β -catenin and TCFs/LEF signaling discordantly regulate IL-6 expression in astrocytes

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Video Byte

Keywords: Astrocytes, β -catenin, TCFs/LEF, IL-6, neuroinflammation, cytokine, signaling, Wnt, central nervous system, CNS, inflammation, brain, Cell Communication and Signaling

Posted Date: October 30th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-100881/v1>

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Abstract

Inflammation in the brain is a hallmark of many neurodegenerative diseases, including Alzheimer's and Huntington's disease. One of the key orchestrators of neuroinflammation is IL-6, a cytokine secreted by brain-resident cells called astrocytes. While low levels of IL-6 support neurons and synapses in the brain higher levels of IL-6 are produced in response to injury or infection, triggering a series of proinflammatory signaling cascades. Unfortunately, how astrocytes regulate IL-6 expression remains unclear. A recent study evaluated signaling pathways involved in IL-6 gene regulation, including β -catenin, TCFs/LEF, C/EBP, and NF- κ B. Using human astrocytes, researchers silenced or overexpressed the signaling proteins and measured IL-6 levels. They found that TCF/LEF induces IL-6 in the presence of ATF2, while β -catenin inhibits IL-6 by interacting with TCF/LEF. Interestingly, neither of these signaling pathways is known to regulate IL-6 in other cell types. The discovery of this novel mechanism of IL-6 control in astrocytes may help to inform brain-specific treatment targets for neuroinflammation providing new hope for those struggling with neuroinflammatory and neurodegenerative diseases.