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Commentary

Unlocking The Potential of Nerve Growth Factor in Serotonergic Neurons

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ABOUT THE STUDY

The neurotrophin Brain-Derived Neurotrophic Factor (BDNF) promotes adult neurogenesis while also influencing structural plasticity and serotonergic neuron function. Both BDNF/TrkB signalling and the serotonergic system modulate behavioural responses to stress and, when dysregulated, can lead to pathological states. The two systems have been shown to mediate antidepressant drug therapeutic effects and to regulate hippocampal neurogenesis. Transgenic mice were less affected by Chronic Social Defeat Stress (CSDS) than wild-type animals, in addition to displaying enhanced hippocampus-dependent contextual learning. Simultaneously, serotonergic axonal sprouting increased in the dentate gyrus and increased neural stem/progenitor cell proliferation in the hippocampus, which was uniformly distributed along the dorsoventral axis. BDNF-overexpressing mice performed similarly to wild-type mice treated with the antidepressant fluoxetine in the forced swim test. The BDNF released from serotonergic projections has this effect in part by promoting adult neurogenesis. Furthermore, regardless of genotype, increased neurogenesis was associated with increased social interaction time after the CSDS, a measure of stress resilience. The small GTPase CDC42 is required for neurogenesis and brain development. The CDC42 splice variant with widespread tissue distribution specifically stimulates the formation of neural progenitor cells, whereas CDC42b, a brain-specific CDC42 variant, does not. Specifically, the ubiquitous form of CDC42 stimulates mTORC1 activity and thus upregulates tissue-specific transcription factors required for neuroprogenitor formation, whereas CDC42b inhibits mTOR expression by collaborating with activated CDC42-associated kinase (ACK). The EGF receptor (EGFR) is an additional and important target of CDC42b and ACK, and that their combined actions in promoting neurogenesis downregulate it. The EGFR activation status determines when neural progenitor cells derived from P19 embryonal carcinoma terminally differentiate into neurons.

The CDC42b promotes EGFR degradation and ACK promote autophagy, which protects emerging neurons from apoptosis and aids in the differentiation of neural progenitor cells into neurons. Furthermore, the CDC42b is found in phosphatidylinositol (3,4,5)-triphosphate-enriched microdomains on the plasma membrane, which is mediated by its polybasic sequence 185KRK187, which is required for determining its distinct functions. Overall, these findings point to a molecular mechanism by which CDC42b and ACK regulate neuronal differentiation and shed light on the functional interplay between EGFR degradation and autophagy during embryonic neurogenesis. The cellular activities of CDC42 are required for embryogenesis, as evidenced by the early embryonic lethality in mice caused by CDC42 tissue-specific conditional knockout. KO CDC42 is also important in embryonic organogenesis and tissue homeostasis in mice. Depletion of CDC42, for example, causes serious defects in the development of the Central Nervous System (CNS). When CDC42 is knocked out in mouse telencephalon apical stem/progenitor cells, these cells are unable to maintain cell polarity and epithelial structures, and eventually fail to adopt their proper cell fate. The brain-specific KO of CDC42 eventually results in hydrocephaly or holoprosencephaly, demonstrating the importance of CDC42 in the formation and maintenance of intricate tissue structures during CNS development. Given the diverse regulatory functions provided by CDC42, it is reasonable to assume that CDC42 sends out multiple signals to influence the various aspects of neural stem/progenitor cell development during embryogenesis. CDC42 plays a role in the cell fate determination of Nestin-positive neural cells. Using embryonal carcinoma P19 cells as a model system, researchers controlled the expression of tissue-specific transcription factors in progenitor cells.

During the cell lineage specification phase of P19 cells, Retinoic Acid (RA) stimulates FGF-dependent and Delta/Notch-dependent signalling pathways, which activate CDC42. When CDC42 is activated, it regulates mTOR activation, which leads to the upregulation of HES5 and PAX6, which are key transcription factors in determining the embryonic apical neural stem/progenitor cell fate. P19 cells spontaneously differentiate into Nestin-positive neural progenitor cells even in the absence of induction when CDC42 is overexpressed or hyperactivated by exogenous expression of WT CDC42 or a constitutively active CDC42 mutant, but they also lose their ability to terminally differentiate into postmitotic neurons. Although CDC42 ectopic expression inhibits terminal differentiation, endogenous CDC42 expression and activation levels continue to rise during the terminal differentiation into neurons time window, even after the neural cell lineage specification phase.

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