HDAC5: a key factor in nerve regeneration

A paper published in a recent issue of *Cell* has identified the protein HDAC5 as a key component of the chain reaction that induces nerve regeneration. The group from Washington University (MO, USA) who are responsible for the paper, hope this finding will contribute to the use of nerve regeneration to treat CNS injuries.

Although some nerve cells in the peripheral nervous system (PNS) have been shown to regenerate damaged axons, injured nerve cells in the CNS – the brain and spinal cord – typically do not replace lost axons. The group tried to identify what differs between the cells in PNS and CNS that allows regeneration in the PNS. They observed that, when peripheral nerve axons are severed, a surge of calcium travels back up the axon that instigates a chain reaction in order to repair the cell.

A key part of this chain reaction was the release of the HDAC5 protein from the cell's nucleus. The release of HDAC5 activates a number of genes, that are involved in the regeneration process, as well as locating to the site of injury to induce the production of microtubules. As part of the cytoskeleteon, microtubules are rigid tubes that support the structural network of nerve cells and help establish the structure of axons.

Valeria Cavalli, Assistant Professor of eurobiology at Washington University and senior author of the paper, said: "We knew several genes that contribute to the regrowth of these nerve cell branches, which are called axons, but until now we didn't know what activated the expression of these genes and, hence, the repair process."

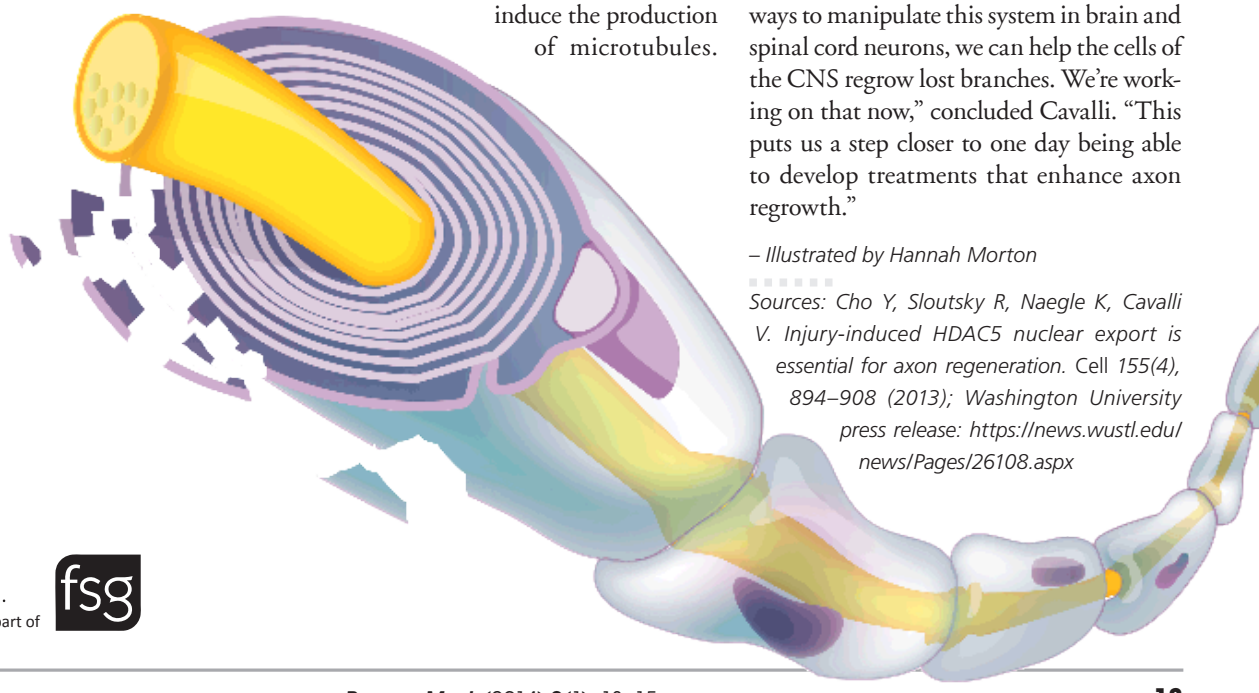
The group extended their investigation by genetically modifying peripheral nerve cells to not release the HDAC5 protein from the nucleus. These cells did not regenerate *in vitro* after they were damaged. In addition, axon regrowth was encouraged *in vivo* when animals were given drugs that increased the level of HDAC5 being released from the nucleus.

This regeneration chain reaction does not occur in CNS nerve cells as HDAC5 does not leave the nucleus when axons are severed.

"This gives us the hope that if we can find ways to manipulate this system in brain and spinal cord neurons, we can help the cells of the CNS regrow lost branches. We're working on that now," concluded Cavalli. "This puts us a step closer to one day being able to develop treatments that enhance axon regrowth."

– Illustrated by Hannah Morton

Sources: Cho Y, Sloutsky R, Naegle K, Cavalli V. Injury-induced HDAC5 nuclear export is essential for axon regeneration. Cell *155(4), 894–908 (2013); Washington University press release: https://news.wustl.edu/news/Pages/26108.aspx*



Future Medicine part of fsg

Transplanted stem cells regenerate damaged colon

A group from the Wellcome Trust has recently published a paper in *Cell Stem Cell* where they used fetal intestinal progenitor cells to regenerate the damaged colon of a mouse *in vivo*. This technique has the potential to be used as a treatment for conditions such as inflammatory bowel disease.

The group first identified a population of proliferative, immature progenitor stem cells in both human and mouse fetal intestines; these cells could be expanded *in vitro* into fetal enterospheres. When these cells were transplanted into mice with inflammatory bowel disease, the cells combined with the gut cells and started to contributed to the repair of the damaged colon tissue.

