PLENARY SESSION 03: B CELL BIOLOGY

PL03-01

Development of anti-HIV antibodies in humans with high titers of broadly neutralizing antibodies

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Antibodies to conserved epitopes on the HIV coat protein can protect against infection in non-human primates, and rare infected individuals show high titers of broadly neutralizing IgG antibodies in their serum, but little is known regarding the specificity and activity of these antibodies. To characterize the memory antibody responses to HIV we cloned 501 antibodies from HIV envelope binding memory B cells from six HIV infected patients with high titers of broadly neutralizing antibodies. The development and selection of these antibodies will be discussed.

PL03-02

From antibody to vaccine – a tale of structural biology and epitope scaffolds

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The multiple means of immune evasion encoded by the HIV-1 envelope glycoproteins – including immunodominant variable loops, extensive glycosylation and conformational flexibility - have frustrated immunogen design. One potential route around these evasion strategies is (1) to define a site of HIV-1 vulnerability recognized by a broadly neutralizing antibody, (2) to transplant the site/epitope into acceptor scaffolds, which are free of the various forms of immune evasion present on the HIV-1 envelope but manage to replicate the conformation and surface accessibility of the site/epitope, and (3) to use these epitope-scaffold immunogens to elicit the desired antibody. We report our efforts with the broadly neutralizing antibody 2F5.

We use structural and computational biology to transplant the 2F5 epitope into seven acceptor scaffolds. Five of these scaffolds were expressed, folded, found to bind 2F5 with better than 20 nM affinity, and displayed up to 1000-fold antigenic discrimination against serum elicited against the unconstrained epitope. Crystallographic characterization of the epitope scaffold with highest affinity and antigenic discrimination showed good to near perfect structural resemblance when free or 2F5-bound, respectively. Immunizations with the epitope scaffolds, meanwhile, elicited antibodies able to recognize all epitope scaffolds, and the structure of a monoclonal antibody elicited by prime/boost immunization with two epitope scaffolds induced a conformation in the flexible epitope similar to that of the parent 2F5. Neutralization by the elicited antibodies is currently borderline, perhaps a consequence of the lack of membrane attachment required for potent neutralization.

PL03-03

Induction and function of the mucosal immune system

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The mucosal immune system provides a first defense line which reduces the need for elimination of penetrating exogenous antigens by proinflammatory systemic immunity. To maintain homeostasis, mucosal immunity employs two layers of adaptive anti-inflammatory mechanisms: (a) immune exclusion provided by secretory antibodies to limit epithelial contact and invasion of microorganisms and other potentially dangerous antigens; and (b) immunosuppression to inhibit overreaction against innocuous luminal antigens. The latter strategy is referred to as 'oral tolerance' when induced via the gut; it depends largely on development of suppressive Treg cells in mesenteric lymph nodes to which mucosal dendritic cells (DCs) carry antigens and become conditioned for tolerance induction. Because Treg cells generally dampen immunopathology, they may also hinder elimination of infectious agents such as HIV. Mucosal immunity is most abundantly expressed in the gut, and the intestinal mucosa contains 80% of the body's activated B cells – terminally differentiated to plasmablasts and plasma cells (PCs). Most mucosal PCs produce dimeric IgA which is exported by secretory epithelia expressing the polymeric Ig receptor (pIgR). Immune exclusion is performed mainly by secretory (S)IgA. Notably, pIgR knockout mice which lack SIgs show increased uptake of food and microbial antigens have a hyper-reactive immune system with disposition for anaphylaxis; but this is counteracted by oral tolerance as a homeostatic back-up mechanism. In the intestine, induction and regulation of mucosal immunity takes place primarily in Peyer's patches together with other parts of gut-associated lymphoid tissue (GALT) and mesenteric lymph nodes. Retinoic acid exerts a positive impact both on differentiation of IgA-producing PCs and their intestinal precursor homing. A complication is the regionalization with regard to migration of mucosal memory/effector B cells to various effector sites. However, after the failure of parenteral AIDS vaccines, there is renewed interest in exploiting musocal immunity in the prevention of this disease.