

Are Mast Cells MASTers in HIV-1 Infection?

Gianni Marone Amato de Paulis Giovanni Florio Angelica Petraroli
Francesca W. Rossi Massimo Triggiani

Division of Clinical Immunology and Allergy, University of Naples Federico II, Naples, Italy

Key Words

AIDS · Basophils · CCR3 · Chemokine · HIV-1 · IL-4 · IL-13 ·
Mast cells · Tat

Abstract

HIV-1 gp120 interacts with IgE V_H3⁺ on the surface of human basophils and mast cells (FcεRI⁺ cells), acting as a viral immunoglobulin superantigen. gp120 from different clades induces mediator release from FcεRI⁺ cells. gp120 also induces IL-4 and IL-13 synthesis in human basophils. The chemokine receptors CCR3 and CXCR4, which are coreceptors of HIV-1 infection, are expressed by human FcεRI⁺ cells. HIV-1 Tat protein is a potent chemoattractant for basophils and lung mast cells, interacting with CCR3. Incubation of basophils with Tat protein upregulates the surface expression of the CCR3 receptor. There is evidence that human FcεRI⁺ cells could be infected in vitro by M-tropic HIV-1 strains.

Copyright © 2001 S. Karger AG, Basel

Introduction

Since their discovery, mast cells have intrigued immunologists, biochemists and pharmacologists because of their complexity and fascinating pleiotropic properties

[1]. Mast cells may be found anywhere, but they are most numerous beneath epithelial and mucosal surfaces. Human mast cells play a central role in the pathogenesis not only of allergic disorders [2], but also of a variety of immunological disorders, through the elaboration of proinflammatory and fibrogenic mediators and various cytokines [3–6]. Recently, the possibility of mast cells and their mediators being involved in the host defense against bacterial infections has been raised [7–10].

In rodents at least, mast cells are involved in the defense against bacterial infections. This role is largely – though not solely – mediated by cytokines produced by mast cells activated by bacterial products, e.g. toxins, lipopolysaccharides or cell wall proteins. Mast cell-derived cytokines such as GM-CSF, TNF-α and IL-8 are capable of modulating the activity of phagocytes. These interactions have been confirmed in animal models of bacterial infection, but little is known about the involvement of FcεRI⁺ cells (basophils and mast cells) in viral infections in man.

The last two decades saw two apparently unrelated events: the appearance of the acquired immunodeficiency syndrome (AIDS) due to the human immunodeficiency viruses HIV-1 and HIV-2 [11] and a pandemic of allergic disorders, the latter affecting up to 15% of the population of industrialized countries [2, 12]. While there is no apparent relation between these two disorders, a number

KARGER

Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2001 S. Karger AG, Basel
1018–2438/01/1252–0089\$17.50/0

Accessible online at:
www.karger.com/journals/iaa

Correspondence to: Prof. Gianni Marone
Division of Clinical Immunology and Allergy
University of Naples Federico II, Via S. Pansini 5
I–80131 Napoli (Italy)
Tel. +39 081 770 7492, Fax +39 081 746 2271, E-Mail marone@unina.it

of features of HIV infection suggest that hypersensitivity arises in these patients. For example, the Th1 and Th2 cytokine profile is deranged in HIV-1 infection because of a shift towards Th2 cytokines [13–21], and serum IgE levels are raised in HIV-1-infected children [22–27] and adults [21, 28–33]. Moreover, HIV-1-infected patients have enhanced symptoms of allergic disorders [34–36] and HIV-1 antigens induce histamine release from basophils [4, 37, 38].

Th1 and Th2 Responses in HIV-1 Infection

The first evidence that there is a shift from a 'Th1-like' toward a 'Th2-like' pattern of cytokine production by peripheral blood lymphocytes during the early stages of HIV-1 infection was provided by Clerici et al. [14] and Clerici and Shearer [15]. Two other groups, however, were unable to confirm an overall shift in the cytokine pattern toward the Th2 subset in either lymph nodes or T cell clones from HIV-1-infected individuals [39, 40]. However, preferential replication of HIV-1 in Th2 and Th0 cells rather than in Th1 clones was demonstrated [40].

