



CDB SEMINAR

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Monday, September 14, 2009
16:00~17:00 C1F CDB Auditorium

Novel family of neurotrophic factors – structure, biology and therapeutic potential

The central symptoms of Parkinson's disease (PD) are caused by the degeneration of nigrostriatal dopamine neurons (DA). All current therapies of PD only alleviate its symptoms and there is no treatment available to slow down or to arrest of neuronal degeneration and the progression of the disease. Neurotrophic factors (NTFs) are capable of sustaining neurons in various animal models of neurodegenerative diseases. The most potent and specific neurotrophic factors for DA neurons described so far are the members of the glial cell line-derived neurotrophic factor (GDNF) family ligands, in particular GDNF and neurturin. However, since recent data showed low clinical benefit of GDNF, and since GDNF caused brain toxicity in primate experiments, its clinical trials have been terminated in 2005. Thus, there is a therapeutic need for new, more selective neurotrophic factors for DA neurons that could slow down or reverse the progression of PD.

During the development most of neuronal populations are initially overproduced and their final number is determined by the ontogenetic programmed cell death process during target tissue innervation that is regulated by target-derived NTFs. Several NTFs, including BDNF, GDNF family ligands, VEGFs, FGFs etc. support the survival of DA neurons *in vitro*. However, only very few NTFs, such as GDNF and neurturin can promote the survival of the midbrain DA neurons *in vivo*, and in animal models of Parkinson's disease. We have recently discovered a novel evolutionarily conserved cerebral dopamine neurotrophic factor CDNF. We showed that CDNF, closely related mammalian MANF and invertebrate MANFs define a novel, evolutionarily conserved protein family. Analysis of the crystal structure revealed that MANF and CDNF protein consist of two domains: an amino-terminal saposin-like domain and a natively unfolded carboxy-terminal domain with a single disulfide bond revealing a structurally novel group of proteins. We found that CDNF and MANF protect and repair DA neurons in the 6-hydroxydopamine-induced unilateral rat model of PD. Based on our *in vivo* studies, CDNF is a potential therapeutic agent for the treatment of Parkinson's disease. To understand the physiological roles for the new neurotrophic factors and GDNF *in vivo*, we have created conditional CDNF-, as well as GDNF conditional knockout (cKO) mouse model where CDNF and GDNF can be removed from specific tissues or brain areas.

(References: **Nature** 448, 73-77, 2007; **Curr Opin Neurobiol** 18, 297-306, 2008)

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