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Electrophilic Vaccine Platform for Intractable Infections Exemplified by HIV/AIDS

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. Upregulated IgG 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*.

Biography

Sudhir Paul, PhD, is Professor of Pathology and Director, Chemical Immunology Research Center at the Univ of Texas Houston Health Sciences Center. After his Ph.D. in Biochemistry from the All-India Institute of Medical Sciences in 1981, Dr. Paul was a Humboldt Fellow until 1983 at Christian Albrechts Univ, Gemany. He served as Asst Professor at Univ of Oklahoma until 1987 and then moved to Univ of Nebraska Medical Center, where he was Assoc Professor and then Professor of Pharmacology, Pathology and Anesthesiology until 1998. Dr. Paul has published more than 190 original articles, reviews and book chapters, and he has edited several books and conference proceedings on catalytic antibodies, HIV vaccination, amyloid disease and autoimmunity. He has delivered over 250 invited seminars and symposium presentations. The Paul lab discovered proteolytic antibodies and identified them as transitional molecules bridging the innate and adaptive features of humoral immunity. A single catalytic antibody molecule is reused to cleave thousands of antigen molecules, and the Paul lab is developing catalytic antibodies as a platform for treating intractable diseases. While developing immunogens for inducing catalytic antibody synthesis, they serendipitously identified an electrophilic immunogen that bound B cells covalently and corrected the immunological defect precluding synthesis of mature antibodies directed to the vulnerable, superantigenic CD4 binding site of HIV. This immunogen induced antibodies that neutralized HIV strains found world-wide. They are now exploring the potential of electrophilic immunization for vaccination against HIV.

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