Version 2.0

Abstract

Back to Hit List

Grant Number: 7R01AI043542-03
PI Name: DUSTIN, MICHAEL L.
PI Email: dustin@saturn.med.nyu.edu
PI Title:
Project Title: REQUIREMENT FOR SENSITIVE T CELL RESPONSE TO ANTIGEN

Abstract: The long term goals of our work are to determine the mechanisms by which T lymphocytes are activated by very small numbers of MHC-peptide complexes (antigen) on the surface of antigen presenting cells. This sensitivity of the T cell to antigens determines the thresholds for processes such as negative and positive selection as well as activation of mature T cells and thus may play an important role in tolerance and autoimmunity. The major focus of this proposal is on the specific roles of adhesion molecules in the extraordinary sensitivity of T cells to antigen which is evident both in vitro and in vivo. T cells respond to as few as 10-100 MHC peptide complex per antigen presenting cell. The solution affinity of T cell antigen receptors for antigenic MHC-peptide complexes is low. Recent work from our lab shows that the mechanism by which T cell adhesion molecules with low solution affinity function to form many bonds in contact areas is to align the apposing membranes with nanometer precision, thus increasing the effective concentration of the receptor and ligand. We hypothesize that sensitive antigen recognition by T cells will depend upon the alignment of the T cell and antigen presenting cell membrane so that the gap between the membranes is 15 nm, the distance between cells that is spanned by the T cell receptor (TCR)- MHC antigen complex. The hypothesis predicts that adhesion mechanisms, such as CD2/ligand interaction, which are predicted to create a gap of 15 nm between the T cell and antigen presenting cell, will be sufficient to promote efficient TCR engagement. Once engagement occurs, adhesion molecules may also contribute to amplification of signals by phosphatase exclusion and recruitment of cytoplasmic proteins to the site of TCR engagement. We will test these hypotheses in 4 Specific Aims. In Alm 1 we will determine whether close contact is sufficient for sensitive antigen recognition. In Aim 2 we will determine whether disrupting close contacts decreases sensitivity. In Aim 3 we will determine whether alternative splicing of ICAM-1 regulates contact area topology and sensitivity to antigen. In Aim 4 we will determine whether the large glycoprotein CD45 is excluded from close contacts and if the exclusion of the phosphatase domain is required for sensitive antigen recognition. The results will contribute to our basic understanding of the antigen recognition process and may define novel therapeutic strategies for autoimmune disease and transplantation medicine based on changing the sensitivity of T cells to antigens through disruption or stabilization of close contact area.

Thesaurus Terms:
T lymphocyte, antigen presenting cell, cell cell interaction, leukocyte activation /transformation, leukocyte adhesion molecule
CD antigen, CD2 molecule, CD28 molecule, MHC class II antigen, T cell receptor, protein tyrosine phosphatase
laboratory mouse, tissue /cell culture, transgenic animal

Institution:	NEW YORK UNIVERSITY SCHOOL OF MEDICINE 550 1ST AVE NEW YORK, NY 10016
Fiscal Year:	2000
Department:	PATHOLOGY
Project Start:	01-MAR-1999
Project End:	31-OCT-2005
ICD:	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
IRG:	ALY

Version 2.0

Abstract

Back to Hit List

Grant Number: 7R01AI044931-03
PI Name: DUSTIN, MICHAEL L.
PI Email: dustin@saturn.med.nyu.edu
PI Title:
Project Title: PHYSIOLOGICAL CHEMISTRY OF INTEGRIN FUNCTION

Abstract: Integrins are a family of cell adhesion/signaling molecules that play an important role in development, wound repair, angiogenesis, immunity, and tissue integrity. Regulation of specific integrins is a potentially powerful therapeutic target for diverse diseases including cancer and autoimmunity. A remarkable characteristic of integrins is the degree of cellular regulation that can be achieved without altering protein expression levels. For example, the integrin LFA-1 is initially inactive on resting lymphocytes, but adhesion activity is rapidly increased by exposure to chemokines or antigen. Changes in LFA-1 affinity for ligand are not the primary mechanism for regulation. In contrast, there is mounting evidence that interactions of integrins with the cytoskeleton is important. Our hypothesis is that integrin activity is regulated by a multistep cascade with the following major steps: 1) the integrin is initially attached to the cytoskeleton to prevent diffusion limited reaction with ligands, 2) activation releases the integrin from cytoskeletal constraints to increase ligand binding, 3) ligand binding induces a conformational change in the integrin, and 4) the ligated integrin binds cytoplasmic factors that regulate local mechanical properties to enhance two dimensional affinity of integrin- ligand interaction. We will test these hypotheses by examining the physiological chemistry of integrin interactions (bonds) using a novel fluorescence based approach. In Aim 1 we will determine how different biologically important modes of lymphocyte activation affect LFA-1 engagement in cell substrate contact areas. In Aim 2 we will determine how different modes of lymphocyte activation affect LFA-1 lateral mobility as an assay for release from the cytoskeleton. In Aim 3 we will determine the most effective strategy to probe integrin cytoskeletal interactions through expression of exogenous cytoplasmic domain.

Thesaurus Terms:
cell adhesion, cytoskeleton, integrin, leukocyte activation /transformation
T lymphocyte, antigen receptor, chemokine, conformation, cytokine receptor, cytoplasm, ligand, phorbol, receptor binding
expression cloning, laboratory mouse, monoclonal antibody, transgenic animal

Institution: NEW YORK UNIVERSITY SCHOOL OF MEDICINE
550 1ST AVE
NEW YORK, NY 10016

Fiscal Year: 2000
Department: PATHOLOGY
Project Start: 01-MAR-1999
Project End: 28-FEB-2003
ICD: NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
IRG: PBC