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The Mucosal Immune System and HIV-1 Infection

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Abstract

Recent progress in HIV-1 and SIV pathogenesis has revealed that mucosal tissues, primarily the gastrointestinal tract, are major sites for early viral replication and CD4+ T-cell destruction, and may be the major viral reservoir, even in patients receiving HAART. This is likely attributable to the fact that the majority of mucosal CD4+ T-cells co-expressing chemokine receptors required for HIV-1 entry, reside in mucosal tissues. Furthermore, the intestinal mucosal immune system is continuously bombarded by dietary antigens, resulting in continual lymphocyte activation, dissemination, and homing of these activated lymphocytes (including CCR5+CD4+ T-cells) throughout mucosal tissues. Thus, the intestinal immune system represents a very large target for HIV-infection, which is continually generating newly activated CD4+ T-cells that are the preferred target of infection. Thus, HIV-1 appears uniquely adapted to persist and thrive in the mucosal-tissue environment. The selective loss of intestinal CD4+ T-cells from immune-effector sites is also likely to explain, at least in part, the preponderance of opportunistic infections at mucosal sites. It is increasingly evident that effective therapies and vaccines must be directed towards eliminating HIV-1 in mucosal tissue reservoirs, protecting mucosal CD4+ T-cells and stimulating effective mucosal immune responses.

Key words

Mucosal Immunity. HIV-1. SIV. AIDS. Immunology.

Introduction

Despite significant progress in HIV research, many aspects of the pathogenesis of HIV-1 infection remain a mystery. Much is known regarding the cellular and molecular mechanisms involved in virus entry of cells *in vitro*, yet very little is known with certainty regarding the mechanisms involved in early viral transmission or replication within vaginal or rectal mucosal tissues. We also do not fully understand how HIV causes immunodeficiency. It is clear that HIV infection eventually leads to a loss of CD4+ T-cells, but there is considerable controversy as to whether this is mediated through direct viral destruction (cell lysis), indirect mechanisms mediated through apoptosis, or even through impaired CD4+ T-cell production.

Perhaps most importantly, we also do not know what immune responses are required to prevent or clear HIV-1 infection. Although there are propo-

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nents of both cell-mediated and humoral immune responses as being a key to controlling HIV-1 infection, viral clearance has not been documented in a single patient, regardless of the levels of HIV-specific humoral and/or cellular immune responses. Thus, the true correlates of protective immunity remain unknown.

Although it is clear that the majority of HIV-1 transmissions occur across mucosal surfaces, it is increasingly evident that mucosal tissues are also fundamentally involved in the pathogenesis and persistence of infection. Moreover, it is increasingly apparent that preventing the global spread of HIV-1 infection and AIDS will require the protection of mucosal surfaces, either through effective vaccination and/or the development of effective treatments or prophylactic microbicides. Current knowledge of early events in vaginal HIV-1 transmission has recently been reviewed[1]. This review summarizes the current state of mucosal immunity and the interplay of HIV-1 infection within mucosal surfaces, primarily focusing on the intestinal immune system.

General mucosal immunology

Mucosal surfaces are moist, epithelial-lined surfaces that are frequently or continuously exposed, either directly or indirectly, to the external environment. These include the tonsils, salivary glands, gastrointestinal and reproductive tracts, certain nasal and lachrymal membranes, and the lungs. Depending on their location and function, mucosal surfaces are frequently exposed to a wide variety, and often large quantities, of foreign antigens in the environment. For example, the gastrointestinal tract is continuously exposed to large amounts of antigens in the form of food and other ingested substances. The challenge of differentiating large quantities of benign antigenic substances (e.g. food) from small quantities of potential pathogens, in conjunction with the need to minimize immune responses to the former, and maximize responses to the latter, has led to the development of a highly specialized and compartmentalized immune system that is separate and distinct from the systemic immune system.

