Are Basophils and Mast Cells Masters in HIV Infection?

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Abstract

The World Health Organization AIDS epidemic update estimates that more than 37 million people are living with HIV infection. Despite the unprecedented success of antiretroviral treatments, significant challenges remain in the fight against HIV. In particular, how uninfected cells capture HIV and transmit virions to target cells remains an unanswered question. Tissue mast cells and peripheral blood basophils can be exposed to virions or HIV products during infection. Several HIV proteins (i.e., envelope glycoproteins gp120 and gp41, Tat, and Nef) can interact with distinct surface receptors expressed by human basophils and mast cells and modulate their functional responses at different levels. Additionally, several groups have provided evidence that human mast cells can be infected *in vitro*, as well as *in vivo*, by certain strains of HIV. Recently, it has been demonstrated that basophils purified from healthy donors and intestinal mast cells can efficiently capture HIV on their cell surface and, cocultured with CD4⁺ T cells, they can transfer the virus to the cocultured cells leading to infection. Direct contact between

human basophils or intestinal mast cells and CD4⁺ T cells can mediate viral *trans*-infection of T cells through the formation of viral synapses. Thus, basophils and mast cells can provide a cellular basis for capturing and then spreading viruses throughout the body. Collectively, these findings suggest that human basophils and mast cells play a complex and possibly distinct role in HIV infection, warranting further investigations.

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Introduction

The UNAIDS/World Health Organization AIDS epidemic update estimates that more than 37 million people were living with HIV in 2015 (global AIDS update 2016, <http://www.unaids.org>). New infections have been occurring in the past few years at a rate of 2.1 million/year, and almost 1.1 million individuals have succumbed to AIDS-related diseases. Although many people are now receiving life-saving antiretroviral treatment (an estimate of 17 million in 2015, and these have been very effective in reducing AIDS-related deaths, i.e., from 1.5 million in 2010 to 1.1 million in 2015), significant challenges remain in the fight against HIV infection and many aspects of its

Table 1. Features of human basophils and mast cells

	Basophils	Mast cells
Origin	hematopoietic stem cells	hematopoietic stem cells
Maturation	bone marrow	connective tissue
Growth factor	IL-3	SCF
Life span	days	months
Primary location	peripheral blood	tissues
Diameter	5–7 mm	6–12 mm
Nucleus	segmented	oval or round
Granules	large and few	small and numerous
Lipid bodies	absent	present
Tryptase	absent	present
Chymase	absent	present
Renin	absent	present
Carboxypeptidase A	absent	present
Secreted phospholipase A ₂	absent	present
Basogranulin	present	absent
Peptidoglycans	chondroitin sulfates	heparin and chondroitin sulfates
Histamine	±1 pg/cell	±3 pg/cell
Lipid mediators	LTC ₄	PGD ₂ , LTC ₄ , LTD ₄ , LTE ₄ , and PAF
Cytokines	IL-3, IL-4, and IL-13	SCF, IL-3, IL-5, IL-6, IL-10, IL-13, IL-16, IL-18, IL-25, GM-CSF, TGF-β, TNF-α, etc.
Chemokines	IL-8/CXCL8 and MIP-1α/CCL3	IL-8/CXCL8, CXCL1, CCL1, CCL2, and CCL3
Angiogenic factors	VEGF-A	VEGF-A and VEGF-B
Lymphangiogenic factors	absent	VEGF-C and VEGF-D

pathogenesis still need to be clarified [1, 2]. Most infections are nowadays acquired through sexual intercourse by means of mucosal transmission [3]. During acute HIV infection, patients experience high levels of plasma viraemia, causing vigorous, though inadequate, cellular and humoral immune responses. Neutralizing antibodies against cell-free virus are detected in the sera of infected individuals, but these are generally ineffective against circulating HIV [4, 5]. How uninfected cells capture HIV and transmit the virus to target cells via the virological synapse or how HIV infects target cells and replicates, persisting in the face of a vigorous immune response, remains unanswered [6, 7].

HIV entry into CD4⁺ T cells is mediated by the virus-encoded envelope glycoproteins gp120 and gp41. These proteins interact with the primary cellular receptor CD4 and its coreceptors (e.g., CCR5, CXCR4, or CCR3), which triggers the fusion of the viral and host cell membranes [8]. However, the details of viral propagation and spread between cells and host tissues are still poorly characterized. Expanding our knowledge on these aspects is essential to understanding the pathogenesis of HIV infection and its progression to AIDS.

Human basophils and mast cells are characterized by expression of the high affinity receptor for IgE (FcεRI) and by the unique ability to release preformed and de novo synthesized mediators [9–11]. Despite some similarities, there are striking differences in the morphological, biochemical, and immunological characteristics of human basophils and mast cells (Table 1) and in their roles played in innate and adaptive immunity [12, 13]. Although the primary location of human basophils is the peripheral blood, under certain pathological conditions basophils are recruited into inflamed tissues [14–16] and in lymph nodes [17, 18].

