Version 2.0

Abstract

Back to Hit List

Grant Number:	1R01HD032105-01A2
PI Name:	HEMMATI-BRIVANLOU, ALI
PI Email:	brvnlou@rockvax.rockefeller.edu
PI Title:	ASSOCIATE PROFESSOR AND HEAD
Project Title:	MOLECULAR BASIS OF NEURAL DEVELOPMENT IN XENOPUS

Abstract: The ultimate objective of this proposal is to characterize the cellular and molecular basis of vertebrate embryonic neural development. Both classical embryology and modern molecular biology will be used to isolate and characterize genes that play key roles in the formation of the vertebrate neuroaxis. The animal chosen for these studies is the frog Xenopus laevis whose large sized embryos facilitate microsurgical manipulations. The proposed studies will focus on follistatin, a specific inhibitor of activin, and Bone Morphogenetic Protein 4 (BMP4). Activin and BMP4, both TGF-beta type growth factors, are neural inhibitors. Follistatin, localized in the organizer, induces neural tissue in intact explants. By investigating the activities of activin, BMP4 and follistatin, the molecular mechanisms of vertebrate ectodermal patterning and neural induction will be elucidated. Four objectives are described for the next five years. First, genes regulated by follistatin in vivo will be isolated in order to map the molecular cascade initiated by follistatin and, thus, the molecular pathway to neural induction. Second, the function of follistatin, which is generally considered an activin- specific antagonist, will be addressed. Other TGFbetas will be assayed for their possible inhibitory interaction with follistatin, and it will be determined if follistatin has a function independent of TGF-beta inhibition. Third, experiments will be carried out to determine the mechanism of ectodermal patterning by BMP4. While both activin and BMP4 inhibit neural induction in dissociated ectodermal explants, only BMP4 acts as an epidermal inducer, the first to be discovered in vertebrates. Since BMP4 is also a strong neural inhibitor, an investigation of the relationships among activin, BMP4 and follistatin is proposed. Fourth, the embryonic mechanisms of neural induction will be analyzed by addressing how a neutralizing signal such as follistatin diffuses and what kind of cell-cell interactions are required for the spread of the signal in vivo. The isolation and characterization of proteins involved in neural and epidermal induction has immediate health related consequences. Factors which induce neural differentiation in ectodermal and mesodermal cells may provide insights into regeneration of neural tissue in adults and, in the long term, may provide therapy for diseases involving loss of neuronal cells, including stroke and neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS). In addition, the characterization of an epidermal inducer may lead to treatments for skin injuries and diseases. The combination of approaches suggested in this proposal should

provide opportunities to answer long-standing questions regarding the process of neurogenesis and epidermal induction in vertebrates at the molecular, cellular and embryological level.

Thesaurus Terms:
developmental genetics, developmental neurobiology, gene expression, genetic regulation, hormone regulation /control mechanism, neurogenesis, peptide hormone, protein structure function, transforming growth factor, vertebrate embryology
biological signal transduction, cell cell interaction, inhibin, intermolecular interaction Xenopus, molecular cloning

Institution:	ROCKEFELLER UNIVERSITY 66TH AND YORK AVE NEW YORK, NY 10021
Fiscal Year:	1996
Department:	LABORATORY OF NEUROBIOLOGY
Project Start:	07-JUN-1996
Project End:	31-MAY-2001
ICD:	NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
IRG:	CBY