Increased Th2 cytokine production has been generally confirmed using different approaches [17–21], and only a few studies have not found a polarized Th2 state during HIV-1 infection [41]. These discrepancies may have a number of explanations, such as different methods, the production of Th2-like cytokines by cells other than lymphocytes (e.g. mast cells and basophils), cell activation by HIV-1 superantigens, and cytokines other than IL-4 (e.g. IL-13) being critical for Th2 cell polarization.

Studies in various geographical regions have reported elevated serum IgE concentrations in HIV-1-infected adults [21, 28–33] and children [22–27]. High IgE levels have been associated with disease progression in both children [22–27] and adults [33–42] and have been suggested as a marker of poor prognosis in these patients.

The elevated IgE levels cannot be explained solely by HIV-1-mediated polyclonal activation. In fact, although polyclonal gammopathy and activated B cells are found in infected individuals [43], no correlation has been found between IgE levels and either IgG or IgA [29, 42, 44].

At least two cytokines (IL-4 and IL-13) play a key role in IgE production in humans [45–47]. IL-4 and IL-13 induce ϵ germline mRNA expression in purified B cells, which accounts for their ability to drive the switching of B cells to the IgE isotype. IL-4 and IL-13 are produced by activated Th2 cells [45–47], human basophils [3, 4, 48–

50] and mast cells [48, 50–54]. An additional signal for IgE synthesis is provided by the interaction of CD40 expressed by B cells with its natural ligand (CD40L) expressed by activated T cells. Activated mast cells and basophils also express CD40L [48, 50], which is overexpressed on mucosal mast cells of allergic individuals [54]. This is consistent with the observation that activated mast cells and basophils, which release IL-4 and IL-13, express CD40L and can induce B cells to synthesize IgE [48, 54].

Activation of IL-4 and IL-13 Release from Fc ϵ RI⁺ Cells by gp120

HIV-1 enters the body mainly through mucosal surfaces, where mast cells are particularly abundant. The envelope glycoprotein gp120 plays a major role in the early events of HIV-1 infection by binding to CD4 on host cells, which causes conformational changes in gp120, i.e. affecting the exposure and/or formation of binding sites for the chemokine receptors (CCR5 or CXCR4) that serve as obligate coreceptors for virus entry [55, 56].

Certain strains of viruses can use CCR3, present on human basophils [57, 58] and mast cells [58, 59], as the coreceptor for HIV-1 infection [60–63]. Interaction with coreceptors induces further conformational changes in the envelope protein and exposure of the fusion domain of the gp41 subunit, which then mediates fusion of the opposed cell and virus membranes [64]. Thus, mast cells and basophils can be exposed to shed or virus-bound gp120 during the early phases of infection.

HIV-1 gp120 is a member of the immunoglobulin superantigen family [65–67] and interacts with immunoglobulin V_H3 gene products. This might explain the superantigenic activation of B lymphocytes in patients with AIDS [43]. We have recently investigated whether gp120 is able to activate human basophils and mast cells. Recombinant gp120 from divergent HIV-1 isolates (gp120_{MN}, gp120_{SF2}, gp120_{LAV}, gp120_{CM}) from different viral clades (B and E) of various geographical origins increased IL-4 and IL-13 mRNA expression, in parallel to the secretion of histamine from basophils and lung mast cells purified from subjects negative for anti-HIV-1 and HIV-2 antibodies [4, 38]. By contrast, IFN- γ mRNA was not detected in any of the gp120-stimulated basophil preparations. This provided evidence that gp120-mediated stimulation of basophils and mast cells induced only cytokines of the Th2 profile. These results also indicate that the capacity to induce Th2-like cytokine release

is a feature of gp120 maintained throughout the evolution of the virus. Figure 1 shows that nanomolar concentrations of gp120 induce IL-4 and IL-13 secretion from basophils from normal donors negative for HIV-1 and HIV-2 antibodies.

gp120 activates human mast cells and basophils through the interaction with specific IgE, since removal of IgE completely blocks the envelope glycoprotein's effect on IL-4 and IL-13 secretion. Preincubation of gp120 with two human monoclonal IgM V_H3⁺ also inhibited its effect on this secretion from basophils. By contrast, preincubation with monoclonal IgM possessing a V_H6 domain had no effect. Thus, binding to the V_H3 domain prevents gp120 interacting with IgE bound to FcεRI on basophils and lung mast cells.