Increasing evidence suggests that mucosal immune responses may be even more specialized and compartmentalized than once thought. The terms “common mucosal immune system” and its associated “mucosal-associated lymphoid tissue” (MALT) were originally coined to describe organized and dispersed lymphoid tissues found in the intestine, tonsil, lung, nasal, lacrimal, mammary, reproductive, and salivary glandular tissues, as a single immune system (reviewed in [2]). However, emerging evidence indicates that mucosal immune responses in these tissues may be more independently regulated and compartmentalized than originally perceived.

The gastrointestinal tract is one of the largest mucosal tissues in the body, and since it harbors the majority of the body’s T-cells and macrophages, it is generally considered to be the largest immunologic organ in the body[3-5]. It is also, perhaps, the most carefully studied mucosal tissue, at least in rodents. Although the number of T-cells has not been determined in humans, calculations in mice indicate that over 40% of the total T-cells in the body are located within the intestinal epithelium alone[6]. This does not include the T-cells in the lamina propria and organized lymphoid tissues of the intestine, which may represent even larger numbers of T-cells than in the epithelium. Furthermore, the vast majority (80-90%) of the body’s immunoglobulin-producing cells (plasma cells) are located in the intestine[7].

Composition of mucosal lymphoid tissues

The gut-associated lymphoid tissue (GALT) consists of both specialized aggregates of lymphoid tissue and widely dispersed immune cells. Aggregates of lymphoid nodules, exemplified by Peyer’s patches in the terminal portion of the small intestine (ileum), are also found in the tonsils, the large intestine (colon) and rectum. Similar, yet solitary, lymphoid nodules are also scattered throughout the intestinal mucosa. Morphologically and functionally similar to lymph nodes, these “inductive” lymphoid tissues are involved in initiating immune responses (Fig. 1). These structures are rich in B-cells (follicular region), T-cells (interfollicular areas), and a variety of antigen-presenting cells, including macrophages and follicular dendritic cells (FDC’s). Peyer’s patches and other lymphoid aggregates in the intestine are covered by a single layer of specialized epithelial cells, known as follicle-associated epithelium (FAE), containing substantial numbers of M-cells (Fig. 1), which play an important role in sampling and presenting luminal antigens to the underlying lymphoid cells[8]. Although usually present in small numbers at birth, the number of Peyer’s patches in the human intestine increases from birth until approximately 12 years of age, and declines thereafter[2]. Such age-related development suggests that these structures develop in response to antigenic exposures.

In considering the gut-associated lymphoid tissues, it is critical to distinguish the properties of “effector” and “inductive” lymphoid tissues (Fig. 1). Antigens draining into inductive mucosal lymphoid tissues from afferent lymphatics (mesenteric lymph nodes), or entering directly through the epithelium (via M-cells in Peyer’s patches), are presented to B- and T-cells in these follicles, and initiate or “induce” immune responses to the presenting antigen[9].

Lymphocytes in inductive lymphoid tissues are thus mostly naive resting cells that have not yet encountered their cognate antigen. Once activated, these cells migrate through efferent lymphatics to the peripheral blood, where they briefly re-

