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Cross-reactivity of HIV vaccine responses and the microbiome

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Abstract

Purpose of review—A successful HIV-1 vaccine will require immunogens that induce protective immune responses. However, recent studies suggest that the response to human immunodeficiency virus-type 1 (HIV-1) and perhaps other viruses may be altered by immune system exposure to intestinal microbiota (IM)-antigens. This review will discuss select aspects of these studies.

Recent findings—Naïve CD4 T and B cell repertoires can be imprinted by IM-antigens to respond to virus epitopes prior to virus infection. A multiclade Env gp145 DNA prime, recombinant adenovirus type 5 boost vaccine tested in a HIV Vaccine Trials Network (HVTN) phase IIb human vaccine efficacy trial (HVTN 505) induced a dominant gp41-reactive antibody response that was non-neutralizing and cross-reactive with IM. This vaccine regimen also induced a dominant gp41-reactive, IM-cross-reactive gp41 antibody response in neonatal and adult Rhesus macaques. Studies of naïve CD4 T cells have demonstrated cross-reactivity to both HIV-1 and influenza peptides.

Summary—HIV-1 Env vaccine-induced CD4 T and B cell responses can originate from a pool of IM-cross-reactive immune cells. Moreover, IM-cross-reactive HIV-1 Env antibodies are ineffective in protection against HIV-1 infection. Thus, IM-imprinting of the B cell repertoire may be one of several roadblocks to the induction of protective HIV-1 antibodies.

Keywords

Microbiome; HIV vaccines; CD4 T cells; B cells; Cross-reactive antibodies

Introduction

Both B cell receptor (BCR) and T cell receptor (TCR) diversity contributes to the development of an effective humoral immune response that can recognize pathogens and environmental antigens (1). Many B cells responding to pathogens are polyreactive, and thus are capable of responding to multiple antigens (2). In this regard, naïve B cell subsets can be stimulated with environmental antigens and become primed for responding to pathogens and vaccine-immunogens with shared properties, including sequence and structural motifs (2-4).

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Conflicts of interest

The authors report no conflicts of interest.

The notion that environmental antigens can prime naïve B cell subsets to respond to pathogens is important for understanding CD4 T and B cell responses to infectious diseases. Here we discuss recent findings of IM cross-reactivity with viruses, focusing on HIV-1 Env cross-reactivity with bacterial IM.

Cross-reactive T cell responses in viral infections

For generating a T cell response, T cells must be present in sufficient numbers to recognize a specific antigen, but given the remarkable number of environmental antigens, the TCR repertoire must be able to recognize a vast array of peptides in the context of major histocompatibility complex (MHC) class I or class II (5). The ability of T cells to bind multiple ligands may be conferred by cross-reactivity with environmental antigens of similarity in epitopes recognized by T cells or the flexibility of TCR recognizing different epitopes presented by the same MHC (6, 7). Intestinal microbiome proteins are candidate environmental antigens with sequence and structural similarities to viruses that may be able to stimulate naïve T cells (7).

Antigen-specific CD4 T helper cells, particularly T follicular helper (Tfh) cells, are required for optimal B cell affinity maturation and class switching (8). Two studies have shown the existence of memory CD4 T cells that cross-reacted with HIV-1 and IM peptides in HIV-1 uninfected individuals (9, 10). Using a human leukocyte antigen (HLA)-restricted, peptide MHC tetramer enrichment technique, Su and colleagues characterized the CD4 T cell repertoire in 26 healthy adults and found T cells that reacted with tetramers derived from HIV-1, cytomegalovirus (CMV) or herpes simplex virus (HSV) epitopes (10). Reactive T cells had surface markers and gene expression profiles of memory T cells and showed evidence of clonal expansion. Su *et al.* demonstrated that one mechanism for accruing virus-specific CD4 T cells was naïve CD4 T cell cross-reactivity with environmental antigens, including microbiota antigens (10). Specifically, peptides derived from intestinal commensal bacteria *Ruminococcus flavefaciens*, *Lachanospiraceae bacterium*, and *Bifidobacterium bifidum* had sequence homology with HIV-1 peptides and were found to cross-react with CD4 T cells (10). Similarly, influenza-reactive T cells from two individuals vaccinated with an influenza vaccine responded to an HA 391-410 peptide sequence and could be activated by peptides from a human skin bacterium *Finegoldia magna* (10). Campion and colleagues used an HLA-unbiased T cell library technique to characterize the naïve and memory T cell repertoires of seven healthy HIV-1 seronegative individuals and found clonally-expanded naïve and memory CD4 T cells that reacted with HIV-1 peptides (9). The HIV-1 peptides that cross-reacted with naïve and memory CD4 T cells from HIV-1-negative individuals had epitope-length matches with microbial sequences of human microbiome proteins, suggesting that microbial proteins could have been responsible for T cell priming (9). Therefore, using two independent approaches, both Su *et al.* and Campion *et al.* found naïve and memory CD4 T cells that cross-reacted with virus and IM-antigens, and provided evidence that virus-reactive T cells may be induced by cross-reactivity with environmental antigens, including commensal microbial antigens. Thus, CD4 T cell anti-viral repertoires may be shaped by microbial antigens and can influence the immune response to HIV-1 vaccines.

