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Attractants prevent nerve cell migration

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A vision is to implant nerve precursor cells in the diseased brains of patients with Parkinson's and Huntington's diseases, whereby these cells are to assume the function of the cells that have died off. However, the implanted nerve cells frequently do not migrate as hoped, rather they hardly move from the site. Scientists at the Institute for Reconstructive Neurobiology at Bonn University have now discovered an important cause of this: Attractants secreted by the precursor cells prevent the maturing nerve cells from migrating into the brain. The results are presented in the journal "*Nature Neuroscience*."

One approach for treating patients with Parkinson's or Huntington's disease is to replace defective brain cells with fresh cells. To do this, immature precursor cells from neurons are implanted into the diseased brains; these cells are to then mature on-site and take over the function of the defective cells. "However, it has been shown again and again that the nerve cells generated by the transplant barely migrate into the brain but remain largely confined to the implant site," says Prof. Dr. Oliver Brüstle, Director of the Institute for Reconstructive Neurobiology at Bonn University. Scientists have believed for a long time that this effect is associated with the fact that in the mature brain, there are unfavorable conditions for the uptake of additional nerve cells.

Immature and more mature nerve cells attract each other like magnets

The researchers from the Institute for Reconstructive Neurobiology of Bonn University have now discovered a fully unexpected mechanism to

which the deficient migratory behavior of the graft-derived neurons can be attributed. The implanted cells mature at different rates and thus there is a mixture of the two stages. "Like magnets, the precursor cells which are still largely immature attract the nerve cells which have already matured further, which is why there is a sort of agglomeration," says lead author Dr. Julia Ladewig, who was recently awarded a research prize of 1.25 million Euro by the North Rhine-Westphalian Stem Cell Network, which is supported by State Ministry of Science and Research.

The cause of the attractive force which has remained hidden to date involves chemical attractants which are secreted by the precursor cells. "In this way, the nerve precursor cells prevent the mature brain cells from penetrating further into the tissue," says Dr. Philipp Koch, who performed the primary work for the study as an additional lead author, together with Dr. Ladewig.

The scientists had initially observed that, the more precursor cells contained in the transplant, the worse the migration of nerve cells is. In a second step, the researchers from the Institute for Reconstructive Neurobiology at Bonn University were able to decode and inactivate the attractants responsible for the agglomeration of mature and immature neurons. When the scientists deactivated the receptor tyrosine kinase ligands FGF2 and VEGF with inhibitors, mature nerve cells migrated better into the animal brains and dispersed over much larger areas.

Promising universal approach for transplants

"This is a promising new approach to solve an old problem in neurotransplantation," Prof. Brüstle summarizes. Through the inhibition of attractants, the migration of implanted nerve precursor cells into the brain can be significantly improved. As the researchers have shown in various models with precursor cells from animals and humans, the mechanism is a fundamental principle which also functions across

species. "However, more research is still needed to transfer the principle into clinical application," says Prof. Brüstle.

More information: "Auto-attraction of neural precursors and their neuronal progeny impairs neuronal migration," *Nature Neuroscience*, DOI: 10.1038/nn.3583

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