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Vaccines 2017- Electrophilic Vaccine Platform for Intractable Infections Exemplified by HIV/AIDS - Sudhir Paul - University of Texas

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Abstract
Our studies suggest covalently reactive electrophilic immunogens (E-immunogens) as candidate vaccines for microbes that use superantigen epitopes to bind the immunoglobulin framework regions (FRs) expressed as B cell receptors (BCRs), thereby suppressing the adaptive antibody response needed for protection against infection. The superantigenic gp120 residues 421-433 (C^{LIN}) bind the CD4 receptor and are essential for establishment of HIV-1 infection. Consistent with C^{LIN} designation as a superantigen, non-infected humans innately produce IgM+ BCRs and secreted IgMs with FRs that recognized C^{LIN} and catalyzed the degradation of gp120 monomers. However, only the C^{LIN}-directed variable (V)-domains of IgGs/IgAs, not IgMs, bound intact HIV and neutralized genetically diverse HIV strains, suggesting that IgM→IgG/IgA class-switching (CS) is a prerequisite for effective HIV vaccination. Study of infected humans and gp120 immunized mice indicated that noncovalent C^{LIN}-BCR binding selectively suppresses IgM→IgG CS of C^{LIN}-directed antibodies. The use of C^{LIN}-containing E-immunogens that bound nucleophilic BCRs covalently corrected the CS defect in animals. UpregulatedIgG synthesis appears to result from high energy covalent FR binding to E-C^{LIN}, together with CDR binding to a neighboring epitope. The C^{LIN}-directed IgGs neutralized HIV subtype A/B/C/D/AE infection of cultured lymphocytes/macrophages and suppressed HIV infection in immunodeficient mice. A further advantage was improved IgG neutralization potency due to E-immunogen driven acquisition of catalytic and irreversible HIV binding activities. The foregoing E-vaccine principles to correct antibody specificity and improve effector function will likely be useful for other microbes that depend on superantigens to establish infection, e.g., *Staphylococcus aureus*.

Immunotherapy
Generally, fungal immunotherapy involves the administration of exogenous immune agents, such as white cells, antibodies, and cytokines, to beneficially alter the course of infection. Reviewed below are monoclonal antibodies (mAbs) and dendritic cell (DC) therapy, and vaccine strategies developed to treat or prevent fungal infections.

Antibody Therapy
Antibodies or immunoglobulins recognize diverse antigens through the genetic rearrangement and somatic hypermutation of its variable regions.

Constant regions, designated by an immunoglobulinsisotype, are recognized by Fc receptors (FcR) on immune cells and C1q, a factor involved in the complement cascade that can lead to bacterial but not fungal lysis. Fungi resist lysis by porting a rigid cell wall composed of a skeletal framework of fibrillar polysaccharides cemented by amorphous polysaccharides decorated with surface proteins. The innermost layer of the fibrillar framework is composed of chitin cross linked to β-1,3-glucans that expand outward. These two polysaccharides are common among fungi, making them attractive therapeutic targets. In many instances, ingestion of pathogens opsonized by antibody and/or complement leads to killing and protection to the host; however, in some cases, antibodies are not protective. For example, H1C, an IgG1 mAb specific for an uncharacterized 70-kDa protein on the surface of H. capsulatum, showed no protective effect when given 2 h before challenge, despite enhancing phagocytosis by a murine macrophage cell line (J774.16). In contrast, the same group treated mice in a similar fashion with IgG1 mAbs against heat shock protein 60, and these mice were protected from infection. This discrepancy illustrates how the identity of the antigen targeted by an antibody is an important factor in determining its effectiveness.

The constant region of an antibody also contributes to its effectiveness. This region is determined by a B cell's activation status and the signals it receives from CD4+ T cells. After binding an antigen recognized by a surface-bound IgD or monomeric IgM, B cells become activated and start producing pentamericIgM. As CD4+ T cells also become activated, they start producing cytokines, such as interleukin-4 (IL-4) or interferon-γ (IFN-γ), and up-regulate the expression of CD40 ligand on their surface. These molecules engage their respective receptors on the surface of B cells and induce the rearrangement of the constant region in the immunoglobulin produced. This rearrangement is known as "isotype switching" and, depending on the cytokine signal, B cells will produce IgE, IgA, or a subclass of IgG instead of IgM. For example, in humans, IL-4 will induce IgG4 or IgE production, whereas IFN-γ induces IgG1. The IgG subclass and isotype induced by each cytokine differ between humans and mice. Therefore, in mice, IL-4 will induce IgG1 and IgE production, whereas IFN-γ induces mainly IgG2a .

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A number of studies have looked at the impact of the constant region on the effectiveness of mAbs. For example, when a human hybridoma cell line (3E5) spontaneously switched from producing a nonprotectiveanticapsular IgG3 antibody against C. neoformans to producing an IgG1 antibody with the same variant regions, the IgG1 isotype was found to prolong survival in mice after infection . Another group used the same hybridoma cell line to test the efficacy of additional human IgG subclasses. constructed recombinant human IgG1, IgG2, IgG3, and IgG4 mAbs by cloning the variable region expressed by 3E5 cells into expression vectors containing the sequence for each IgG subclass. After challenge with C. neoformans, IgG2 and IgG4 were shown to provide better protection than IgG1 or IgG3.

The emergence of resistance to mAbs would most likely occur for therapies that target fungal proteins, which can lose or mask the antibody-binding site while maintaining function. Additionally, antibodies that require recognition by host factors to be protective may be ineffective in patient populations in which these factors fail to optimally function with that specific antibody isotype. These variations may be a result of single nucleotide polymorphisms or severe immunodeficiencies that may be contingent on that patient's risk factors in contracting the infection. For example, if the mechanism by which a specific antibody delivers protection requires a healthy neutrophil population, then neutropenic patients would not be expected to benefit from such treatment. Finally, antibody therapy may be most effective when the organism burden is low early in infection, which would require better diagnostic tools than are available today. However, the study of how mAbs specific for fungi affects disease outcome not only contributes to the development of potential therapies but could also assist in the development of better diagnostic tools and help provide clues on how to design a protective vaccine.

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