Human mast cells and basophils have long been regarded as critical effector cells in IgE-associated allergic disorders [10, 11]. However, there is now evidence that mast cells and basophils are versatile effector and regulatory cells able to initiate and modulate both innate and adaptive immune responses to parasites and bacterial pathogens [12, 19, 20]. Similarly, basophils and mast cells have been involved in many physiological and pathological processes, such as autoimmunity [21, 22] and cancer [10], where they can play multifaceted roles with both pro- and anti-inflammatory/immunomodulatory func-

Fig. 1. Schematic representation of the virological synapse between human basophils and CD4⁺ T cells. Human basophils can efficiently capture HIV on the cell surface through the interaction between gp120 and IgE V_H3⁺ or gp120 and integrin α4β7 expressed by basophils and CD4⁺ T cells. Direct contact between basophils and CD4⁺ T cells and the formation of virological synapses facilitate *trans*-infection of HIV into circulating naïve CD4⁺ T cells from infected donors. Also some of the interactions between HIV, HIV products, human basophils, and T lymphocytes are shown. Shed- or virus-bound gp120 can interact with variable, heavy chain 3⁺ (V_H3⁺) IgE bound to basophils to induce the release of IL-4 and IL-13. IL-4 and IL-13 interact with their receptors on lymphocytes. gp41 and extracellular Tat can interact with FPR1 and CCR3, respectively, to stimulate basophil chemotaxis. Nef is a potent chemoattractant for basophils through the engagement of CXCR4. CCR5, CXCR4, and CCR3 are coreceptors for several strains of HIV.

tions [21, 23]. The role of basophils and mast cells in viral infections is more enigmatic and has been less well studied [13]. In particular, the extent of mast cell/basophil involvement in the response to HIV infection and the resulting pathophysiological implications have not been thoroughly investigated [24–26].

The majority of HIV infections are nowadays acquired by mucosal exposure, with sexual transmission as the leading mode of infection worldwide [3]. Mast cells can be found in almost all vascularized tissues, but they are most abundant beneath epithelial and mucosal surfaces. In addition, early phases of HIV infection are associated with a high level of viremia [1, 27]. Thus, mast cells and basophils can be exposed to virions or viral products during the early phases of HIV infection, the former at the site of viral entry and the latter in circulation during the viremic phase.

Effects of HIV Proteins on Human Basophils and Mast Cells

In the course of HIV infection, the gp160 envelope glycoprotein is enzymatically cleaved, yielding 2 proteins, i.e., the transmembrane gp41 and the surface gp120 [28]. In the early events of HIV infection, gp120 binds to CD4

on immune cells, causing conformational changes in the envelope glycoprotein. This event induces exposure of binding sites for chemokine receptors (CCR5 or CXCR4) that serve as obligated coreceptors for virus entry [29, 30]. Certain strains of virus can use CCR3 present on human basophils [31] and mast cells [31, 32] as the coreceptor for HIV infection [33, 34]. The interaction with coreceptors induces further conformational changes in the envelope glycoprotein and exposure of the fusion domain of the gp41 subunit that mediates the fusion of the target cell and virus membranes [35, 36].

gp120 is a member of the immunoglobulin superantigen family [37] and binds to the V_H3 region of human immunoglobulins. These findings could explain the superantigenic activation of B lymphocytes observed in patients with HIV infection [38]. gp120 isolated from different HIV strains of various geographical origins was shown to induce IL-4 and IL-13 production from basophils purified from healthy donors negative for HIV-1 and HIV-2 antibodies [39, 40]. gp120 activates basophils through the interaction with IgE V_H3⁺ since removal of IgE completely blocks the envelope glycoprotein's effect on IL-4 and IL-13 release. During the early phase of HIV infection associated with a high level of viraemia [1, 41], basophils can be exposed to virus-bound or shed gp120. This may be an initial and critical source of IL-4 and IL-

13, thereby favoring a shift toward a Th2 phenotype [42], and it might explain the elevated IgE concentration in HIV-infected adults and children [43, 44]. IL-4 release from basophils might also indirectly affect HIV entry into CD4⁺ cells. Indeed, IL-4 upregulates CXCR4 [8] and facilitates HIV infection of T cells [45].

gp120 proteins from different HIV subtypes bind to the heterodimeric $\alpha 4\beta 7$ integrin [46]. This interaction contributes to generating the virological synapses in HIV infection between dendritic cells and CD4⁺ cells or between donor and targeted CD4⁺ cells [7]. Virological synapses facilitate the efficient cell-to-cell transfer of virions in HIV infection.

gp41 is thought to mediate the fusion between viral and cellular membranes by insertion of a hydrophobic N-terminus into the plasma membrane [28]. gp41 also exerts multiple effects on the host immune system. We found that envelope gp41, as well as several synthetic peptides encompassing its structure, promote the migration of human basophils through the interaction with formyl peptide receptors [47]. Together, these findings indicate the complexity of the interactions between HIV envelope peptides (i.e., gp120 and gp41) and different receptors expressed by human basophils.