Kim Jensen, a Wellcome Trust researcher and Lundbeck Foundation fellow, who led the study, said: "We've identified a source of gut stem cells that can be easily expanded in the laboratory, which could have huge implications for treating human inflammatory bowel diseases." Jensen continued: "We found that the cells formed a living plaster over the damaged gut. They seemed to respond to the environment they had been placed in and matured accordingly to repair the damage."

Jensen explained that: "One of the risks of stem cell transplants like this is that the cells will continue to expand and form a tumor, but we didn't see any evidence of that with this immature stem cell population from the gut."

> "We found that the cells formed a living plaster over the damaged gut. They seemed to respond to the environment they had been placed in and matured accordingly to repair the damage."

In addition to these progenitor cells being isolated from both mice and humans, the group was also able to generate similar cells using induced pluripotent stem cells.

Jensen concluded: "The next step will be to see whether the human cells behave in the same way in the mouse transplant system, and then we can consider investigating their use in patients."

Sources: Fordham RP, Yui S, Hannan NR et al. *Transplantation of expanded fetal intestinal progenitors contributes to colon regeneration after injury.* Cell Stem Cell *doi:10.1016/j.stem.2013.09.015 (2013) (Epub ahead of print); Wellcome Trust press release: www.wellcome.ac.uk/News/Media-office/Press-releases/2013/Press-releases/WTP054261.htm*

Nanoporous particles used to differentiate embryonic stem cells *in vivo*

A paper published in a recent issue *Stem Cells Translational Medicine* has shown that silica nanoporous particles can be used to deliver differentiation factors to transplanted murine embryonic stem cells *in vivo*.

There is great potential is using stem cell transplantation for the replacement of damaged cells in the nervous system. However, one of the major obstacles for clinical application is the poor long-term survival and insufficient differentiation of transplant stem cells *in vivo*.

In order to overcome this issue, a collaborative international research group (from the Uppsala University [Sweden], the RIKEN Brain Science Institute [Japan] and the Panum Institute at Copenhagen University [Denmark]) developed a novel technological approach for the local delivery of motor neuron differentiation factors to transplanted embryonic stem cells using specifically designed silica nanoporous particles.

Elena Kozlova, codirector of the study and Associated Professor at the Department of Neuroscience, Uppsala University, explained the findings, saying: "We demonstrated that delivering key molecules for the differentiation of stem cells *in vivo* with these particles enabled not only robust functional differentiation of motor neurons from transplanted embryonic stem cells but also improves their long-term survival."

Alfonso Garcia-Bennett, from Department of Materials and Environmental Chemistry, Stockholm University (Sweden), and one of the leading authors of the study, said: "We are working to provide standard and reproducible methods for the differentiation and implementation of stem cell therapies using this type of approach, which couples material science with regenerative medicine."

It is hoped that these results may lead to improvements in the way stem cell-based neurodegenerative diseases are treated.

Sources: Garcia-Bennett AE, Kozhevnikova M, König N et al. *Delivery of differentiation factors by mesoporous silica particles assists advanced differentiation of transplanted murine embryonic stem cells.* Stem Cells Transl. Med. *2(11), 906–915 (2013); Stockholm University press release: www.su.se/english/about/news-and-events/press/press-releases/a-new-take-on-efficient-delivery-in-regenerative-medicine-1.152630*

Biopatch developed for bone regeneration

Researchers from the University of Iowa (IA, USA) have developed a biopatch that assists with bone regeneration, as reported in a recent issue of *Biomaterials*.

The group used a collagen scaffold biopatch to deliver nonviral plasmid DNA to human bone marrow stromal cells in order to encourage bone repair and regeneration. The plasmid DNA encoded PDGF-B, and, when transfected into the bone cells, enabled the cells to produce the required growth factor protein.

Aliasger Salem, professor in the College of Pharmacy (University of Iowa) and one of the authors on the paper, said: "The delivery mechanism is the scaffold loaded with the plasmid. When cells migrate into the scaffold, they meet with the plasmid, they take up the plasmid, and they get the encoding to start producing PDGF-B, which enhances bone regeneration."

> "We can make a scaffold in the actual shape and size of the defect site, and you'd get complete regeneration to match the shape of what should have been there."

The hope is this method will have potential density applications as well as regenerating bone to repair birth defects where individuals are missing bone around the head or face. Satheesh Elangovan, Assistant Professor in the University of Iowa's College of Dentistry, described the possible applications of this technology, saying: "We can make a scaffold in the actual shape and size of the defect site, and you'd get complete regeneration to match the shape of what should have been there."

The use of plasmid DNA allowed the investigators to overcome the shortcomings of protein delivery of growth factors. Salem explained that: "We delivered the DNA to the cells, so that the cells produce the protein and that's how the protein is generated to enhance bone regeneration. If you deliver just the protein, you have to keep delivering it with continuous injections to maintain the dose." Salem continued: "With our method, you get local, sustained expression over a prolonged period of time without having to give continued doses of protein."

> "The hope is this method will have potential density applications as well as regenerating bone to repair birth defects..."

As the biopatch delivery system is nonviral, the plasmid is less likely to cause an undesired immune response and is easier to produce in mass quantities, lowering the manufacturing cost. "The most exciting part to me is that we were able to develop an efficacious, nonviral-based gene-delivery system for treating bone loss," concluded Sheetal D'Mello, a graduate student in pharmacy and one of the paper's authors.

Sources: Elangovan S, D'Mello SR, Hong L et al. *The enhancement of bone regeneration by gene activated matrix encoding for platelet derived growth factor.* Biomaterials *35(2), 737–747 (2014); University of Iowa press release: http://now.uiowa.edu/2013/10/bio-patch-can-regrow-bone*

– All stories written by Theo Bond

About the News

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