Pre-existing naïve CD8 T cells that can recognize viral antigens have also been described. Schmidt and colleagues found naïve CD8 T cells that cross-reacted with Hepatitis C virus (HCV)-epitopes in seven HCV-uninfected individuals (11). Interestingly, the HCV epitope that most commonly reacted with naïve precursor CD8 T cells in the uninfected individuals was the most frequently targeted epitope in an independent cohort of 26 HCV infected individuals, suggesting that immunodominance in HCV infection was linked to precursor frequency of CD8 T cells cross-reactive with HCV-specific epitopes (11).

Cross-reactive B cell responses in viral infections

Humans have a diverse B cell repertoire capable of generating antibodies that can mediate immune effector functions against viruses and virus-infected cells (1). High affinity anti-pathogen antibodies are generally monospecific since host tolerance mechanisms, including clonal deletion, anergy and receptor editing normally restrict the maturation of high affinity autoreactive B cells during B cell development (12, 13). However, ~20% of mature naïve B cells are low affinity self-reactive or polyreactive, and provide breadth of response to the B cell receptor repertoire (13). Interestingly, HIV-1 Env-reactive antibodies, including bnAbs are frequently polyreactive (14, 15), and have been suggested to be derived from a polyreactive pool of B cells such as marginal zone B cells and to be controlled by immune tolerance mechanisms (14, 16-18). Polyreactivity may be beneficial for HIV-1 Env-reactive antibodies, since neutralizing antibody epitopes on glycosylated HIV-1 Envs mutate extensively during viral evolution, are shielded by glycans, and each virion contains ~7-10 functional viral spikes (15, 19). Polyreactivity of HIV-1 Env-reactive antibodies may be conferred by high levels of somatic mutations (15), thus suggesting that polyreactive B cells may be positively selected in response to HIV-1 infection.

In acute HIV-1 infection (AHI), the initial humoral immune response consists of plasma IgM and IgG antibodies that target the gp41 region of HIV-1 envelope (Env) and are non-neutralizing and ineffective at controlling viremia (20). It was interesting to note that in AHI, both IgM and IgG responses arise at the same time, implying a mixture of IgM and IgG BCR-expressing responding B cells in AHI (20). Two subsequent studies addressed the origin of predominant gp41-reactive antibodies during AHI (3, 4). Ninety-one percent (61/67) of the Env-reactive antibodies isolated from plasma cells of the five AHI subjects were gp41-reactive, consistent with immunodominance of gp41-reactive plasma antibodies (3, 20). Moreover, plasma cell-derived gp41-reactive antibodies from AHI were highly mutated and thus led to the hypothesis that they originated from a pool of preexisting mutated B cells that cross-reacted with HIV-1 Env gp41 (3). Liao and colleagues went on to isolate gp41-reactive antibodies from plasma cells in peripheral blood of two uninfected individuals and demonstrated that the gp41-reactive antibodies from uninfected and AHI subjects were indeed cross-reactive with IM-antigens (3). Trama and colleagues studied the plasma cell and memory B cell repertoires of the terminal ileum in early and chronically HIV-1 infected individuals (4). Mutated gp41-reactive antibodies that cross-reacted with IM-antigens were also dominant in terminal ileum of six early-HIV-1-infected and three HIV-1-uninfected individuals (4). Thus, both of these studies suggested that the initial gp41-reactive antibody response observed in AHI were derived from a pool of preexisting IM-cross-reactive B cells (3, 4). That gp41-IM cross-reactive antibodies were class-switched and

mutated, supported the hypothesis that these antibodies were derived from a pool of preexisting B cells primed by IM-antigens.