The HIV *trans*-activator protein (Tat), secreted by HIV-infected cells [48–50], can be taken up by neighboring cells [51] in which it can reactivate a latent infection [50]. Thus, extracellular Tat mimics some of the effects of HIV on immune cells, suggesting an important role for this protein in the pathogenesis of HIV infection. We found that Tat is a potent chemoattractant for human basophils and mast cells obtained from healthy individuals through engagement of the CCR3 receptor expressed on these cells [52]. Thus, during HIV infection, associated with a high level of Tat in serum and other biological fluids [48], Tat induces the directional migration of Fc ϵ RI⁺ cells, thereby contributing to their recruitment to sites of HIV infection.

The *nef* gene is only present in the genomes of primate lentiviruses (i.e., HIV-1, HIV-2, and SIV). The protein is translated from a multiply spliced mRNA and it is highly expressed from the early stages of HIV infection. HIV Nef is required to maintain a high virus production within infected cells [53], and the loss of Nef results in delayed or absent disease progression [54]. Nef does not possess enzymatic activity, but it exerts its cellular functions by modulating the expression of several cell surface molecules [55]. Recently, de Paulis and collaborators found that Nef proteins, in concentrations similar to the ones found in the sera of infected patients [56], influences the

directional migration of basophils isolated from healthy subjects via interaction with the chemokine receptor CXCR4 [57].

Thus, at least 4 HIV proteins, i.e., gp120, gp41, Tat, and Nef, were shown to interact with specific surface receptors expressed by human basophils and mast cells and can modulate several functional activities of these cells (Fig. 1).

Can Human Basophils and Mast Cells Be Infected by HIV?

The finding that several HIV proteins can interact with different surface receptors on human basophils and mast cells [24, 39, 40, 47, 52, 58] prompted the intriguing hypothesis that these cells may be a reservoir of HIV infection. The group of Krilis reported that a population of mast cells/basophils in the peripheral blood of allergic patients can be infected in vitro by M-tropic strains of HIV [59]. Another group showed that human mast cell progenitors (CXCR4⁺, CCR5⁺, and CCR3⁺) can be infected in vitro by M-tropic, but not T-tropic, viruses [60]. Similarly, HIV-infected mast cells/basophils were found in the peripheral blood of AIDS patients [61]. Sundstrom et al. [62] reported that progenitor mast cells developed in vitro from CD34⁺ cord blood stem cells can be experimentally infected with CCR5-tropic strains of HIV. In addition, they found that infected mast cells, particularly when triggered through Toll-like receptors, were capable of establishing productive infection in target cells. These results suggest that human mast cells may serve both as a viral reservoir and as a model of latency in HIV infection. Certain strains of HIV can infect also the human mast cell line HMC-1 through the interaction with CXCR4 [63]. In addition, mast cells cultured in vitro from circulating CD34⁺ pluripotent progenitors, but not mature mast cells, are susceptible to HIV infection [64]. Importantly, the authors provided evidence that placental mast cells isolated from HIV-infected women harbor HIV. The same group reported that progenitor mast cells comprise a reservoir of HIV infection. In conclusion, progenitor mast cells derived from CD34⁺ precursors are susceptible in vitro to CCR5(R5)-tropic viruses, but only marginally to CXCR4(X4)-tropic HIV [65]. In conclusion, it is conceivable that human mast cell and/or basophil progenitors present in peripheral blood could be infected by certain strains of HIV, although it remains to be confirmed whether these findings are also true in vivo, as for example the active virus replication in tissue mast cells has not been confirmed [66].

Can Human Basophils and Mast Cells Capture HIV and Mediate Viral Infection of Other Immune Cells?

In order to gain a foothold in an uninfected host, cell-free or cell-associated HIV must infect target cells at, or proximal to, the portal of entry into the body and subsequently disseminate throughout the body [67]. HIV infection of target cells can occur via 2 different mechanisms: HIV can infect target cells (i.e., dendritic cells) and replicate, producing virions which in turn infect new target cells (i.e., CD4⁺ T cells) (*cis*-transmission). An alternative and probably more efficient mechanism is *trans*-transmission through the virological synapse [68, 69]. In this process, uninfected cells capture HIV and transmit virus to target cells via the virological synapse or via HIV-bearing exosomes [6]. In the latter mechanism, there is no viral replication in the original cells and the process is associated with polarization of specific receptors (i.e., $\alpha 4\beta 7$, CXCR4, CCR5, and CD4) on target cells [6, 7]. Cell-associated HIV infection (i.e., *trans*-transmission) has been shown to play a pivotal role in HIV spread [70–72].

