Lewis: Ab Specificity & Fc-Mediated Protection

OVERVIEW

It is well accepted that direct virus neutralization, in which the binding of the variable domains of antibodies to epitopes on the envelope glycoprotein prevent viral entry into target cells, is an important element of antibody-mediated protection against HIV-1. Less is known about the role of Fc-mediated effector functions, i.e. those functions that depend on the nature of the constant regions of antibodies, in the control of HIV-1. Epidemiological studies of HIV infected individuals have shown an inverse relationship between disease progression and antibody-dependent cell mediated cytotoxicity (ADCC), which is supported by a correlation between Fc-receptor genotype and reduced risk of progression. More recently, results from the Vax004 vaccine efficacy trial and the RV144 vaccine trial in Thailand provide further evidence that vaccine-elicited non-neutralizing antibodies might play a role in protection from infection.

Dr. George Lewis and colleagues at the University of Maryland are pursuing the hypothesis that anti-envelope antibodies directed against conserved domains, exposed upon virus entry/attachment, are capable of providing protective humoral immunity through Fc-dependent effector functions, even in the absence of a direct neutralizing function. In this scenario, diverse effector mechanisms need not be mutually exclusive, might be complimentary, and might apply differentially according to the mode of exposure.

RESEARCH OBJECTIVES

Resolution of the role of Fc-mediated effector function, particularly antibody-dependent cellular cytotoxicity (ADCC), is being pursued through five objectives. Objective 1 is to streamline and standardize an ADCC assay such that it can be used for high throughput use. Objective 2 is to isolate and characterize new monoclonal antibodies (mAbs) based on specificity, neutralization, and Fc-mediated effector function. Objective 3 determines epitope exposure during viral entry. Objective 4 maps epitopes recognized by new mAbs using X-ray crystallography. Objective 5- synthesizes information from the preceding objectives to design passive immunization studies against SHIV in animal model to resolve the relationships between neutralization and Fc-mediated effector function in protective immunity against HIV-1.

Grant at a Glance

Principal Investigator
George K. Lewis, PhD

Grantee Institution
Institute of Human Virology, University of Maryland, Baltimore, USA

Project Title
Antibody Specificity, Fc-Mediated Effector Function, and HIV-1 Vaccines

OPPID
1033109

Grant Award
Up to $7 Million, awarded in October, 2011

Collaborating Institutions
◊ Advanced Biosciences Laboratory

PROGRESS

Their team has characterized a large panel of mAbs for neutralization breadth and potency as well as Fc-mediated effector functions, in particular ADCC. The epitopes recognized by these antibodies have been characterized by mutagenesis and X-ray crystallography. Further, their exposure during viral entry or virus budding has been determined using single particle imaging. Two significant observations have emerged. First, a broadly neutralizing antibody has isolated that recognizes a new glycan shield epitope involving elements of the V1/V2 and V3 regions as well as a glycan at residue 301, which distal to the glycan at 332 recognized by other glycan shield monoclonal antibodies. Further, this mAb employs a moderately mutated heavy chain variable region and a near germline light chain variable region. This mAb protects rhesus macaques completely from a high-dose challenge with SHIV. It also decreases viral loads in SHIV infected Rhesus Macaques. Based on these observations, we are now determining the role of Fc-mediated effector function for protection in rhesus macaques.

Second, two highly conserved ADCC hotspots recognized by non-neutralizing mAbs have been mapped in gp120 and gp41. An epitope group in the gp120 hotspot has been implicated as a target for potentially protective antibodies in both HIV-1 infected people and in the RV144 vaccine trial. This epitope group has been characterized by both mutagenesis and X-ray crystallography, providing the first picture of this site at atomic resolution, which was published recently in the Journal of Virology. This information is being used to design a new vaccine candidate as well as to determine the protective role of antibodies against this region via both active and passive immunization models in animals. In addition, this information is being used to evaluate immunologic pressure against this epitope region in HIV-1 infected people. Collectively, these two lines of investigation are leading to new knowledge about the mechanisms of antibody-mediated protection against HIV as well as new vaccine candidates and new antibodies for therapy.