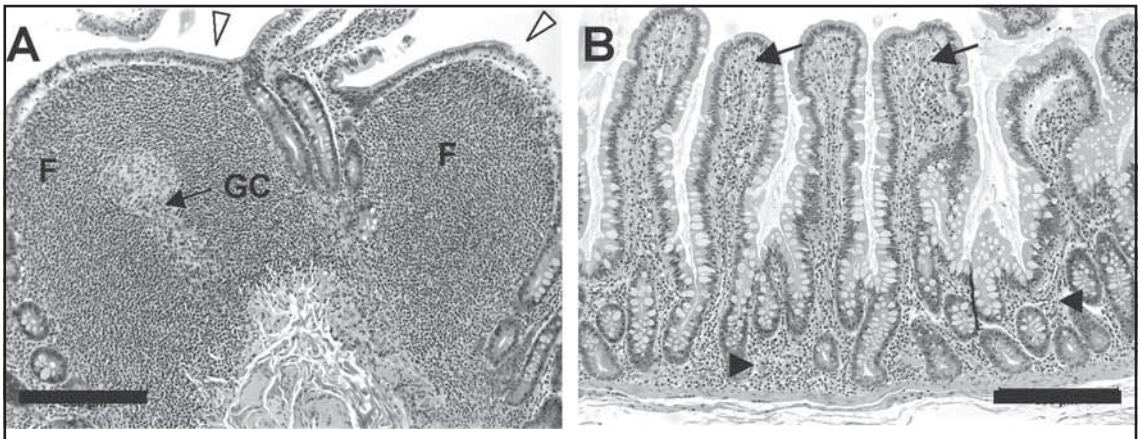

***Figure 1**. Comparison of inductive (**A**) and effector (**B**) lymphoid tissues in the intestine of a rhesus macaque. **A**: Photomicrograph of a Peyer's patch consisting of aggregates of lymphoid follicles (F), covered by follicle-associated epithelium (open arrowheads). A germinal center (GC) is apparent in the center of one follicle. **B**: Photomicrograph of the jejunum demonstrating intestinal villi and lamina propria. Lamina propria lymphocytes are present throughout the superficial lamina propria of the villi (arrows) as well as the deep lamina propria (arrows). Bars = 500 mm.*

circulate and eventually return to "effector" sites, usually the diffuse lamina propria of the tissue where they were originally activated[10]. Effector lymphoid tissues thus consist primarily of widely dispersed T- and B-cells distributed throughout the lamina propria and/or submucosa of mucosal tissues (Fig. 1). Since lymphocytes have homed to this region following antigenic stimulation, the majority are highly activated, terminally-differentiated, memory T-cells or B-cells (plasma cells). Since HIV-1 selectively replicates within activated lymphocytes, this has tremendous significance for both HIV-1 pathogenesis and persistence as discussed below.

Regulation of mucosal recirculation and homing

Tissue-selective homing of T and B lymphocytes is mediated by specific adhesion molecules, chemokines, and their ligands (reviewed in [11]). For example, memory cells destined to home to the skin express the cutaneous lymphocyte antigen (CLA), whereas memory T-cells homing to the intestine express high levels of the $\alpha_4\beta_7$ integrin, whose ligand (MAdCAM-1) is predominantly expressed on endothelial cells lining postcapillary venules in the intestinal lamina propria[10,12]. Another integrin, $\alpha E\beta 7$ (CD103), regulates the homing of lymphocytes specifically to the mucosal epithelium via expression of E-cadherin on epithelial cells[13]. Still other mucosal-homing lymphocytes in circulation express high levels of the VCAM-1 receptor $\alpha_4\beta_1$, which may play a role in the selective homing of lymphocytes to bronchus-associated lymphoid tissues[11]. Thus, even within the "common" mucosal immune system, selective homing mechanisms may direct site-specific homing of mucosal lymphocytes to different organs.

Chemokines and their receptors are also important in lymphocyte homing. The chemokines TARC/CCL17 and CTACK/CCL27 mediate trafficking of CLA+ lymphocytes to the skin via CCR4 and CCR10, respectively[11,12]. In contrast, intestinal lymphocyte homing is further regulated by the chemokine receptor CCR9, whose ligand is CCL25 (also known as thymus-expressed chemokine or TECK). TECK/CCL25 is selectively expressed on thymic and small-intestinal epithelium[14]. Interestingly, TECK/CCL25 is highly expressed in the small intestine, and only weakly expressed in the colon, suggesting that even differential trafficking of lymphocytes to the small and large intestine occurs[11,15].

Homing of mucosal immunoglobulin-secreting cells is also highly regulated by specific adhesion molecules and chemokines. The mucosa-associated epithelial chemokine, MEC/CCL28, produced by mucosal epithelial cells, is selectively chemotactic for IgA-secreting cells expressing CCR10[15,16]. MEC attracts IgA- (but not IgG- or IgM-) secreting cells from both inductive and effector tissues, including the intestines, lungs, and lymph nodes draining the lungs and oral mucosal surfaces. Similarly, TECK/CCL25 attracts a subpopulation of IgA-secreting cells (in addition to CCR9+ T-cells) to the small intestine[16]. This homing may partially explain the selective production of IgA in mucosal tissues.