Jiang et al. [73] elegantly demonstrated that basophils purified from healthy donors capture HIV and mediate viral *trans*-infection of CD4⁺ T cells. First, they confirmed that human basophils express CXCR4 and CCR5. Then, they found that human basophils efficiently capture HIV particles on the cell surface. Interestingly, basophils, but not neutrophils, perform viral capture efficiently. They also confirmed [39, 40] that gp120 binds to basophils. Importantly, they found that purified basophils pulsed with HIV and then cocultured with CD4⁺ T cells were able to transfer HIV to the cocultured cells, leading to robust infection. No viral replication was observed in basophils, suggesting that surface-bound HIV particles play the greatest role in viral transfer. Using confocal microscopy, they found that contact between basophils and CD4⁺ T cells is required for viral transfer. More recently, the same group extended the previous observations showing that also human intestinal mast cells can capture HIV and mediate viral *trans*-infection of CD4⁺ T cells [74]. Collectively, these fascinating results suggest that direct contact between basophils/mast cells and CD4⁺ T cells and the formation of infection synapses facilitate *trans*-infection of HIV particles. In conclusion, these studies suggest that circulating naïve basophils from early-infected donors can capture HIV particles and mediate viral *trans*-infection of encountered CD4⁺ T cells. Thus, basophils can provide a cellular basis for capturing and then spreading viruses throughout the body. The mechanism by which

HIV is captured by human basophils/mast cells may involve the superantigenic interaction between IgE V_H3⁺ and virus-bound gp120 [39, 40]. In addition, gp120 glycoproteins from different HIV subtypes bind to integrin $\alpha 4\beta 7$ [46], which is highly expressed by human basophils [73] and CD4⁺ T cells [46] (Fig. 1).

Jiang et al. [73] also found that the basophil count remains fairly stable during HIV progression. This observation suggests that basophils might provide a stable cellular source for viral capture and efficient cell-to-cell transfer of virions during HIV infection. Collectively, these interesting results offer novel insights into the role of human basophils/mast cells in HIV dissemination.

Differential Role of Human Basophils and Mast Cells in HIV Infection?

The erroneous view that basophils are a minor and redundant variant of tissue mast cells was held for several decades [12, 13, 15]. Despite some similarities (i.e., the expression of Fc ϵ RI and the release of several chemical mediators), human basophils and mast cells display striking differences in their development, life cycle, and fundamental immunological characteristics (Table 1). For example, human basophils produce large quantities of a restricted profile of Th2-like cytokines (IL-4/IL-13 and IL-3) in response to different stimuli [58, 75–78], while human mast cells produce a much wider range of cytokines/chemokines and proinflammatory mediators. In addition, human basophils synthesize only the proangiogenic VEGF-A [79], while mast cells produce both angiogenic and lymphangiogenic molecules [80, 81]. The differences between basophils and mast cells have been recently confirmed by evidence that human mast cells possess a unique expression profile, sharing only few transcripts with basophils [82]. Therefore, it is likely that basophils and mast cells play distinct roles in different physiopathological conditions [10, 12, 13].

Although the physiological role of mast cells and basophils remains enigmatic, there is now increasing evidence that these cells are critically involved not only in allergic disorders but also in autoimmune and infectious diseases, immunodeficiencies, and cancer [13–15, 17, 83], with multifaceted roles due to their ability to mediate both pro- and anti-inflammatory/immunomodulatory responses [21, 23, 84].

Regarding their role in HIV infection, human mast cells can be infected *in vitro* and probably *in vivo* by certain HIV strains [59–65]. By contrast, there is no evidence

that human basophils can be infected by HIV [73]. However, recent evidence suggests that human basophils and mast cells can capture HIV and can mediate viral *trans*-infection of CD4⁺ T cells [73, 74]. A strategy designed to prevent basophil/mast cell-mediated viral capture and transfer may represent a novel direction for the development of anti-HIV treatment.

Taken together, these observations suggest complex, but probably distinct, roles for basophils and mast cells in HIV infection, which deserve further investigations.

