco also focuses on neuronal stem cells and progenitor cells that produce neurons in the growing embryonic brain. His team was one of the first to identify so-called radial glial cells - brain cells that are not neurons - as stem cells of the brain. These cells produce a group of precursor cells in two niches in the brain, which in turn produce specific subtypes of nerve cells. "Our team has started to investigate the genetic activity of progenitor cells and young neurons in order to clearly classify the cells. We want to find out how these cells contribute to the enormous proliferation of nerve cells typical of the human cerebrum", says Professor Kriegstein.

As reported by Professor Kriegstein at the FENS Forum, his research group was able to gain new insights in the mechanisms of brain development on the basis of these investigations. For example, by examining organoids, the team was able to analyse in more detail the processes that cause a serious malformation of the brain called lissencephaly, the brain is smooth and the folds of the cerebral cortex are missing. Children with lissencephaly have seizures and muscle spasticity. Their movement is impaired and some do not survive for more than a few years.

Professor Kriegstein's team was able to reverse the genetically-determined migration disorder of the nerve cells in the mini-brain, which is the cause of the disease, by transferring the missing section of the genome. Organoids were also used by the scientists to elucidate the causes of congenital brain defects in children whose mothers were infected with the Zika virus during pregnancy. "The investigations into brain organoids were able to establish the causal connection between infection and destruction of neuronal progenitor cells," says Professor Kriegstein. "Their ability to differentiate, to organize themselves and to form complex structures make brain organoids ideal models of brain development and for the investigation of brain disorders and diseases. "They have advantages compared to conventional rodent models because they are human."

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Symposium S41: *Stem cells and the brain: Neurons, niches and organoids*

Abstract Reference
Expanding the niche: Long-range regulation of adult neural stem cells, Fiona Doetsch
Human brain development; modeled by cerebral organoids?, Arnold Kriegstein

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NOTES TO EDITORS

Prof. Dr. Fiona Doetsch, *Biocenter at the University of Basel*
https://www.biozentrum.unibas.ch/research/researchgroups/overview/unit/doetsch/research-group-fiona-doetsch/

Prof. Dr. Pierre Vanderhaeghen from the Flanders Institute for Biotechnology (VIB/KU Leuven) in Leuven
http://dev.ulb.ac.be/pvdhlab/

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https://www.nottingham.ac.uk/psychology/people/tobias.bast

The 11th FENS Forum of Neuroscience, the largest basic neuroscience meeting in Europe, organised by FENS and hosted by the German Neuroscience Society will attract more than 7,000 international delegates. The Federation of European Neuroscience Societies (FENS) was founded in 1998. With 43 neuroscience member societies across 33 European countries, FENS as an organisation represents 24,000 European neuroscientists with a mission to advance European neuroscience education and research. https://forum2018.fens.org/

Further Reading
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and neurogenesis
Science. 2017 Jun 30;356(6345):1383-1386. doi: 10.1126/science.aal3839.

Vanderhaeghen:
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Nat Rev Neurosci. 2017 October; 18(10): 573–584. doi:10.1038/nrn.2017.107.