Recent studies have assessed how changes in the microbiome following HIV-1 infection may impact disease progression towards AIDS. In a cohort of HIV-1-infected Ugandan individuals, post-infection fecal virome DNA was characterized using next generation sequencing, and the bacterial microbiome was characterized using 16S rRNA gene amplification (21). Analysis in HIV-1 infected Ugandans revealed alterations of virome and bacterial microbiome that were associated with low peripheral CD4 T cell counts. HIV-1 infected Ugandan subjects with CD4 T cell count <200 had significantly less bacterial phylogenetic diversity compared to infected subjects with CD4 T cell count >200 and HIV-1 uninfected subjects (21). In a cohort of rhesus macaques that received an Ad26 prime, Env protein vaccine prior to simian immunodeficiency virus (SIV) challenge, the overall bacterial communities remained relatively stable after SIV infection independent of vaccine-mediated protection, but the fecal samples of unprotected animals had a higher frequency of gastrointestinal adeno-associated viruses and picornaviruses compared to the fecal samples from vaccine-protected animals (22). Moreover, detection of adenovirus sequences in SIV-infected macaques was associated with macaque death due to AIDS-related complications, suggesting a possible emergence of pathogens during lentivirus infections (22). Thus, these studies demonstrated that gut viruses and bacteria are impacted by lentivirus infection and SIV vaccination may prevent overgrowth of pathogens that promote disease progression (21, 22).

Microbiota regulation of B cell responses has also been reported to impact Ab responses to influenza. Germ-free mice immunized with trivalent inactivated influenza vaccine (TIV) had impaired TIV-specific antibody responses that were restored upon recolonization of germ-free mice with strains of E. coli microbiota antigen, thus demonstrating a role for gut microbiota in response to influenza vaccines (23).

Cross-reactive B cell responses in HIV-1 Env vaccination

A National Institute of Health (NIH) Vaccine Research Center (VRC) DNA prime, recombinant adenovirus type 5 (rAd5) boost vaccine (VRC vaccine) that was studied in an HVTN phase IIb human vaccine efficacy trial (HVTN 505) in adult participants showed futility for protection against HIV-1 acquisition (24). This VRC vaccine was also studied in HVTN phase 1b (HVTN 082) and phase 2a (HVTN 204) human clinical trials (25, 26). The dominant plasma and memory B cell-derived antibodies induced by this VRC vaccine were neither neutralizing nor mediated FcR-dependent anti-HIV-1 activities (24, 26). The dominant blood-derived vaccine-induced antibody responses targeted the gp41 region of Env, gp41-reactive antibodies cross-reacted with IM-antigens, and gp41-reactive antibodies originated from B cells cross-reactive with both IM and HIV-1 Env that were present prior to vaccination (26). This phenomenon of dominant gp41 antibody response to gp41-containing Env vaccine was similarly observed in another human clinical trial HVTN 205 that studied a DNA prime, Modified Vaccina Ankara (MVA) boost with HIV-1 Env gp140 (27).

Infants live in a relatively sterile environment prior to birth (28), but neonate B cell repertoires may be imprinted soon after birth by microbiota antigens (29, 30). Thus, one hypothesis for induction of HIV-1 protective antibodies is to vaccinate infants early in life. The immune cells of neonates and adults have phenotypic and functional differences (31), but infants can respond robustly to some vaccines (32). We recently immunized neonate macaques with the VRC DNA prime, rAd5 boost vaccine at ~2-6 days after birth and found that vaccine-induced memory B cell-derived antibodies were predominantly gp41-reactive, and 16S rRNA-derived IM taxa profile was similar for neonate and adult macaques immunized with the same VRC vaccine (33). These data confirmed that the imprinting of the B cell repertoire occurs soon after birth. A recent review highlighted studies that suggested that the infant microbiome can in some cases be seeded *in utero* (34). Additionally, neonate B cells have been shown to express CD5 and CD1c, markers of marginal zone B cells (35, 36), and marginal zone B cells have low affinity IgM, autoreactive and polyreactive BCRs (37, 38). Since HIV-1 bnAbs are frequently autoreactive and subjected to immune tolerance controls during B cell lineage development in adults (14, 18), the polyreactive nature of infant B cells could be exploited for bnAb induction via HIV-1 vaccination. Indeed, human infants that are HIV-1 infected have a higher frequency of bnAbs and generate them sooner than HIV-1 infected adults (39, 40). HIV-1-induced immune dysfunction with disrupted immune tolerance has been associated with bnAb induction (41). Thus, one hypothesis to explain these observations in infants is that infant immune systems have possibly less stringent immune tolerance controls or respond to HIV-1 infection with more HIV-1-induced immune dysregulation.