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References

- 1 Saez-Cirion A, Jacquelin B, Barre-Sinoussi F, Muller-Trutwin M: Immune responses during spontaneous control of HIV and AIDS: what is the hope for a cure? *Philos Trans R Soc Lond B Biol Sci* 2014;369:20130436.
- 2 Piot P, Abdool Karim SS, Hecht R, Legido-Quigley H, Buse K, Stover J, Resch S, Ryckman T, Mogedal S, Dybul M, Goosby E, Watts C, Kilonzo N, McManus J, Sidibe M: Defeating AIDS – advancing global health. *Lancet* 2015;386:171–218.
- 3 Haase AT: Targeting early infection to prevent HIV-1 mucosal transmission. *Nature* 2010;464:217–223.
- 4 Frost SD, Trkola A, Gunthard HF, Richman DD: Antibody responses in primary HIV-1 infection. *Curr Opin HIV AIDS* 2008;3:45–51.
- 5 Gallerano D, Cabauatan CR, Sibanda EN, Valenta R: HIV-specific antibody responses in HIV-infected patients: from a monoclonal to a polyclonal view. *Int Arch Allergy Immunol* 2015;167:223–241.
- 6 Dale BM, McNerney GP, Thompson DL, Hubner W, de Los Reyes K, Chuang FY, Huser T, Chen BK: Cell-to-cell transfer of HIV-1 via virological synapses leads to endosomal virion maturation that activates viral membrane fusion. *Cell Host Microbe* 2011;10:551–562.
- 7 Shimauchi T, Piguet V: DC-T cell virological synapses and the skin: novel perspectives in dermatology. *Exp Dermatol* 2015;24:1–4.
- 8 Gallo SA, Finnegan CM, Viard M, Raviv Y, Dimitrov A, Rawat SS, Puri A, Durell S, Blumenthal R: The HIV Env-mediated fusion reaction. *Biochim Biophys Acta* 2003;1614:36–50.
- 9 Hoffmann HJ: News in cellular allergology: a review of the human mast cell and basophil granulocyte literature from January 2013 to May 2015. *Int Arch Allergy Immunol* 2015;168:253–262.
- 10 Marone G, Varricchi G, Loffredo S, Granata F: Mast cells and basophils in inflammatory and tumor angiogenesis and lymphangiogenesis. *Eur J Pharmacol* 2016;778:146–151.
- 11 Galli SJ: The mast cell-IgE paradox: from homeostasis to anaphylaxis. *Am J Pathol* 2016;186:212–224.
- 12 Karasuyama H, Mukai K, Obata K, Tsujimura Y, Wada T: Nonredundant roles of basophils in immunity. *Annu Rev Immunol* 2011;29:45–69.
- 13 Marone G, Borriello F, Varricchi G, Genovese A, Granata F: Basophils: historical reflections and perspectives; in Bergmann K-C, Ring J (eds): *History of Allergy*. Basel, Karger, 2014, p 172.
- 14 Schroeder JT: Basophils: emerging roles in the pathogenesis of allergic disease. *Immunol Rev* 2011;242:144–160.
- 15 Borriello F, Granata F, Marone G: Basophils and skin disorders. *J Invest Dermatol* 2014;134:1202–1210.
- 16 de Paulis A, Prevete N, Fiorentino I, Walls AF, Curto M, Petraroli A, Castaldo V, Ceppa P, Fiocca R, Marone G: Basophils infiltrate human gastric mucosa at sites of *Helicobacter pylori* infection, and exhibit chemotaxis in response to *H. pylori*-derived peptide Hp(2–20). *J Immunol* 2004;172:7734–7743.
- 17 De Monte L, Wormann S, Brunetto E, Heltai S, Magliacane G, Reni M, Paganoni AM, Recalde H, Mondino A, Falconi M, Aleotti F, Balzano G, Algul H, Doglioni C, Protti MP: Basophil recruitment into tumor-draining lymph nodes correlates with Th2 inflammation and reduced survival in pancreatic cancer patients. *Cancer Res* 2016;76:1792–1803.
- 18 Charles N, Hardwick D, Daugas E, Illei GG, Rivera J: Basophils and the T helper 2 environment can promote the development of lupus nephritis. *Nat Med* 2010;16:701–707.
- 19 Galli SJ, Tsai M: Mast cells in allergy and infection: versatile effector and regulatory cells in innate and adaptive immunity. *Eur J Immunol* 2010;40:1843–1851.
- 20 Abraham SN, St John AL: Mast cell-orchestrated immunity to pathogens. *Nat Rev Immunol* 2010;10:440–452.
- 21 Rivellesse F, Suurmond J, Habets K, Dorjee AL, Ramamoorthi N, Townsend MJ, de Paulis A, Marone G, Huizinga TW, Pitzalis C, Toes RE: Ability of interleukin-33- and immune complex-triggered activation of human mast cells to down-regulate monocyte-mediated immune responses. *Arthritis Rheumatol* 2015;67:2343–2353.
- 22 Yu X, Kasprick A, Petersen F: Revisiting the role of mast cells in autoimmunity. *Autoimmun Rev* 2015;14:751–759.
- 23 Rivellesse F, Suurmond J, de Paulis A, Marone G, Huizinga TW, Toes RE: IgE and IL-33-mediated triggering of human basophils inhibits TLR4-induced monocyte activation. *Eur J Immunol* 2014;44:3045–3055.
- 24 Marone G, Florio G, Triggiani M, Petraroli A, de Paulis A: Mechanisms of IgE elevation in HIV-1 infection. *Crit Rev Immunol* 2000;20:477–496.
- 25 Marone G, Florio G, Petraroli A, de Paulis A: Dysregulation of the IgE/Fc epsilon RI network in HIV-1 infection. *J Allergy Clin Immunol* 2001;107:22–30.
- 26 Marone G, Florio G, Petraroli A, Triggiani M, de Paulis A: Role of human Fc epsilon RI+ cells in HIV-1 infection. *Immunol Rev* 2001;179:128–138.
- 27 Fauci AS: The AIDS epidemic – considerations for the 21st century. *N Engl J Med* 1999;341:1046–1050.
- 28 Freed EO, Martin MA: The role of human immunodeficiency virus type 1 envelope glycoproteins in virus infection. *J Biol Chem* 1995;270:23883–23886.
- 29 Feng Y, Broder CC, Kennedy PE, Berger EA: HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. *Science* 1996;272:872–877.
- 30 Moore JP: Coreceptors: implications for HIV pathogenesis and therapy. *Science* 1997;276:51–52.
- 31 Romagnani P, De Paulis A, Beltrame C, Annunziato F, Dente V, Maggi E, Romagnani S, Marone G: Tryptase-chymase double-positive human mast cells express the eotaxin receptor CCR3 and are attracted by CCR3-binding chemokines. *Am J Pathol* 1999;155:1195–1204.