Both T- and B-lymphocyte homing and homeostasis is thus mediated by complex and highly selective molecular interactions, resulting in the compartmentalization and separation of mucosal and systemic immune responses. This results in a remarkably efficient system of immune responses that selectively distributes antigen-specific immune responses directly to tissues affected by the inciting pathogen, and widely disseminates these immune responses to protect the entire organ. In most cases, this results in protective immune responses being disseminated throughout the tissue at risk, without generating significant immune responses in systemic tissues that could waste immunologic resources or produce undesirable side effects. Unfortunately, HIV-1 is apparently adapted to both subvert and

exploit the unique immunologic properties of the mucosal immune system. The same features that limit or prevent most pathogens from infecting and spreading throughout the host, apparently work to the advantage of HIV-1 by providing optimal sites for viral attachment, entry, amplification, dissemination, and persistence of the virus.

Mucosal CD4+ T-cells and HIV-1 replication

As described above, mucosal effector tissues are normally in a state of "physiologic inflammation". Most of the lymphocytes in effector lymphoid tissues are activated, terminally differentiated cells actively engaged in either cytokine production, immunoglobulin secretion, proliferation, and/or increased expression of adhesion molecules and/or other inflammatory mediators. Regardless of the cell involved, "activation" is usually associated with some type of transcription. Viruses that require incorporation into host-cell DNA, and subsequent host-mediated transcription for replication and assembly (i.e. retroviruses), are thus likely to replicate more efficiently in activated cells. It has been clearly established that HIV-1 replicates much more efficiently in activated T-cells *in vitro*[17-20], presumably for these reasons. Since the intestine contains the vast majority of the body's activated CD4+ T-cells, this fact alone would suggest that the intestinal tract would be a preferred site of viral replication *in vivo*. In support of this, intestinal mucosal T-cells have been demonstrated to be much more susceptible to HIV infection, and support higher levels of viral replication on a per-cell basis as compared to peripheral blood T-cells[21].

Although studies of the intestinal immune system during primary HIV-1 infection have not been performed, it is evident from studies in SIV-infected macaques that mucosal CD4+ T-cells are selectively and profoundly depleted within days of SIV infection, regardless of the route of inoculation[22-24]. Similar results have been observed in early HIV-1 infection of humans, as CD4+ T-cell depletion is more pronounced in the intestine as compared to blood[25,26]. It is also important to point out that this depletion is specific for CD4+ T-cells in effector lymphoid tissues (lamina propria) and that naive, resting CD4+ T-cells localized in inductive lymphoid tissues are spared at this stage of infection[25,27]. This selective elimination of mucosal effector CD4+ T-cells may be attributed to their increased levels of cellular activation and chemokine receptor expression.

HIV-1 and chemokine receptors in mucosal tissues

It is now known that, in addition to CD4, HIV-1 requires a coreceptor for efficient viral attachment and entry into host cells[28]. The principal coreceptor for HIV-1 entry into cells is CCR5[29,30], the natural ligands for which are the chemokines CCL3, CCL4, and CCL5 (previously known as RANTES, MIP-1α, and MIP-1β, respectively)[31,32]. However, some strains of HIV-1 may use CXCR4 in addition to, or instead of, CCR5[33]. Nonetheless, it is increasingly apparent that the majority of HIV-1 strains obtained from patients in early stages of infection utilize CCR5[34-36], suggesting that CCR5 strains are selectively transmitted across mucosal surfaces.