Macaques are used as an animal model to study human HIV-1 infections and for testing candidate HIV-1 vaccines (42). Thus, evaluating gp41 immunodominance induced by HIV-1 Env gp140 in macaques is important for the HIV-1 vaccine field. Han and colleagues recently showed that, as in humans, the VRC DNA prime, rAd5 boost vaccine induced a dominant gp41-reactive, memory B cell response in both neonate and adult macaques (33). In this study, Han and colleagues also showed IM-cross-reactivity of the VRC vaccine-induced gp41-reactive antibodies. Thus, neonatal non-human primates may be a model to define immunoregulatory controls of bnAb induction in HIV-1 infection, and to elucidate roles the microbiome might have in imprinting the B cell repertoire to respond to pathogens.

HIV-1 Env and IM crossreactive epitopes

Many cross-reactive epitopes between HIV-1 proteins and human proteins have been described (43, 44). Studies of HIV-1 Env immunization in humans (24-27) and macaques (33) raised the hypothesis that IM-primed B cells can respond to the gp41 component of a HIV-1 Env vaccine. Two IM antigens have been identified, bacterial E. coli RNA polymerase and pyruvate flavodoxin oxidoreductase, that shared sequence and structural motifs with a region in the heptad-repeat 1 (HR1) region of gp41 containing the LLRAIE amino acid residues (4, 26). Interestingly, Han *et al.* demonstrated that human gp41-IM cross-reactive antibodies bound macaque IM and provided evidence of neonate and adult macaque IM bacterial proteins that encode the gp41-IM cross-reactive epitope found on E. coli RNA polymerase (33). Whether the LLRAIE amino acid sequence motif in Env gp41 HR1 region (26) is the principal candidate IM cross-reactive epitope on gp41 remains

unknown. Interestingly, it is likely that additional IM proteins have Env-cross-reactive epitopes, since gp120-reactive antibodies induced by the VRC DNA prime, rAd5 boost vaccine (26, 33) and HIV-1 infection (45) have also been isolated that cross-react with IM. Identifying IM-antigens and epitopes for Env-IM cross-reactivity will provide a toolbox of IM proteins that can be used to evaluate the IM-cross-reactivity of candidate HIV-1 Env vaccine immunogens. The new generation of stabilized trimers (SOSIPs) has been designed to present only bnAb epitopes that can be recognized by the immune system during vaccination (46-49). The membrane proximal external region (MPER) region targeted by gp41-reactive bnAbs was not included in the SOSIP trimers, but a portion of the gp41 ectodomain region remained at the base of these proteins. While most studies have found SOSIP trimers to induce primarily autologous tier 2 nAbs (50-52), a recent study in mice have shown that BG505 SOSIP.664 trimers induced non-neutralizing antibodies that targeted the base of the SOSIP (53). It will be key to determine if the new generation of HIV-1 Env immunogens induce gp41-dominant responses in non-human primates or in humans.

Conclusions

The microbiome can shape the repertoire of immune cells to respond to viruses, and influence the response to vaccine immunogens (Figure 1). Analysis of individuals vaccinated with Env-immunogens has demonstrated that IM-antigen cross-reactivity with HIV-1 Env can possibly divert HIV-1 Env vaccine-induced antibody responses away from protective immunity. Here we have reviewed evidence for three hypotheses: (i) the microbiome can influence the specificity of B and CD4 T cell responses to infections; (ii) the microbiome can modulate the response to HIV-1 Env immunization; and (iii) modification of the microbiome may enhance vaccine responses.

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Key bullet points

- The microbiome can influence immune responses to infections.
- Cross-reactivity of naïve and memory CD4 T and B cells occurs with intestinal microbiota antigens
- The microbiome can modulate antibody responses to HIV-1 Env vaccines.
- Modification of the microbiome and HIV-1 Env-Intestinal microbiota cross-reactive epitopes may enhance HIV-1 Env vaccine responses.