- 32 Ochi H, Hirani WM, Yuan Q, Friend DS, Austen KF, Boyce JA: T helper cell type 2 cytokine-mediated comitogenic responses and CCR3 expression during differentiation of human mast cells in vitro. *J Exp Med* 1999; 190:267–280.
- 33 Choe H, Farzan M, Sun Y, Sullivan N, Rollins B, Ponath PD, Wu L, Mackay CR, LaRosa G, Newman W, Gerard N, Gerard C, Sodroski J: The beta-chemokine receptors CCR3 and CCR5 facilitate infection by primary HIV-1 isolates. *Cell* 1996;85:1135–1148.
- 34 He J, Chen Y, Farzan M, Choe H, Ohagen A, Gartner S, Busciglio J, Yang X, Hofmann W, Newman W, Mackay CR, Sodroski J, Gabuzda D: CCR3 and CCR5 are co-receptors for HIV-1 infection of microglia. *Nature* 1997; 385:645–649.
- 35 Kwong PD, Wyatt R, Robinson J, Sweet RW, Sodroski J, Hendrickson WA: Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody. *Nature* 1998;393:648–659.
- 36 Acharya P, Lusvardi S, Bewley CA, Kwong PD: HIV-1 gp120 as a therapeutic target: navigating a moving labyrinth. *Expert Opin Ther Targets* 2015;19:765–783.
- 37 Karray S, Juompan L, Maroun RC, Isenberg D, Silverman GJ, Zouali M: Structural basis of the gp120 superantigen-binding site on human immunoglobulins. *J Immunol* 1998;161: 6681–6688.
- 38 Schnittman SM, Lane HC, Higgins SE, Folks T, Fauci AS: Direct polyclonal activation of human B lymphocytes by the acquired immune deficiency syndrome virus. *Science* 1986;233:1084–1086.
- 39 Patella V, Florio G, Petraroli A, Marone G: HIV-1 gp120 induces IL-4 and IL-13 release from human Fc epsilon RI+ cells through interaction with the VH3 region of IgE. *J Immunol* 2000;164:589–595.
- 40 Florio G, Petraroli A, Patella V, Triggiani M, Marone G: The immunoglobulin superantigen-binding site of HIV-1 gp120 activates human basophils. *AIDS* 2000;14:931–938.
- 41 Fauci AS: Host factors and the pathogenesis of HIV-induced disease. *Nature* 1996;384: 529–534.
- 42 Clerici M, Hakim FT, Venzon DJ, Blatt S, Hendrix CW, Wynn TA, Shearer GM: Changes in interleukin-2 and interleukin-4 production in asymptomatic, human immunodeficiency virus-seropositive individuals. *J Clin Invest* 1993;91:759–765.
- 43 Agarwal SK, Marshall GD Jr: In vivo alteration in type-1 and type-2 cytokine balance: a possible mechanism for elevated total IgE in HIV-infected patients. *Hum Immunol* 1998; 59:99–105.
- 44 Vigano A, Principi N, Crupi L, Onorato J, Vincenzo ZG, Salvaggio A: Elevation of IgE in HIV-infected children and its correlation with the progression of disease. *J Allergy Clin Immunol* 1995;95:627–632.
- 45 Penn ML, Grivel JC, Schramm B, Goldsmith MA, Margolis L: CXCR4 utilization is sufficient to trigger CD4+ T cell depletion in HIV-1-infected human lymphoid tissue. *Proc Natl Acad Sci USA* 1999;96:663–668.
- 46 Arthos J, Cicala C, Martinelli E, Macleod K, Van Ryk D, Wei D, Xiao Z, Veenstra TD, Conrad TP, Lempicki RA, McLaughlin S, Pascuccio M, Gopaul R, McNally J, Cruz CC, Censoplano N, Chung E, Reitano KN, Kottilil S, Goode DJ, Fauci AS: HIV-1 envelope protein binds to and signals through integrin alpha4beta7, the gut mucosal homing receptor for peripheral T cells. *Nat Immunol* 2008; 9:301–309.
- 47 de Paulis A, Florio G, Prevete N, Triggiani M, Fiorentino I, Genovese A, Marone G: HIV-1 envelope gp41 peptides promote migration of human Fc epsilon RI+ cells and inhibit IL-13 synthesis through interaction with formyl peptide receptors. *J Immunol* 2002;169:4559–4567.
- 48 Ensoli B, Barillari G, Salahuddin SZ, Gallo RC, Wong-Staal F: Tat protein of HIV-1 stimulates growth of cells derived from Kaposi's sarcoma lesions of AIDS patients. *Nature* 1990;345:84–86.
- 49 Westendorp MO, Frank R, Ochsenbauer C, Stricker M, Dhein J, Walczak H, Debatin KM, Krammer PH: Sensitization of T cells to CD95-mediated apoptosis by HIV-1 Tat and gp120. *Nature* 1995;375:497–500.
