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Abstract

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Grant Number: 1P01HD039948-010001
PI Name: KLINGENSMITH, JOHN A.
PI Email: j.klingensmith@cellbio.duke.edu
PI Title:
Project Title: BMP SIGNALING IN DORSAL NEURAL TUBE DEVELOPMENT

Abstract: Description (Provided by applicant): Neural tube defects (NTDs) are among the most common human congenital malformations, occurring in approximately I of every 1.000 live births, and at a higher frequency in aborted fetuses. The medical and psychological costs pertaining to these children are enormous. The molecular causes of NTDs have been frustratingly difficult to pinpoint, but clearly can involve either environmental or genetic damage which upsets the normal process of neurulation, whereby the neural tube is formed, or formation of the axial skeleton, which encases the neural tube. The mouse is proving to be an excellent model in which to address the underlying molecular embryology of NTDs. Analysis indicates that any of several cellular defects can be associated with these malformations. In this proposal, the investigators will use mouse genetic and molecular tools to understand the role of signaling by Bone Morphogenetic Proteins (BMPs) in neurulation and its anomalies. Evidence from embryological studies primarily with chicks has implicated BMPs (particularly the BMP 2/4 signalling pathway) as promoting normal development of the dorsal neural tube and axial skeleton. BMP activity is putatively involved in formation of dorsal neurons, the neural crest, and the dorsal portions of vertebrae. However, due to early lethality and redundancy revealed by null mutants, the roles of BMPs in dorsal development in mouse remain unclear. Nevertheless, mouse pups lacking the BMP antagonist Noggin display fully penetrant NTDs, suggesting that successful neurulation requires proper modulation of BMP signalling. The investigators= studies are based on this finding, and are designed to determine the basis of the NTDs in noggin mutants and to test the roles of BMP signalling in dorsal neural tube development. The investigators will activate the BMP signalling pathway specifically in the dorsal neural tube to determine the consequences on neurulation, hypothesizing that this will result in a NTD. They will also specifically preclude BMP2/4 signalling in the same domain, and in this case they predict a different NTD. In doing these experiments, the investigators will also address hypotheses about the roles of BMP signalling in neural crest and neuronal patterning, as well as in neural arch development. The investigators= system will also allow to test the function of BMP signalling in other domains relevant to NTDs.

Thesaurus Terms:

biological signal transduction, bone morphogenetic protein, congenital nervous system disorder, developmental neurobiology, molecular pathology, neural plate /tube, neurogenetics, neuroregulation, protein structure function
diet therapy, dietary supplement, disease /disorder model, folate, gene environment interaction, gene expression, inositol, mammalian embryology, nervous system disorder therapy, neurogenesis, nonhuman therapy evaluation, transgenic animal
embryo /fetus, gene mutation, gene targeting, laboratory mouse, nutrition related tag

Institution:	DUKE UNIVERSITY DURHAM, NC 27706
Fiscal Year:	2001
Department:	
Project Start:	01-SEP-2001
Project End:	31-AUG-2006
ICD:	NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
IRG:	ZHD1

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Abstract

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Grant Number: 1P01HD039948-019001
PI Name: KLINGENSMITH, JOHN A.
PI Email: j.klingensmith@cellbio.duke.edu
PI Title:
Project Title: CORE--MOUSE

Abstract: Description (Provided by applicant): Much of the investigators analysis of the developmental mechanisms of neural tube defects (NTDs) will use the mouse as a model system. Some of the research will examine the molecular and cellular basis of NTDs in existing mouse NTD mutant strains. Other experiments will manipulate signaling pathways via transgenesis to address specific hypotheses about the roles of these pathways in the ontogeny of normal neurulation and NTDs. Although mouse work is expensive relative to most embryological models, the Core will make the investigators= research much more cost-effective than if each investigator of the program were to have an individual colony. All of the mouse strains needed are likely to be used by two or more projects, allowing fewer cages and less maintenance. A Core technician will decrease and streamline the mouse husbandry work-load by providing common services. Production of transgenics by the Core eliminates the need for each project to set up and learn the production system. The Core will provide the following resources and services: (1) Production of wildtype embryos and chimeric mice: The Core will provide embryos on demand from timed matings of wildtype outbred mice. Midgestation embryos will be provided for adhesion assays, in situ hybridization, immunohistochemistry, and cell death/proliferation assays. Early embryos will be produced for use in morula aggregation, blastocyst ES cell injection, and DNA pronuclear injection. A colony of vasectomied males will be used to induce pseudopregnancy in a population of females to be used as recipients of embryo transfers. Additional females will be required for mating to chimeras and for amplification of outbred stocks. (2) Maintenance of mutant and transgenic stocks: The Core will maintain all the mutant and transgenic stocks used and made by the various Components. Per the instructions and oversight of the Component staff, stocks for a given Component will be maintained in the numbers required for successful execution of experiments. Core services will include setting up matings, splitting cages, weaning, culling, taking biopsies for genotyping, and preparation of genomic DNA. Genotyping by DNA analysis will be performed in collaboration with Component staff. (3) Generation of mutant and transgenic embryos: Working in close collaboration with Component staff, the Core will assist in the generation of mutant and transgenic embryos for experimental analysis. Timed matings will be set up and plugs checked daily. Core staff will assist in the dissection of mutant embryos