It is therefore possible that during the early phase of HIV-1 infection, when there are high levels of viremia and spreading of the virus [13], basophils and mast cells may be exposed to virus-bound or shed gp120 [68]. This may be an initial, critical source of IL-4 and IL-13, thereby favoring a shift toward a Th2 phenotype. In advanced HIV-1 infection, when CD4⁺ T cells are decreased, FcεRI⁺ cells might also provide a useful pool of Th2-like cytokines.

Our findings might also be important from a quantitative viewpoint. Th2 cells account for 0.2–2% of CD4⁺ cells [69], and basophils account for 1% of peripheral blood leukocytes [1, 70, 71]. In addition, human lymphocytes produce less IL-4 than is generated by immunologically challenged basophils [49, 50]. Therefore, during both early and advanced HIV-1 infection, basophils and mast cells might be a source of cytokines that contribute to the polarization of CD4⁺ cells toward Th2 cells and to the increased IgE levels.

Cytokines released from FcεRI⁺ cells might also indirectly affect HIV-1 entry into CD4⁺ cells. Upregulation of CXCR4 by IL-4 [72] facilitates HIV-1 infection of T cells [73], suggesting an amplification loop of polarized Th2 responses based on the induction of chemokine receptors by gp120-stimulated IL-4 and IL-13 from FcεRI⁺ cells.

The evidence that FcεRI⁺ cells could contribute to the immune dysregulation in HIV-1 infection by acting as a source of Th2 cytokines (IL-4 and IL-13) might reconcile the apparently conflicting results of several investigators [39–41]. In fact, these findings all highlight the importance of a specific viral superantigen, gp120, acting on cell types other than lymphocytes in the production of Th2-like cytokines during HIV-1 infection.

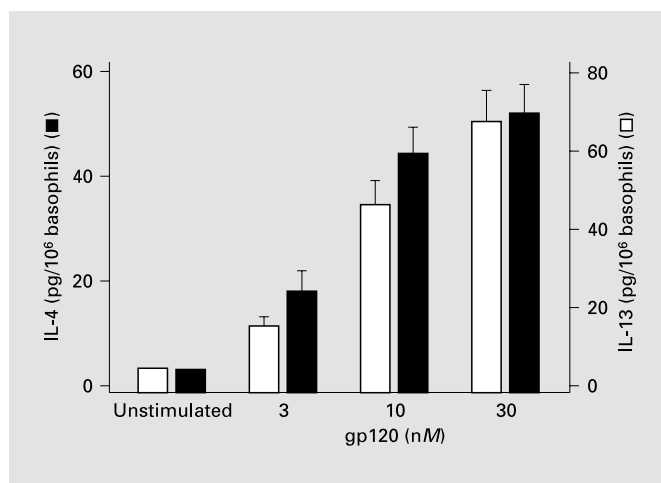


Fig. 1. Effect of increasing concentrations of gp120 on IL-4 and IL-13 release from human basophils from normal donors negative for HIV-1 and HIV-2 antibodies (mean ± SEM from three separate experiments). Error bars are not shown when graphically too small.

Effect of HIV-1 Tat Protein on Human FcεRI⁺ Cells

Another important area of interest is the interaction between HIV-1 Tat protein and human FcεRI⁺ cells. Tat protein is expressed in HIV-1-infected cells and plays a primary role in viral gene expression and replication [74]. The protein is also secreted by HIV-1-infected cells [75–77] and can reactivate latent infection [78]. Extracellular Tat protein can activate uninfected cells in a paracrine fashion, thus reproducing some of the effects of HIV-1 on immune cells.