- 50 Helland DE, Welles JL, Caputo A, Haseltine WA: Transcellular transactivation by the human immunodeficiency virus type 1 tat protein. *J Virol* 1991;65:4547–4549.
- 51 Frankel AD, Pabo CO: Cellular uptake of the tat protein from human immunodeficiency virus. *Cell* 1988;55:1189–1193.
- 52 de Paulis A, De Palma R, Di Gioia L, Carfora M, Prevete N, Tosi G, Accolla RS, Marone G: Tat protein is an HIV-1-encoded beta-chemokine homolog that promotes migration and up-regulates CCR3 expression on human Fc epsilon RI+ cells. *J Immunol* 2000;165: 7171–7179.
- 53 Carl S, Greenough TC, Krumbiegel M, Greenberg M, Skowronski J, Sullivan JL, Kirchhoff F: Modulation of different human immunodeficiency virus type 1 Nef functions during progression to AIDS. *J Virol* 2001;75:3657–3665.
- 54 Henao-Mejia J, Liu Y, Park IW, Zhang J, Sanford J, He JJ: Suppression of HIV-1 Nef translation by Sam68 mutant-induced stress granules and nef mRNA sequestration. *Mol Cell* 2009;33:87–96.
- 55 Landi A, Iannucci V, Nuffel AV, Meuwissen P, Verhasselt B: One protein to rule them all: modulation of cell surface receptors and molecules by HIV Nef. *Curr HIV Res* 2011;9:496–504.
- 56 Fujii Y, Otake K, Tashiro M, Adachi A: Soluble Nef antigen of HIV-1 is cytotoxic for human CD4+ T cells. *FEBS Lett* 1996;393:93–96.
- 57 Rossi FW, Prevete N, Rivellesse F, Lobasso A, Napolitano F, Granata F, Selleri C, de Paulis A: HIV-1 Nef promotes migration and chemokine synthesis of human basophils and mast cells through the interaction with CXCR4. *Clin Mol Allergy*, in press.
- 58 Genovese A, Borgia G, Björck L, Petraroli A, de Paulis A, Piazza M, Marone G: Immunoglobulin superantigen protein L induces IL-4 and IL-13 secretion from human Fc epsilon RI+ cells through interaction with the kappa light chains of IgE. *J Immunol* 2003;170: 1854–1861.
- 59 Li Y, Li L, Waldey R, Reddel S, Qi J, Archis C, Collins A, Clark E, Cooley M, Kouts S, Hassan N, Mohammed A, Cunningham A, Wong G, Stevens R, Krilis S: Identification of a novel population of mast cells/basophils in human peripheral blood of allergic patients which is HIV-1 susceptible due to its surface expression of CD4, CCR5, and CXCR4. *J Allergy Clin Immunol* 2000;105:S86–S87.
- 60 Bannert N, Farzan M, Friend DS, Ochi H, Price KS, Sodroski J, Boyce JA: Human Mast cell progenitors can be infected by macrophage-tropic human immunodeficiency virus type 1 and retain virus with maturation in vitro. *J Virol* 2001;75:10808–10814.
- 61 Qi JC, Stevens RL, Wadley R, Collins A, Cooley M, Naif HM, Nasr N, Cunningham A, Katsoulotos G, Wanigasek Y, Roufogalis B, Krilis SA: IL-16 regulation of human mast cells/basophils and their susceptibility to HIV-1. *J Immunol* 2002;168:4127–4134.
- 62 Sundstrom JB, Little DM, Villinger F, Ellis JE, Ansari AA: Signaling through Toll-like receptors triggers HIV-1 replication in latently infected mast cells. *J Immunol* 2004;172:4391–4401.
- 63 Taub DD, Mikovits JA, Nilsson G, Schaffer EM, Key ML, Petrow-Sadowski C, Ruscetti FW: Alterations in mast cell function and survival following in vitro infection with human immunodeficiency viruses-1 through CXCR4. *Cell Immunol* 2004;230:65–80.
- 64 Sundstrom JB, Ellis JE, Hair GA, Kirshenbaum AS, Metcalfe DD, Yi H, Cardona AC, Lindsay MK, Ansari AA: Human tissue mast cells are an inducible reservoir of persistent HIV infection. *Blood* 2007;109:5293–5300.
- 65 Sundstrom JB, Hair GA, Ansari AA, Secor WE, Gilfillan AM, Metcalfe DD, Kirshenbaum AS: IgE-Fc epsilon RI interactions determine HIV coreceptor usage and susceptibility to infection during ontogeny of mast cells. *J Immunol* 2009;182:6401–6409.
- 66 Nelson AM, Auerbach A, Man YG: Failure to detect active virus replication in mast cells at various tissue sites of HIV patients by immunohistochemistry. *Int J Biol Sci* 2009;5:603–610.
- 67 Piguet V, Sattentau Q: Dangerous liaisons at the virological synapse. *J Clin Invest* 2004; 114:605–610.

