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Abstract

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Grant Number:	1R01CA078375-01
PI Name:	CHANG, DAVID D.
PI Email:	ddchang@mednet.ucla.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	ICAPL AND BETA 1 INTEGRIN SIGNALING

Abstract: Cell adhesion to the extracellular matrix mediated by the integrin family of cell surface receptors is a crucial physiological determinant of cell proliferation and cell survival. A long term goal of this proposal is to define the mechanism of adhesion dependent cell signaling. How the information that originates when integrins bind to the extracellular matrix is processed to initiate intracellular signals is not known. We have recently identified a novel 200 amino acid protein, Icap1alpha, that specifically interacts with beta1 integrins. We have sown that the binding of Icap1alpha to beta1 integrins request the conserved C-terminal Asn-Pro-Lys-Tyr motif and Valine 792 of the beta1 integrin cytoplasmic domain. In addition, we have demonstrated that Icap1alpha undergoes an adhesion dependent protein phosphorylation. In this proposal, we will study the proximal events of integrin signaling, focusing on the interaction between Icap1alpha and the beta1 integrin cytoplasmic domain. First, a structure-function analysis of Icap1alpha will be carried out. The amino acid sequence requirements for the interaction between the beta1 integrin and Icap1alpha, and the subcellular localization of Icap1alpha will be determined. Second, the amino acid sequences on the beta1 integrin cytoplasmic domain that are required for the initiation of intracellular signaling will be characterized. The hypothesis that Icap1alpha is involved in integrin- mediated signaling will be tested by studying the effects of Valine792 mutation on cell adhesion and cell proliferation. Third, the function of Icap1alpha, in the context of integrin-mediated intracellular signaling events, will be investigated. Both the wild type Icap1alpha and Icap1beta, an Icap1alpha variant that does not bind to beta1 integrins, will be expressed in the cell to determine the function of Icap1alpha. Proteins that interact with Icap1alpha will be identified. Results from this study will enhance our understanding of adhesion- dependent cell signaling and may provide a knowledge basis for modulating cell adhesion and cell proliferation.

Thesaurus Terms:
biological signal transduction, cell adhesion, integrin, protein structure /function
cell growth regulation, cell proliferation, chimeric protein, focal adhesion kinase, gene expression, interleukin 2, protein sequence, receptor binding, valine
3T3 cell, antisense nucleic acid, site directed mutagenesis, transfection vector, yeast two

hybrid system

Institution:	UNIVERSITY OF CALIFORNIA LOS ANGELES 405 HILGARD AVE LOS ANGELES, CA 90024
Fiscal Year:	1998
Department:	MEDICINE
Project Start:	01-JUL-1998
Project End:	30-APR-2003
ICD:	NATIONAL CANCER INSTITUTE
IRG:	PBC

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Grant Number:	1R21GM058215-01
PI Name:	CHANG, DAVID D.
PI Email:	ddchang@mednet.ucla.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	TRANSFORMATION RELATED GENES IN ORAL CANCERS

Abstract: DESCRIPTION: (adapted from the investigator's abstract) The ability to identify the gene expression differences that can account for phenotypic changes would greatly advanced our current understanding of several important biological events, including development, differentiation, transformation, and senescence. A long-term goal of this proposal is to study the gene expression differences between transformed cells and their normal counterparts. There are two outstanding issues in differential gene expression analysis. First, there is a need for methods that allow identification of a large cohort of differentially expressed genes. Second, as the differential cloning methods improve, there is a need for a mechanism that allows functional analysis of a large number of genes. In Specific Aim 1, they will concentrate on identification of differentially expressed genes, using an in vitro oral carcinogenesis model that allows independent examination of both the early and late events of oncogenic transformation. Representational difference analysis (RDA) will be improved so that a sufficiently large fraction of the gene expression differences between transformed cells and their normal counterparts can be cloned. cDNA array hybridization will be used to establish the expression profile of the cloned differentially expressed genes in other cancer cells. In Specific Aim 2, they will employ an expression cloning strategy to detect genes that can alter growth properties. The output of RDA will be used to construct an eukaryotic expression library. The complexity of such a library, compared to a standard cDNA expression library, is expected to be low and will favor the success of expression cloning. The expression cloning strategy, if successful, will significantly alter the overall approach toward differential gene expression analysis. It is certain that this investigation will lead to the development of many valuable reagents and methods for additional studies in molecular mechanisms of human epithelial cell carcinogenesis and other complex biological events.

Thesaurus Terms:
gene expression, neoplastic transformation, oral pharyngeal neoplasm
cell growth regulation, genetic library
molecular cloning, representational difference analysis, tissue /cell culture

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Fiscal Year: 1998
Department: MEDICINE
Project Start: 01-AUG-1998
Project End: 31-JUL-2000
ICD: NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
IRG: PTHB