We recently reported that Tat protein causes concentration-dependent chemotaxis of basophils and mast cells purified from donors negative for antibodies to HIV-1 and HIV-2 [79]. Like many other chemokines, Tat protein caused a rapid, transient increase in the intracellular Ca²⁺ concentration that was abolished by preincubation with anti-Tat monoclonal antibody. Preincubation of human FcεRI⁺ cells with an anti-CCR3 monoclonal antibody also blocked the chemoattractant effect of Tat as well as the chemotactic activity of eotaxin. There is compelling evidence that certain strains of HIV-1 can use CCR3 as a coreceptor [60–63]. Interestingly, preincubation of purified basophils with Tat protein upregulated the surface expression of CCR3 on these cells [79].

These findings demonstrate that HIV-1 Tat protein is functionally active on human FcεRI⁺ cells through its

Table 1. Role of human mast cells and basophils in HIV-1 infection

HIV-1 gp120 induces histamine and leukotriene C ₄ release from human basophils and mast cells of normal donors negative for antibodies to HIV-1 and HIV-2
HIV-1 gp120 induces Th2 cytokines (IL-4 and IL-13) from human basophils from normal donors negative for antibodies to HIV-1 and HIV-2 through interaction with IgE V _H 3 ⁺
HIV-1 Tat protein is chemotactic for human basophils and mast cells
HIV-1 Tat protein upregulates CCR3 receptors on human basophils and mast cells
HIV-1 Tat protein induces IL-4 and IL-13 release from human basophils from normal donors negative for antibodies to HIV-1 and HIV-2
Cord blood mast cells express CXCR4 and CCR5 receptors
CCR3 and CXCR4 receptors are constitutively expressed by isolated human mast cells and basophils
Human mast cell/basophil precursors can be infected in vitro by M-tropic HIV-1 strains

interaction with the CCR3 receptor. In addition, upregulation of CCR3 on human basophils and mast cells by this protein could facilitate infection of FcεRI⁺ cells by certain strains of HIV-1.

Thus, during HIV-1 infection, when there are high levels of Tat protein in serum and in biological fluids [77], Tat protein could possibly influence the directional migration of human FcεRI⁺ cells, contributing to the recruitment of these cells at sites of HIV-1 infection. In addition, the Tat-mediated upregulation of CCR3 in human FcεRI⁺ cells might facilitate these cells' interaction with HIV-1.

Are Human Mast Cells and Basophils Susceptible to HIV-1 Infection?

Two distinct HIV-1 proteins (gp120 and Tat) can interact with different surface molecules on FcεRI⁺ cells. In addition, either directly or indirectly, i.e. through the release of cytokines, both can upregulate chemokine receptors (CCR3 and CXCR4) acting as coreceptors for HIV-1. These cells might therefore be a novel reservoir of HIV-1 infection. Table 1 summarizes several findings that support the role of human FcεRI⁺ cells in HIV-1 infection.

Li et al. [80] have presented evidence that a population of mast cells/basophils in human peripheral blood of allergic patients expresses CD4 and the chemokine receptors CCR3, CCR5 and CXCR4. They also reported that this

population of cells can be infected in vitro by a M-tropic strain of HIV-1. This interesting observation suggests that mast cell/basophil progenitors in peripheral blood could be infected by M-tropic HIV-1 strains.

Although these in vitro results must be extended to see whether this finding applies in vivo, they carry potential implications for HIV-1 pathophysiology. Infected mast cell/basophil precursors can migrate to lymphoid organs and brain tissue, thus serving as a reservoir of HIV-1. Interestingly, lymph nodes from AIDS patients have increased mast cell density [81], and mast cells are one of the few immune cells in the brain [82]. Thus, infected FcεRI⁺ cells might turn out to be a carrier of HIV-1 to lymph nodes and across the blood brain barrier to microglia and astrocytes.