One possible explanation for this is that mucosal tissues contain the vast majority of CD4+CCR5+ T-cells in the body. Most of the CD4+ T-cells residing in the lamina propria of the intestine and vagina express high levels of both CCR5 and CXCR4[21,24,37-39]. In contrast, the majority of CD4+ T-cells in the peripheral blood and lymph nodes express CXCR4, but not CCR5. Peripheral blood cells that do express CCR5 have fewer such receptors on their surface compared to mucosal CD4+CCR5+ T-cells[21,24,37,39-41]. However, CCR5 expression is not necessarily limited to mucosal tissues, and there is evidence that CCR5 expression is involved in non-specific inflammation rather than site-specific homing[12]. In support of this, CCR5 expression may be rapidly induced on select subpopulations of peripheral-blood CD4+ T-cells upon certain types of activation *in vitro*[42]. Interestingly, only antigen-activated "memory" CD4+ or CD8+ T-cell subsets upregulate CCR5, whereas mitogen or CD3+ stimulation of naive cells fails to induce CCR5 upregulation[42]. Combined, these data indicate that most CD4+ T-cells co-expressing CCR5 are located in the mucosal effector tissues, primarily because they have previously encountered their cognate antigen, become activated, and homed to these sites. This could be important in explaining much of the confusion in HIV-1 pathogenesis, as most studies of HIV-1 are performed using naive, resting cells obtained from the peripheral blood, rather than from mucosal tissues.

Thus, it has been proposed that mucosal CD4+ T-cells are highly susceptible to HIV and SIV infection and loss, because they have an activated, memory phenotype and express higher levels of CCR5 than peripheral lymphoid tissues[21,24,37,39,43,44]. It has also been shown that SIV and HIV-1 selectively deplete activated, CCR5-expressing, memory CD4+ T-cells from all immune compartments of the body, but profound overall CD4 depletion alone is only observed in mucosal compartments, because of the high prevalence of this particular phenotype in these tissues[39,44,45]. More recently, we have observed that, very occasionally, an SIV-infected macaque does not have marked mucosal CD4+ T-cell depletion. Remarkably however, residual CD4+ T-cells in mucosal tissues of these macaques are completely devoid of CCR5 expression[24]. Similar results are being observed in HIV-1 infected humans. Intestinal CD4+ T-cells co-expressing CCR5 are also profoundly and consistent-

ly depleted in HIV-1 infected humans, even if residual CD4+ (CCR5neg) T-cells remain[46]. Similarly, marked and persistent depletion of mucosal-homing ($\alpha4\beta7$+) CCR5+CD4+ T-cells has been demonstrated in the peripheral blood of HIV-1 infected humans in early HIV infection, despite control of viral replication by antiretroviral treatment[45]. Although the mechanisms involved in this selective CD4+CCR5+ T-cell depletion are still under investigation, it likely that direct HIV-1 infection and viral-mediated cell destruction play a major role.

Mucosal HIV-1 localization and persistence

Mucosal tissues are being recognized as major sites for viral replication, and persistence in HIV-1 infected patients. HIV-1 infected T-cells and macrophages are consistently found in the intestine of HIV-infected patients[47-50]. Moreover, HIV DNA and RNA can consistently be detected in intestinal biopsies of HIV-1 infected patients on highly active antiretroviral therapy (HAART), even when plasma virus is undetectable[51]. Furthermore, levels of HIV in the intestine do not correlate with the number of years patients received HAART, indicating that no decay in tissue reservoirs occurs despite prolonged HAART[51].

SIV-infected cells are also consistently detected in the intestine of SIV-infected macaques. Their location depends largely on the stage of infection, which provides additional clues to the pathogenesis of mucosal CD4+ T-cell loss. Relatively large numbers of SIV-infected lymphocytes are detected in the intestinal lamina propria in primary SIV infection (7-14 days of infection), which immediately precedes the marked depletion of CD4+ T-cells specifically within this compartment. After lamina propria CD4+ T-cells are depleted, SIV-infected lymphocytes, macrophages, and dendritic cells, are predominantly found within organized lymphoid tissues, and infected cells are less frequent in the lamina propria[22,27,52].

