Cell-Cell Signaling in Development and Regeneration of Visual Connections

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Country

USA

Title of project or programme

Cell-Cell Signaling in Development and Regeneration of Visual Connections

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,094,072.48

Start date of award

30/09/1996

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Chondroitin Sulfate Proteoglycan, retinotectal, intercellular communication, Amyloid beta-Protein Precursor, Protein Tyrosine Phosphatase

Research Abstract
Correct functioning of the visual system requires a precise set of axonal connections from the

eye to the brain. If these connections develop abnormally, or are later damaged by injury or degeneration, vision may be impaired or lost. The broad long-term objective of the project is to identify and characterize cell-cell signaling molecules involved in the development and regeneration of visual neuronal connections. In the adult visual system, like other parts of the CNS, axons show very limited capacity for regeneration. This is due, at least in part, to endogenous regeneration inhibitors, leading to great interest in strategies that might overcome the effect of these inhibitors, and thus promote plasticity and regeneration. Chondroitin sulfate proteoglycans (CSPGs) have long been known as an important class of inhibitors, but no corresponding receptor had been identified, limiting further molecular progress in this area. In recent work, we identified Protein Tyrosine Phosphatase sigma (PTPsigma) as a receptor for CSPGs, opening up new opportunities to study mechanisms in regeneration and potential therapeutic strategies. The role of this receptor in regeneration is confirmed by the effects of PTPsigma gene deficiency, which enhances regeneration, including of retinal axons in the optic nerve. In other recent work, we have shown that PTPsigma acts as a ligand- specific molecular switch, mediating not only CSPG inhibition but also heparan sulfate proteogylcan (HSPG) promotion of axon extension, providing a paradigm to understand opposing effects of CSPGs and HSPGs. Aim 1 has two inter-related goals: first, to better understand the basic biology of the interaction between PTPsigma and its proteoglycan ligands; and second, to explore compounds that can promote axon growth and optic nerve regeneration. Whereas Aim 1 focuses on extracellular interactions of PTPsigma, Aim 2 explores downstream transmembrane and intracellular signaling mechanisms. The prior work identifying HSPG and CSPG ligands for PTPsigma opens up new opportunities to understand the downstream mechanistic basis for the contrasting effects of these proteoglycans, and simultaneously to make new progress in understanding basic mechanisms of signaling by the receptor PTP family. Finally, Aim 3 proposes to continue studies of the Amyloid Precursor Protein (APP) and its binding partners expressed in the developing retinotectal system. While APP processing to beta-amyloid is known to have important roles in pathology, neither the normal developmental functions of APP nor the mechanisms that regulate its processing are yet well understood. Binding partners for APP have been identified which are prominently expressed in retinotectal development, and can affect retinal axon growth and APP processing. Further studies will provide improved understanding of these molecular interactions, with potential implications for development, degeneration and regeneration.

Lay Summary
Project Narrative For the visual system to function, a precise set of neuronal connections must exist from the eye to the brain. If these connections develop abnormally, or are damaged by injury or degeneration, vision may be permanently impaired or lost. The project involves identification and characterization of molecular cues involved in the development, degeneration, and regeneration of visual neural connections.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

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