Closing Remarks

We have provided evidence that human FcεRI⁺ cells may be directly or indirectly involved in HIV-1 infection by showing that gp120 from different clades is a potent stimulus of IL-4 and IL-13 release from basophils and mast cells. gp120 functions as a viral superantigen by interacting with the V_H3 region of IgE. Because the V_H3 family is the largest of the human repertoire (approximately 50%), it is likely that shed or virus-bound gp120 interacts frequently with V_H3⁺ IgE bound to basophils of normal or early-infected individuals. HIV-1 Tat protein also induces IL-4 and IL-13 from human basophils. Thus, these two unrelated HIV-1 proteins, gp120 and Tat, can induce the synthesis of Th2 cytokines, thereby favoring a shift toward a Th2 phenotype. IL-4 and IL-13 induced by these proteins from FcεRI⁺ cells might also interact with specific receptors on B cells, in turn inducing ε germline mRNA expression and causing the switch to the IgE isotype. This sequence of events, schematically represented in figure 2, could help explain the elevated IgE levels in HIV-1-infected children and adults [21–33].

Human FcεRI⁺ cells might be involved in HIV-1 infection in other ways as well. HIV-1 Tat protein, secreted by HIV-1-infected cells [75–77], is a potent chemoattractant for human FcεRI⁺ cells and upregulates the expression of CCR3 receptor on their surface [79]. Human mast cells [58, 59] and basophils [57, 58, 79] express CCR3 receptor, which can be used by several strains of HIV-1 [60–63]. It has also been shown that cord blood-derived mast cells [59, 83, 84], mature mast cells and basophils [84] express the CXCR4 receptor, a coreceptor for HIV-1 [55, 56]. Together, these data provide strong

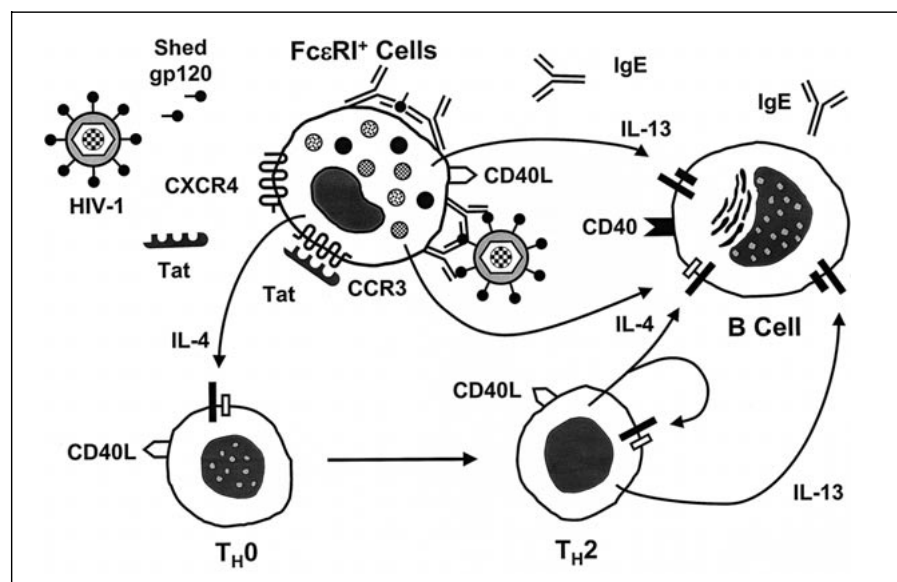


Fig. 2. Schematic representation of the interactions between HIV-1 and human mast cells and basophils (FcεRI⁺ cells). Mast cells are particularly abundant on human mucosal surfaces, a common port of entry of HIV-1 virus. In addition, the early phases of HIV-1 infection are associated with high levels of viremia. Therefore, mast cells and basophils can be exposed to HIV-1 during the early phases of infection. Shed gp120 or virus-bound gp120 interacts frequently with V_H3⁺ IgE bound to FcεRI⁺ cells of early-infected individuals. This interaction induces IL-4 and IL-13 release, thereby favoring a shift toward a Th2 phenotype. IL-4 and IL-13 might also interact with

specific receptors, inducing ε germline mRNA expression in B cells switching to the IgE isotype. HIV-1 Tat protein secreted by infected cells is a potent chemoattractant for human basophils and mast cells, interacting with the chemokine receptor CCR3. Extracellular Tat can also influence IL-4 and IL-13 release from these cells. Mast cells from cord blood express CXCR4 and CCR5, the principal coreceptors for HIV-1. Human basophils and mast cells also express CXCR4. The observation that human FcεRI⁺ cells express CCR3 and CXCR4, coreceptors of several strains of HIV-1, raises the possibility that, under certain conditions, these cells can be infected by HIV-1.

