ΠΑΝΕΠΙΣΤΗΜΙΟ ΚΡΗΤΗΣ

ΤΜΗΜΑ ΦΥΣΙΚΗΣ

ΓΕΝΙΚΟ ΣΕΜΙΝΑΡΙΟ ΤΜΗΜΑΤΟΣ ΦΥΣΙΚΗΣ

PHYSICS COLLOQUIUM

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17:00 -18:00

3rd Floor Seminar Room

"Biopharmaceuticals and biophysics of neuronal repair"

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Abstract

Neurotrophins control brain development and maintenance during adulthood and in aging. They act through prosurvival tyrosine kinase Trk and pan-neurotrophin p75NTR receptors, exerting potent neuroprotective and neurogenic effects in various neurodegenerative diseases. Unluckily, their polypeptidic nature limits their therapeutic potential. We have recently shown that a small molecule, neurosteroid dehydroepiandrosterone (DHEA) binds with high affinity to NGF receptors (Lazaridis et al, PLoS Biol 2011). DHEA exert potent neuroprotective effects, inducing the expression of anti-apoptotic Bcl-2 proteins (Charalampopoulos et al, PNAS 2004). It appears that DHEA exerts at least part of its anti-apoptotic effects by directly interacting with TrkA and p75NTR receptors (Kd: 5-10 nM), efficiently inducing TrkA phosphorylation, and NGF receptor-mediated prosurvival signaling, resulting in the induction of neuroprotective mir21 and anti-apoptotic Bcl-2 proteins. This sequence of events prevents the apoptotic loss of NGF receptor positive sensory and sympathetic neurons in ngf -/- mice. However, DHEA is metabolized to estrogens and androgens, affecting the endocrine system and increasing the risk for hormone-dependent tumors. We have synthesized 17-spiro analogs of DHEA with strong neuroprotective properties (EC50 at nanomolar levels), which are deprived of endocrine effects (Calogeropoulou et al, J Med Chem 2009). These findings render the development of neurotrophin-like small molecules (microneurotrophins) a realistic immediate target. Microneurotrophins interact with NGF receptors, activate phosphorylation of TrkA and

dissociation of RhoGDI from p75NTR receptor. They also rescue NGF-dependent embryonic sensory neurons of ngf-/- mice. Microneurotrophins are now tested in various animal models of neurodegenerative diseases: 1) Microneurotrophin BNN27 prevents and suppresses the development of experimental allergic encephalomyelitis (EAE) in mice (an animal model for Multiple Sclerosis-MS), inducing the expression of transcription factor FoxP3, the subsequent activation of Treg lymphocytes and the production of anti-inflammatory IL10, controlling thus the activation of neurotoxic Th17 response. 2) BNN27 exerts potent in vivo and in vitro neurogenic effects: it increases the number of BrdU positive neurons in the hippocampus of adult mice and induces self-renewal of neural stem cells, isolated from E14 mouse embryos. Neural stem cells (NSC) have emerged as new therapeutic agents with potential applications in neuronal injury and repair, particularly in spinal cord injuries related to mechanical trauma or to MS. Our group is developing 3D laser-engineered micro/nano scaffolds (3DLS) for hosting NSC 3D cultures. The 3DLS-NSC networks will be used as neuroimplants for effectively bridging interrupted spinal cord in animal models. The efficacy of 3DLS-NSC neuroimplants is boosted by their in vivo exposure to microneurotrophin. In conclusion, we combine pharmacology and stem cell implant technologies to address neuronal repair in neurodegenerative conditions.