Modulation of an ageing pathway protects neurons and facilitates regeneration in models of Parkinson's disease

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Abstract

Advancing age is the greatest risk factor for the development of idiopathic Parkinson 's disease (PD). While this dogma is mostly supported by epidemiological observations, the identification of molecular mechanisms governing neuronal senescence and linking to PD is still missing. The elucidation of these signals is essential to a better understanding of the cause of PD. Using an in vitro screening for inhibitors of the human kinome, we identified the IGF-1 pathway, the best characterized and the evolutionary conserved regulator of longevity, as a key modulator of alpha-synuclein level and toxicity.Using pharmacological and genetic strategies, we have demonstrated that the inhibition of IGF-1 signaling is complementary and supportive, and that it is more confirmed by transcriptomic analysis. In summary, we provide evidence that the IGF-1 pathway represents a molecular connection between age and sporadic PD, and that reduced IGF-1 signaling in nigral dopamine neurons may prevent the development of this devastating age-related neurodegenerative disorder.

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