Combined, these data suggest that once the cells most capable of supporting viral replication (activated, effector CD4+CCR5+ T-cells in the lamina propria) are eliminated from the mucosa, the virus then infects other cell types that are less conducive to infection and rapid viral replication (i.e. macrophages, naive CD4+ T-cells) in inductive sites such as Peyer's patches. Through continual antigen exposures in intestinal inductive sites, these cells, some of which may be latently infected, are activated and better able to support viral replication, which may result in a continual source of viral dissemination throughout host tissues.

Virus-specific cytotoxic T-cells in mucosal tissues

Additional evidence for the importance of mucosal tissues as major viral reservoirs of virus in chronically infected patients comes from studies of virus-specific cytotoxic T-cells (CTL's). Although the development and magnitude of SIV-specific CTL responses in the intestine and blood in primary infection are comparable[53], emerging evidence indicates that the percentages of virus-specific CTL responses are considerably higher in the intestinal and vaginal mucosal than in blood or lymph nodes in chronically infected macaques[54-56]. Similarly, percentages of virus-specific CTL's were recently reported to be much higher in the intestines than in the blood of HIV-1 infected humans[46]. It has been postulated that the levels of CTL's correlate directly with levels of viral replication in these tissues[54,57]. If so, these data argue that higher levels of viral replication occur in these compartments as compared to peripheral blood or lymph nodes, and that mucosal tissues are the major tissue reservoirs for chronic HIV/SIV infection.

Although virus-specific CTL's are consistently observed in HIV-1/SIV infection, their levels are obviously not sufficient for protection. Inverse correlations between levels of virus-specific CTL's in the blood and plasma viremia have been documented[58-60]; however, no patients have cleared HIV infection, regardless of CTL levels. Furthermore, typical percentages of virus-specific CTL's in HIV-1 infected patients (1-2%) may be rather small compared to those reported in other viral infections. For example, up to 45% of the total CD8-cells in acute EBV infections may be directed against a single viral epitope[61]. If these levels are indicative of what is required for protection from viral infections, CTL levels in HIV-1 patients tested to date are apparently insufficient. Conceivably, the low levels of HIV-specific CTL's in HIV-infected patients may reflect inadequate CD4+ T-cell help, as increasing evidence points to a requirement for CD4+ T-cells in CTL production and expansion[62-64].

Mucosal CD4+ T helper cells

CD4+ T-cells have been referred to as the "orchestrating cells" of the immune system, and their help is essential in the regulation of CD8+ T-cell responses[58,62-65]. A profound and rapid loss of mucosal effector CD4+ T-cells is, thus, likely to impart a profound immunodeficiency, particularly in mucosal tissues of HIV-1 infected patients. This may explain why opportunistic infections almost invariably target mucosal surfaces. It has also been postulated that the level of CD4+ T-cell activation and/or the presence of opportunistic infections (OI's) may accelerate CD4+ T-cell turnover and depletion, resulting in faster progression to AIDS[38]. In support of this, recent evidence suggests that increased immune activation is associated with accelerated CD4+ T-cell depletion and more severe immunodeficiency in HIV-1 infection[66,67]. Other studies have demonstrated that patients with concurrent OI's placed on HAART reconstitute their intestinal CD4+ T-cells at a much

greater rate than those without OI's[68], suggesting that CD4+ T-cell turnover and repopulation may be directly correlated with antigenic stimuli in mucosal tissues.

CD4+ T-cell responses have been the subject of intense research, as it has been demonstrated that vigorous CD4+ T-cell responses were associated with lower viral loads in HIV-1 infected patients[69]. Unfortunately, other studies have demonstrated that even HIV-1-specific CD4+ T-cells are highly susceptible to HIV-1 infection and capable of supporting high levels of viral replication, which lends caution to the theory of stimulating CD4+ T-cells as therapy for HIV-1 infection[70]. Regardless, HIV-1 seems to have developed multiple, overlapping mechanisms that thwart the development of effective immune responses, and ensure its survival in infected hosts through infecting and eliminating the very cells necessary for generating and maintaining protective immune responses.