at the desired stage.

Thesaurus Terms:
animal care, biomedical facility, congenital nervous system disorder, disease /disorder model, laboratory mouse, model design /development, neural plate /tube, transgenic animal embryo /fetus, gene targeting

Institution:	DUKE UNIVERSITY DURHAM, NC 27706
Fiscal Year:	2001
Department:	
Project Start:	01-SEP-2001
Project End:	31-AUG-2006
ICD:	NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
IRG:	ZHD1

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Grant Number:	1R01DE013674-01A1
PI Name:	KLINGENSMITH, JOHN A.
PI Email:	j.klingensmith@cellbio.duke.edu
PI Title:	
Project Title:	ROLES OF CHORDIN AND NOGGIN IN CRANIOFACIAL DEVELOPMENT

Abstract: DESCRIPTION (Adapted from the Investigator's Abstract): Craniofacial development is a uniquely complex morphogenetic process in vertebrate ontogeny, creating evolutionary plasticity but also developmental vulnerability. The head and face are derived from many tissue precursors, which require a precise orchestration of pattern formation, cell migration, proliferation, apoptosis, and inductive interactions to achieve a functional end. Many of these events are mediated by secreted cytokines, whose activity must be precisely regulated to preclude inappropriate cellular responses. Bone Morphogenetic Proteins (BMPs) are a family of secreted ligands which have potent effects on many aspects of craniofacial development, particularly the closely related proteins BMP2 and BMP4. Their activity is thought to be important in the growth or patterning of such diverse tissues as the brain, the skull, the pituitary gland, the teeth, and the precursors of the face. Research from Drosophila and Xenopus indicate that BMP2/4 signal transduction is regulated in large part by antagonistic proteins such as Chordin (Chd) and Noggin (Nog). In frogs, Chd and Nog promote anterior development, and Chd is essential for normal head development in zebrafish. Preliminary work described in this proposal shows that these genes are required for development of the mammalian head. Lack of Chd in an inbred genetic background results in a group of craniofacial skeletal and soft-tissue defects involving neural crest derivatives, similar to those seen in certain human syndromes. Chd and Nog together are required early for head development, but are also involved specifically in development of the forebrain, mouth, nose, mandible, numerous bones of the skull, and other craniofacial tissues. The major aims of this proposal are: 1) to characterize the spatiotemporal expression patterns of Chd and Nog to clarify their roles in craniofacial development; 2) to determine the critical sites and times of action for Chd and Nog in head induction using embryonic stem cell chimeras and tissue recombinants; 3) to determine the functions of these genes in growth and patterning of craniofacial tissues; and 4) to assess whether ectopic BMP signaling reproduces the craniofacial defects of the mutants.

Thesaurus Terms:
biological signal transduction, bone development, bone morphogenetic protein, craniofacial,

developmental genetics, gene expression, histogenesis, protein structure function
allele, congenital oral /facial /cranial defect, ectoderm, embryogenesis, endoderm, gene induction /repression, gene mutation, genetic marker, mutant, phenotype
embryo /fetus cell /tissue, embryonic stem cell, laboratory mouse, nucleic acid sequence

Institution:	DUKE UNIVERSITY DURHAM, NC 27706
Fiscal Year:	2001
Department:	CELL BIOLOGY
Project Start:	01-APR-2001
Project End:	31-MAR-2006
ICD:	NATIONAL INSTITUTE OF DENTAL & CRANIOFACIAL RESEARCH
IRG:	OBM