support for the suggestion that human basophils and mast cells play a role in the progression and immune dysregulation of HIV-1 infection.

Unraveling the complex interactions in HIV-1 infection in which mast cells and basophils play prominent roles should help clarify whether they are simply effectors or rather master cells, at the same time or at different times in the disease process.

Acknowledgements

We dedicate this paper to Rita Levi-Montalcini, who first suggested an involvement of FcεRI⁺ cells in HIV-1 infection. The Istituto Superiore Sanità (AIDS project 40B.64 and 40A.67), CNR (Target project Biotechnology No. 99.00216.PF31 and No. 99.00401. PF49) and MURST are acknowledged for supporting our work.

References

- 1 Marone G, Lichtenstein LM, Galli SJ (eds): Mast Cells and Basophils. San Diego, Academic Press, 2000.
- 2 Marone G: Asthma: Recent advances. *Immunol Today* 1998;19:5–9.
- 3 Patella V, Giuliano A, Bouvet J-P, Marone G: Endogenous superallergen protein Fv induces IL-4 secretion from human FcεRI⁺ cells through interaction with the V_H3 region of IgE. *J Immunol* 1998;161:5647–5655.
- 4 Patella V, Florio G, Petraroli A, Marone G: HIV-1 gp120 induces IL-4 and IL-13 release from human FcεRI⁺ cells through interaction with the V_H3 region of IgE. *J Immunol* 2000; 164:589–595.
- 5 de Paulis A, Marinò I, Ciccarelli A, de Crescenzo G, Concardi M, Verga L, Arbustini E, Marone G: Human synovial mast cells. I. Ultrastructure in situ and in vitro immunologic characterization. *Arthritis Rheum* 1996;39: 1222–1233.
- 6 de Paulis A, Minopoli G, Arbustini E, de Crescenzo G, Dal Piaz F, Pucci P, Russo T, Marone G: Stem cell factor is localized in, released from, and cleaved by human mast cells. *J Immunol* 1999;163:2799–2808.
- 7 Lantz CS, Boesiger J, Song CH, Mach N, Kobayashi T, Mulligan RC, Nawa Y, Dranoff G, Galli SJ: Role for IL-3 in mast cell and basophil development and in immunity to parasites. *Nature* 1998;392:90–93.