Mucosal vaccines for AIDS

Developing an effective vaccine for HIV-1 has proven problematic. However, rapid progress in understanding mucosal and vaccination immunology could result in an effective AIDS vaccine within the next several years. It is increasingly evident that inducing protective immune responses specifically within mucosal tissues will be crucial for such a vaccine[71]. Recent studies are providing evidence that eliciting immune responses specifically in mucosal sites may be required for effective vaccination against SIV/SHIV[72,73]. In general, vaccines administered systemically promote systemic, but not mucosal, immune responses[74-76]. A seeming paradox to these observations is that systemic administration of attenuated SIV/SHIV, or live viral vectors containing various SIV/SHIV peptides, has been shown to induce fair-to-excellent protection in nonhuman primate models[58,77-81]. However, virus-specific mucosal immune responses have been demonstrated in macaques vaccinated with recombinant viral vectors, regardless of the route of administration[82]. As discussed above, levels of mucosal immune responses (CTL) may directly correlate with levels of viral replication and persistence in these compartments. Perhaps the common theme in vaccines that have demonstrated efficacy in animal models, is that they all result in delivery of viral antigens to mucosal tissues. For example, the parental viruses that served as the starting point of the viral vectors that have demonstrated efficacy in macaques thus far (vaccinia[58], SIV/SHIV[77,80], vesicular stomatitis virus[78], poliovirus[81]) are all known to replicate within mucosal tissues. Thus, all of these vectors are likely to replicate in, and deliver their recombinant viral peptide antigens to, mucosal tissues. Although the route of immunization may also prove to be important, vaccination strategies that utilize either live-attenuated or recombinant viruses, or peptide-based vaccines delivered with adjuvants that effectively deliver and maintain HIV-1 antigens directly in mucosal tissues, are likely to prove critical for an effective HIV-1 vaccine.

Conclusions and future directions

Numerous studies now indicate that HIV-1 infection causes a profound and persistent depletion of mucosal CD4+ T-cells, particularly those that are activated, memory, and co-express CCR5. Given the importance of these "effector" T-cells for both cell-mediated and humoral immune responses, it is probable that this results in severe impairment of mucosal immune responses throughout the course of infection, which probably plays a major role in the failure to develop effective immune responses and contain infection. Regardless of whether these cells are lost through direct viral-mediated destruction or bystander mechanisms, it is clear that preserving and/or replenishing these cells will be key to restoring normal immune responses in HIV-1 infected patients. However, therapies aimed at increasing CD4+ T-cell proliferation, or activating naive CD4+ T-cells, should be approached with caution, as these could simply provide more "fuel" for viral replication, and accelerate the onset of AIDS. New therapies that act by blocking or downregulating CCR5 expression to prevent infection of new cells are currently in clinical trials[83], and these may provide additive benefits when used in conjunction with existing therapies; however it is doubtful that even this approach will be curative. Alternative approaches aimed at decreasing cell activation have been proposed, but as described above, a constant state of "physiologic inflammation" is normal in the mucosal immune system, and it is uncertain what effects such therapies could have on normal mucosal immune maintenance and function. More research into the different types of immune activation is needed before we can determine whether, or which, anti-inflammatory therapies would be beneficial in HIV-1 infection. Furthermore, research is desperately needed to identify markers of latently infected cells *in vivo,* so that specific drugs and/or immune therapies may be directed towards eliminating viral reservoirs, particularly in mucosal tissues.

Since no cures for HIV-1 infection are on the immediate horizon, our best prospects for slowing the epidemic appear to be in preventing new infections, either through implementing more-effective social programs (i.e. encouraging condom use), developing prophylactic compounds that can prevent mucosal transmission when applied to the vagina or rectum (i.e. microbicides), and/or by creating and distributing effective vaccines.

Almost since the disease was discovered, it was recognized that mucosal tissues were major sites of HIV-1 transmission. However, it is now being recognized that mucosal tissues are fundamentally involved in viral pathogenesis throughout the course of infection, regardless of the route of

transmission. Promoting effective immune responses specifically within mucosal tissues is likely to prove paramount in developing effective treatment strategies and vaccines for AIDS.

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