CDB SEMINAR

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16:00~17:00 C1F CDB Auditorium

Life and Death in Dopamine Neurons – Insights from TGFbeta-HIPK2 Signaling Pathway

Summary

Neurotrophic factors and cytokines are known to promote survival and differentiation of dopamine (DA) neurons in cultures. However, the in vivo functions of these factors are not fully elucidated. Using genetic and cell biology approaches, we show that transforming growth factor beta (TGFbeta) and its downstream transcriptional coactivator HIPK2 critically regulate survival and differentiation of DA neurons in ventral midbrain and in the enteric nervous system. Our previous results show that loss of TGFbeta3 or HIPK2 leads to increased apoptosis during programmed cell death of midbrain DA neurons. As a consequence, adult Hipk2-/- mutant mice exhibit severe psychomotor abnormalities, including tremor, postural instability and reduced response to novel environment. The mechanism by which HIPK2 regulates survival of DA neurons is mediated through its ability to interact with Smad2 and to promote phosphorylation and transcriptional activity of Smad2. Loss of HIPK2 leads to a selective failure for DA neurons to survive in the presence of TGFbeta. Our recent results indicate that HIPK2 and its associated signaling mechanism have broader roles in regulating survival and differentiation in other neuron types. Specifically, about 40% of Hipk2-/- mutant mice die within 7 days after birth due to abnormalities in gut motility. Further characterizations of Hipk2-/- enteric neurons show that loss of HIPK2 does not affect migration of neural crest cells into the intestinal wall. Instead, Hipk2-/- mutants show a significant loss of neurons, including those of dopaminergic subtype, in myenteric and submucosal plexuses. Many of the remaining enteric neurons in Hipk2-/- mutants are reduced in size and show much fewer intraganglionic synapses. Taken together, these results indicate that TGFbeta-HIPK2 signaling supports survival and differentiation of ventral midbrain DA neurons and enteric neurons. These results further indicate that HIPK2 can be used as a therapeutic target to promote survival and differentiation of DA neurons during development and in adult life.

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