

AD-A246 030



AD _____

2

REGULATION OF IMMUNE RESPONSES TO PROTOZOAL PATHOGENS SEMINAR

FINAL REPORT

RICHARD G. TITUS

DECEMBER 1, 1991

DTIC
SELECTE
FEB 03 1992
S B D

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21702-5012

Grant No. DAMD17-91-Z-1022

Harvard School of Public Health
665 Huntington Avenue
Boston, Massachusetts 02115

Approved for public release; distribution unlimited.

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents

92-02582



92 1 31 108

REPORT DOCUMENTATION PAGEForm Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE December 1, 1991	3. REPORT TYPE AND DATES COVERED Final 3 May 91 - 30 Sep 91	
4. TITLE AND SUBTITLE Regulation of Immune Responses to Protozoal Pathogens Seminar			5. FUNDING NUMBERS DAMD17-91-Z-1022	
6. AUTHOR(S) Richard G. Titus				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Harvard School of Public Health 665 Huntington Avenue Boston, Massachusetts 02115			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research & Development Command Fort Detrick Frederick, Maryland 21702-5012			10. SPONSORING/MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution unlimited			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words)				
14. SUBJECT TERMS			15. NUMBER OF PAGES	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT	

American Society for Microbiology
National meeting, May 1991, Dallas, Texas
Section 250, Regulation of Immune Response to Protozoal Pathogens
Support for speaker expenses obtained from the U.S. Army
Grant #DAMD17-91-Z-1022

Summary of speaker presentations

Dr. Richard Titus

The role of parasite-specific T cells in the immune response to *Leishmania major* was studied in the mouse model system. Parasite-specific CD4⁺ T cell clones were derived from genetically-resistant C3H mice infected with *L. major*. Protective T cell clones were found to secrete interleukin-2 (IL-2), interferon- γ (IFN- γ), tumor necrosis factor (TNF) and migration inhibition factor (MIF). Exacerbative T cell clones secreted IL-2 and IL-4 but not IFN- γ , TNF or MIF. Curiously, exacerbative CD4⁺ T cell clones derived from genetically-susceptible BALB/c mice were found to produce IL-2 and IFN- γ , but not IL-4. Finally, the role of mast cells in cutaneous leishmaniasis was also investigated. It was found that the course of disease was much less severe in mice that are genetically deficient in mast cells compared to congenic mast cell-bearing control mice.

Dr. Rick Tarleton

The acute phase of T. cruzi infection is characterized by a profound but selective suppression of immune responses. The most prominent feature of this suppression is the regulation of IL-2 production. The regulation of IL-2 production may be indicative of an overall regulation of the TH1 compartment but is not a result of a strong TH2 response and is a result of either transcriptional or post-transcriptional (mRNA stability) regulation. T cells other than the TH1 and TH2 populations appear to contribute strongly to the immune response in T. cruzi-infected mice, before, during, and after the period of intense immunosuppression.



Accession For	
NTIS GRA&I	☒
DTIC TAB	☐
Unannounced	☐
Justification	
By _____	
Distribution/	
Availability Codes	
Dist	Avail and/or Special
A-1	

The cellular immune response to *Toxoplasma gondii* . LLOYD H. KASPER* and IMTIAZ A. KHAN. Dartmouth Medical School, Hanover, NH 03756

The importance of the cell mediated immune response to *T. gondii* is well recognized. Over the past several years, we have identified a variety of parasite antigens that are critical in eliciting this response, in particular P30. This tachyzoite membrane antigen has an approximate Mr of 30Kd, comprises 3-5% of the total parasite protein and is excreted into the parasitophorous vacuole. It is the major seroreactive protein identified by infected humans and experimental hosts. In humans and mice, this protein induces the production of high titer IFN-gamma as well as parasitocidal cytotoxic T cells. CD8+ cytotoxic T cells derived from immunized mice kill infected syngenic APC in an MHC restricted fashion. P30 used with the appropriate adjuvant is able to induce near 100% protection against acute and chronic toxoplasmosis in mice. This protective response is mediated by antigen-specific cytotoxic CD8+ T cells that can be adoptively transferred into naive recipients. These CD8+ T cells produce high titer IFN-gamma and are cytotoxic and kill extracellular *T. gondii*.

Dr. Fidel Zavala

ABSTRACT

Immunization of BALB/c mice with radiation-attenuated Plasmodium yoelii sporozoites induces cytotoxic T. lymphocytes (CTL) specific for an epitope located within the amino acid sequence 277-288 of the P. yoelii circumsporozoite (CS) protein. Several CD8⁺ CTL clones were derived from the spleen cells of sporozoite-immunized mice, all displaying an apparently identical epitope specificity. All the clones induced high levels of cytolysis "in vitro" upon exposure to peptide incubated MHC compatible target cells. The adoptive transfer of two of these clones conferred complete protection against sporozoite challenge to naive mice. This protection is species and stage specific. Using P. yoelii specific ribosomal RNA probes to monitor the "in vivo" effects of the CTL clones, we found that their target was the intrahepatocytic stage of the parasite.

Onesmo OleMoi-Yoi ILRAD, Nairobi, Kenya

Immunity to intracellular protozoal pathogens: Theileria parva

Theileria parva, the causative agent of East Coast Fever (ECF) in cattle, is an intracellular protozoan parasite which induces lymphoblastogenesis and clonal expansion of infected cells. Such cells are immortalized and, therefore, can be propagated indefinitely in vitro. T. parva-infected cells are pleiomorphic, have short (16-25 hr) generation times, form tumor-like masses which metastasize and infiltrate organs upon injection into athymic mice and exhibit alterations in surface phenotype. These cells are thus considered to be transformed.

In our attempts to determine the mechanism of T. parva-induced transformation, we have identified a parasite casein kinase (CK) II enzyme which, along with its bovine homolog, is highly active in infected cells. It has recently been shown that among the substrates of CKII are nuclear proteins most of which may be involved in the regulation of gene expression and cell growth.

Interestingly, several of these proteins from oncogenic viruses appear critical to the transformation process itself as well as to the capacity of such cells to elicit cytotoxic host cell responses. Because immunity to T. parva, like that of several other intracellular protozoal parasites, appears to have a substantial cellular component, we have identified and are in the process of characterizing CKII substrates as potential candidates mediating recognition, in conjunction with MHC class I molecules, by cytotoxic T lymphocytes.