New clue into how brain stem cells develop into cells which repair damaged tissue

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The joint research, funded by the National Multiple Sclerosis Society and the UK MS Society as well as the National Institutes of Health and Howard Hughes Medical Institute, was conducted by scientists at the University of California San Francisco (UCSF) and University of Cambridge and was published today in the journal *Genes and Development*.

Multiple sclerosis is an autoimmune disease which is caused by the body's immune system attacking nerve fibres and their protective insulation, the myelin sheath, in the central nervous system. This damage prevents the nerves from 'firing' properly, and then leads to their destruction, resulting in physical and intellectual disabilities.

It is currently thought that two components determine clinical outcomes in MS. First, it is important to stop ongoing damage (mainly achieved by controlling inflammation in the central nervous system). The second is to repair the damage that has occurred to the protective myelin sheaths surrounding the nerve fibres (this involves a regenerative process called remyelination in which new myelin sheaths are restored to nerve fibres).

While there exist several effective treatments to reduce inflammatory damage, no treatments are available to augment remyelination to repair the damage to nerve fibres. Critical to the development of such repair therapies is to understand how the brain's own stem cells can replace the myelin forming cells (oligodendrocytes) lost in the disease. During early stages of the disease the brains own stem cells are surprisingly good at

repairing damage in MS. However, for reasons that until now have not been well explained, they become less efficient as the disease progresses.

In this study the researchers have identified the Wnt pathway, which plays an active role in the maintenance and proliferation of stem cells, as a crucial determinant of whether oligodendrocytes can efficiently make myelin. Their studies demonstrate that if the Wnt pathway is abnormally active, then the process is inhibited. This opens up the exciting possibility that the repair can be enhanced in MS patients by drugs that block the Wnt pathway.

Professor Robin Franklin from the University of Cambridge, a co-senior author of the study, explained the significance of their findings: "The pathway we identified plays a critical role in whether repair to the damaged cells will or will not occur. Interestingly, mutations in this particular pathway are also involved in several cancers. In this regard, drugs that inhibit this pathway from signaling have been sought which might suppress tumour growth. These same drugs may also find a role in promoting repair in MS."

Lead author of the study, Stephen Fancy, PhD, a postdoctoral fellow in the lab of co-senior author David Rowitch, MD, PhD, a Howard Hughes Medical Institute Investigator at the University of California, San Francisco, said: "We believe we have made a significant step forward in understanding why repair might fail in neurological diseases such as MS by identifying a pathway which inhibits the myelin repair process," said the

MS Society Director of Research, Jayne Spink, said: "We are delighted with the outcome of this outstanding research, which gives us greater knowledge of the mechanics of MS. This works opens up new avenues of research and lends itself to more study. Being able to uncover the secrets behind the damage caused in MS will take us forward in our

understanding of this debilitating condition."

"Our studies work have implications for other diseases," said UCSF's Rowitch. "In a condition called periventricular leukomalacia (PVL), which can lead to cerebral palsy in extremely premature infants, recent studies show a similar inability of oligodendrocytes to perform their important repair function. In respect to failed myelin repair, we see a parallel between the chronic demyelinated plaques of multiple sclerosis and the lesions of PVL."

Source: University of Cambridge (news : web)