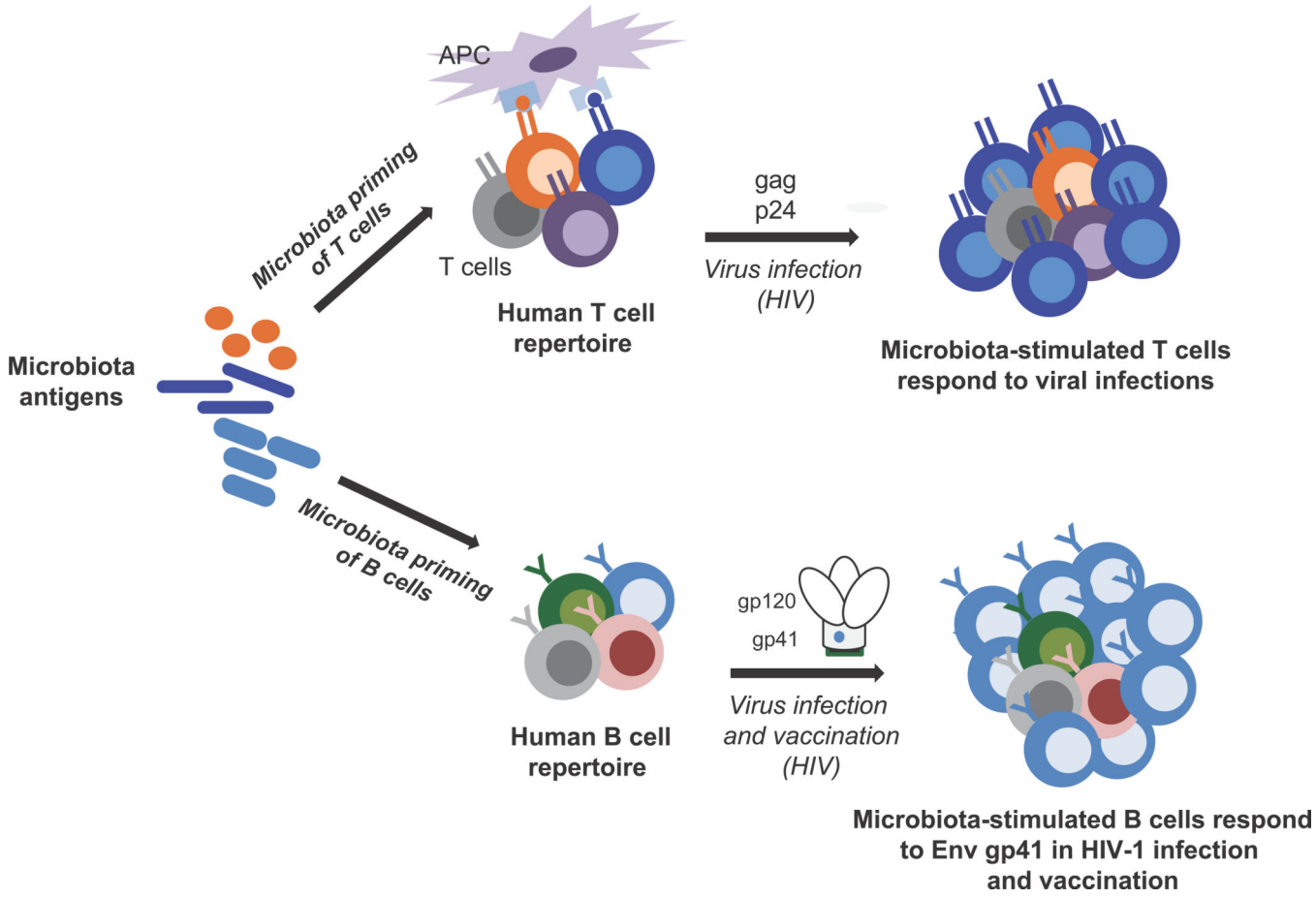

Figure 1.

Microbiota priming of CD4 T and B cell repertoires. For T cells (upper path); HIV-1-reactive T cells can be activated by antigens with sequence homology between HIV and microbiota proteins. For B cells (lower path); a dominant B cell response to HIV-1 infection and vaccination can be shaped by microbiota stimulation of a pre-existing pool of polyreactive B cells. Thus, microbiota-stimulated CD4 T and B cells can respond to viral antigens in the setting of infection or vaccination.