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How a protein controls the production of nerve cells in the brain

Researchers at the University of Cologne have discovered that the protein YME1L regulates the production of new nerve cells and the maintenance of neuronal stem cells in the adult brain. This holds great potential for regenerative treatments after brain injuries and other diseases / publication in 'Cell Reports'

By investigating changes in the metabolic profile of neural stem cells, a research team led by Professor Dr. Matteo Bergami from the CECAD Cluster of Excellence for Aging Research at the University of Cologne discovered that the protein YME1L is essential in coordinating the shift between cellular proliferation (cell division) and quiescence (a resting state). The protein YME1L is responsible for balancing the conversion of the brain's neural stem cells, which are limited in number and cannot be produced again, into neurons. Defects in the functioning of this protein can lead to a premature conversion of neural stem cells into specialized cells, and hence impair neural regeneration in the long term. The article 'Metabolic control of adult neural stem cell self-renewal by the mitochondrial protease YME1L' has been published in *Cell Reports*.

Neural stem cells are maintained in only a few regions of the adult mammalian brain, where they sustain the production of new neurons throughout life. Understanding how neural stem cell activity is regulated and maintained in these regions has critical implications for regenerative approaches following brain trauma and disease. Mutations in YME1L have also been linked to brain disorders and intellectual disability in human patients.

YME1L is a protease (an enzyme which cleaves other proteins) localized in mitochondria, the powerhouses of the cells. As for other mitochondrial proteases, YME1L plays an important role in the quality control of proteins within mitochondria. By analysing the level of those proteins known to be targeted by YME1L, the scientists now found that the enzymatic activity of YME1L precisely reflects different metabolic states in neural stem cells. Higher YME1L activity marks a quiescent (dormant) state while lower YME1L activity matches with a proliferative state.

This balance in YME1L activity is required to maintain the stemness properties of neural stem cells, as impairments in YME1L function force cells to exit their status of stem cells and prematurely specialize into different types of nerve cells, leading to the overall loss of stem cells from brain tissue. Ultimately, this stem cell loss has a major impact on the long-term neurogenic capacity of the brain, as no further neurons can be produced.

'Our results show that the activity of a single mitochondrial protease can significantly affect the fate of neural stem cells and the production rate of new nerve cells. These findings not only reveal a new layer of regulation in the biology of neural stem cells but may also have important implications for patients bearing mutated YME1L,' Bergami said.

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