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Abstract

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Grant Number:	5R01AI040608-04
PI Name:	ASHTON-RICKARDT, PHILIP G.
PI Email:	pashtonr@midway.uchicago.edu
PI Title:	ASSISTANT PROFESSOR
Project Title:	'ROLE OF SELF-PEPTIDES IN THE SELECTION OF T LYMPHOCYTES

Abstract: Pathogenic viruses pose a world-wide public health problem of great importance. The immune system has evolved strategies to combat viral infections, an important one being the detection and illimination of virally infected host-cells by cytotoxic T lymphocytes (CTLs). The T lymphocytes antigen receptor (TCR) recognizes virally infected cells by detecting peptide fragments of virus, expressed on the surface of cells in complexes with self-MHC (Major Histocompatibility Complex) molecules. How T cells distinguish between viral-peptide and self- peptides is unclear. However, the impairment of this ability can lead to the development of autoimmunity. The TCR repertoire displayed by CTLs is determined through the development of T cells in the thymus. Within the thymus, T cell development selects for cells that recognize peptide antigen presented by self-MHC, but are not reactive to MHC/self-peptide complexes. However, we have shown that the recognition of self-peptide/self-MHC complexes, expressed on the surface of thymic stromal cells, is required to trigger the development of cells destined to become CTLs. We aim to determine how thymic self-peptides shape the antigenic repertoire of CTLs. Using a combination of chromatographic and mass-spectroscopic techniques, we will purify and sequence self-peptides for thymic-MHC molecules, which are recognized by CTLs specific for two different pathogenic viruses, Influenza (IF) and Lymphocytic Choriomeningitis virus (LCMV). By adding synthetic self-peptides to a fetal thymic organ culture (FTOC) system utilizing TAP1- mice, we will examine how self-peptides specific for a given TCR (anti-IF peptide or anti-LCMV peptide) trigger the differentiation of CTLs with the same TCR. Using a similar FTOC system, we will also study how the recognition of the thymic self-peptides gives rise to the development of the diverse array of antigenic specificity~s displayed by CTLs. Analysis of mice, with impaired peptidase activity and impaired thymic selection of CTLs, will allow us to identify which thymic self-peptides trigger the development of CTLs. This proposal seeks to understand how the recognition of self during development gives rise to an immune system which can respond specifically to non-self pathogens. It is hoped that this study lead to a better understanding of how autoimmune disease can be prevented as well as facilitate our understanding of how antiviral immunity develops.

Thesaurus Terms:
T cell receptor, autoantigen, cytotoxic T lymphocyte, developmental immunology, peptide MHC class I antigen, antigenic peptide transporter, autoimmunity, cellular immunity, receptor sensitivity, thymus, virus protein
laboratory mouse, protein purification, protein sequence, transgenic animal

Institution:	UNIVERSITY OF CHICAGO 5801 S ELLIS AVE CHICAGO, IL 60637
Fiscal Year:	2000
Department:	PATHOLOGY
Project Start:	01-JUL-1997
Project End:	31-OCT-2005
ICD:	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
IRG:	IMB

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Abstract

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Grant Number:	1R01AI045108-01A1
PI Name:	ASHTON-RICKARDT, PHILIP G.
PI Email:	pashtonr@midway.uchicago.edu
PI Title:	ASSISTANT PROFESSOR
Project Title:	DEVELOPMENT AND PERSISTENCE OF MEMORY T LYMPHOCYTES

Abstract: DESCRIPTION (Adapted from the Investigator's abstract): The cardinal feature of the immune system lies in its ability to specifically recognize, then "remember" its encounter with a microbe or foreign antigen. Lymphocytes that mature in the thymus (so called, T lymphocytes) recognize antigenic peptides, expressed on the surface of cells with self-MHC (Major Histocompatibility Complex) molecules. When a T-cell recognizes antigen for the first time (naive T-cell), it becomes activated and undergoes rapid cell division and differentiates into effector cells, which eliminate the antigen and memory cells, which persist after the antigen is cleared. Memory T-cells respond vigorously to re-challenge by antigen, and so give protection against recurrent infection. A key to understanding immunological memory is to determine how long-lived, memory T-cells develop and persist after antigen challenge. The precise lineage relationship between memory and effector cells is not well understood. They will use an assay that will allow them to "count" the number of cell divisions that occur after T-cells encounter antigen and differentiate into effector cells. The application will test the ability of different generations of antigen-activated T-cells to give rise to memory cells 70 days after transfer to antigen-free mice. This will allow them to determine whether CD8+ memory T-cells arise from terminally differentiated effector CTLs or from an earlier progenitor. Mature T-cells express T-cell receptors (TCRs), which are weakly reactive to self-peptide/MHC as a result of positive selection in the thymus. The aim will test the hypothesis that the long-term survival and function of T-cells relies on the specific recognition of self-peptide/MHC. The survival of TCR-transgenic CD8+ cells specific for a male antigen (H-Y) or one of two viruses (influenza or Lymphocytic Choriomengitis virus) in transgenic mice which express single, self-peptide/MHC molecules will be tested. The self-peptide requirements for the maintenance of a diverse and functional repertoire of CD8+ T-cells will also be tested in similar experiments. This application will help determine whether self-reactivity, that can sometimes lead to autoimmune disease, is an intrinsic property of the immune system which ensures immunological memory.

Thesaurus Terms:
T lymphocyte, histocompatibility antigen, immunologic memory, leukocyte activation

/transformation
HY antigen, Orthomyxoviridae, T cell receptor, autoimmunity, cytotoxic T lymphocyte, lymphocytic choriomeningitis virus, passive immunization, virus antigen
laboratory mouse, transgenic animal

Institution:	UNIVERSITY OF CHICAGO 5801 S ELLIS AVE CHICAGO, IL 60637
Fiscal Year:	2000
Department:	PATHOLOGY
Project Start:	01-FEB-2000
Project End:	31-JAN-2005
ICD:	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
IRG:	IMB