- 68 Haller C, Fackler OT: HIV-1 at the immunological and T-lymphocytic virological synapse. *Biol Chem* 2008;389:1253–1260.
- 69 Barrero-Villar M, Cabrero JR, Gordon-Alonso M, Barroso-Gonzalez J, Alvarez-Losada S, Munoz-Fernandez MA, Sanchez-Madrid F, Valenzuela-Fernandez A: Moesin is required for HIV-1-induced CD4-CXCR4 interaction, F-actin redistribution, membrane fusion and viral infection in lymphocytes. *J Cell Sci* 2009; 122:103–113.
- 70 Wu L, KewalRamani VN: Dendritic-cell interactions with HIV: infection and viral dissemination. *Nat Rev Immunol* 2006;6:859–868.
- 71 Wang JH, Janas AM, Olson WJ, Wu L: Functionally distinct transmission of human immunodeficiency virus type 1 mediated by immature and mature dendritic cells. *J Virol* 2007;81:8933–8943.
- 72 Ahmed Z, Kawamura T, Shimada S, Piguet V: The role of human dendritic cells in HIV-1 infection. *J Invest Dermatol* 2015;135:1225–1233.
- 73 Jiang AP, Jiang JF, Guo MG, Jin YM, Li YY, Wang JH: Human blood-circulating basophils capture HIV-1 and mediate viral *trans*-infection of CD4+ T Cells. *J Virol* 2015;89: 8050–8062.
- 74 Jiang AP, Jiang JF, Wei JF, Guo MG, Qin Y, Guo QQ, Ma L, Liu BC, Wang X, Veazey RS, Ding YB, Wang JH: Human mucosal mast cells capture HIV-1 and mediate viral *trans*-infection of CD4+ T cells. *J Virol* 2015;90: 2928–2937.
- 75 Seder RA, Paul WE, Dvorak AM, Sharkis SJ, Kagey-Sobotka A, Niv Y, Finkelman FD, Barbieri SA, Galli SJ, Plaut M: Mouse splenic and bone marrow cell populations that express high-affinity Fc epsilon receptors and produce interleukin 4 are highly enriched in basophils. *Proc Natl Acad Sci USA* 1991;88: 2835–2839.
- 76 Voehringer D, Shinkai K, Locksley RM: Type 2 immunity reflects orchestrated recruitment of cells committed to IL-4 production. *Immunity* 2004;20:267–277.
- 77 Schroeder JT, MacGlashan DW Jr, Kagey-Sobotka A, White JM, Lichtenstein LM: IgE-dependent IL-4 secretion by human basophils: the relationship between cytokine production and histamine release in mixed leukocyte cultures. *J Immunol* 1994;153:1808–1817.
- 78 Schroeder JT, Chichester KL, Bieneman AP: Human basophils secrete IL-3: evidence of autocrine priming for phenotypic and functional responses in allergic disease. *J Immunol* 2009;182:2432–2438.
- 79 de Paulis A, Prevete N, Fiorentino I, Rossi FW, Staibano S, Montuori N, Ragno P, Longobardi A, Liccardo B, Genovese A, Ribatti D, Walls AF, Marone G: Expression and functions of the vascular endothelial growth factors and their receptors in human basophils. *J Immunol* 2006;177:7322–7331.
- 80 Detoraki A, Staiano RI, Granata F, Giannatasio G, Prevete N, de Paulis A, Ribatti D, Genovese A, Triggiani M, Marone G: Vascular endothelial growth factors synthesized by human lung mast cells exert angiogenic effects. *J Allergy Clin Immunol* 2009;123:1142–1149, 1149 e1141–e1145.
- 81 Detoraki A, Granata F, Staibano S, Rossi FW, Marone G, Genovese A: Angiogenesis and lymphangiogenesis in bronchial asthma. *Allergy* 2010;65:946–958.
- 82 Dwyer DF, Barrett NA, Austen KF: Expression profiling of constitutive mast cells reveals a unique identity within the immune system. *Nat Immunol* 2016;17:878–887.
- 83 Varricchi G, Galdiero MR, Marone G, Granata F, Borriello F: Controversial role of mast cells in skin cancers. *Exp Dermatol* 2016, DOI: 10.1111/exd.13107.
- 84 Suurmond J, Rivellese F, Dorjee AL, Bakker AM, Rombouts YJ, Rispens T, Wolbink G, Zaldumbide A, Hoeben RC, Huizinga TW, Toes RE: Toll-like receptor triggering augments activation of human mast cells by anti-citrullinated protein antibodies. *Ann Rheum Dis* 2015;74:1915–1923.