- 8 Malaviya R, Ikeda T, Ross E, Abraham SN: Mast cell modulation of neutrophil influx and bacterial clearance at sites of infection through TNF- α . *Nature* 1996;381:77–80.
- 9 Genovese A, Bouvet JP, Florio G, Lamparter-Schummert B, Björck L, Marone G: Bacterial immunoglobulin superantigen proteins A and L activate human heart mast cells by interacting with immunoglobulin E. *Infect Immun* 2000;68:5517–5524.
- 10 Patella V, Bouvet JP, Marone G: Protein Fv produced during viral hepatitis is a novel activator of human basophils and mast cells. *J Immunol* 1993;151:5685–5698.
- 11 Fauci AS: The AIDS epidemic – considerations for the 21st century. *N Engl J Med* 1999;341:1046–1050.
- 12 Marone G, Austen KF, Holgate ST, Kay AB, Lichtenstein LM (eds): *Asthma and Allergic Diseases. Physiology, Immunopharmacology, and Treatment*. London, Academic Press, 1998.
- 13 Fauci AS: Host factors and the pathogenesis of HIV-induced disease. *Nature* 1996;384:529–534.
- 14 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.
- 15 Clerici M, Shearer GM: A TH1→TH2 switch is a critical step in the etiology of HIV infection. *Immunol Today* 1993;14:107–111.
- 16 Barcellini W, Rizzardi GP, Borghi MO, Fain C, Lazzarin A, Meroni PL: TH1 and TH2 cytokine production by peripheral blood mononuclear cells from HIV-infected patients. *AIDS* 1994;8:757–762.
- 17 Meyaard L, Otto SA, Keet IPM, van Lier RAW, Miedema F: Changes in cytokine secretion patterns of CD4⁺ T-cell clones in human immunodeficiency virus infection. *Blood* 1994;84:4262–4268.
- 18 Meroni L, Trabattoni D, Balotta C, Riva C, Gori A, Moroni M, Villa ML, Clerici M, Galli M: Evidence for type 2 cytokine production and lymphocyte activation in the early phases of HIV-1 infection. *AIDS* 1996;10:23–30.
- 19 Klein SA, Dobmeyer JM, Dobmeyer TS, Pape M, Ottmann OG, Helm EB, Hoelzer D, Rossol R: Demonstration of the Th1 to Th2 cytokine shift during the course of HIV-1 infection using cytoplasmic cytokine detection on single cell level by flow cytometry. *AIDS* 1997;11:1111–1118.
- 20 Zou W, Dulioust A, Fior R, Durand-Gasselin I, Boue F, Galanaud P, Emilie D: Increased T-helper-type 2 cytokine production in chronic HIV infection is due to interleukin (IL)-13 rather than IL-4. *AIDS* 1997;11:533–535.
- 21 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.
- 22 Viganò A, Principi N, Crupi L, Onorato J, Zucotti GV, 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.
- 23 Viganò A, Principi N, Villa ML, Riva C, Crupi L, Trabattoni D, Shearer GM, Clerici M: Immunologic characterization of children vertically infected with human immunodeficiency virus, with slow or rapid disease progression. *J Pediatr* 1995;126:368–374.
- 24 Koutsonikolis A, Nelson RP Jr, Fernandez-Caldas E, Brigino EN, Seleznick M, Good RA, Lockey RF: Serum total and specific IgE levels in children infected with human immunodeficiency virus. *J Allergy Clin Immunol* 1996;97:692–697.
- 25 Secord EA, Kleiner GI, Auci DL, Smith-Norowitz T, Chice S, Finkielstein A, Nowakowski M, Fikrig S, Durkin HG: IgE against HIV proteins in clinically healthy children with HIV disease. *J Allergy Clin Immunol* 1996;98:979–984.
- 26 Bacot BK, Paul ME, Navarro M, Abramson SL, Kline MW, Hanson IC, Rosenblatt HM, Shearer WT: Objective measures of allergic disease in children with human immunodeficiency virus infection. *J Allergy Clin Immunol* 1997;100:707–711.
- 27 Onorato J, Esposito S, Scovena E, Morandi B, Morelli M, Pizzi M, Zisa G, Marchisio P, Principi N: Eosinophil involvement and serum IgE level in HIV-1-infected children. *J Allergy Clin Immunol* 1999;104:245–247.
- 28 Lucey DR, Zajac RA, Melcher GP, Butzin CA, Boswell RN: Serum IgE levels in 622 persons with human immunodeficiency virus infection: IgE elevation with marked depletion of CD4⁺ T-cells. *AIDS Res Hum Retroviruses* 1990;6:427–429.
- 29 Wright DN, Nelson RP Jr, Ledford DK, Fernandez-Caldas E, Trudeau WL, Lockey RF: Serum IgE and human immunodeficiency virus (HIV) infection. *J Allergy Clin Immunol* 1990;85:445–452.
- 30 Miguez-Burbano MJ, Shor-Posner G, Fletcher MA, Lu Y, Moreno JN, Carcamo C, Page B, Quesada J, Sauberlich H, Baum MK: Immunoglobulin E levels in relationship to HIV-1 disease, route of infection, and vitamin E status. *Allergy* 1995;50:157–161.
- 31 Shor-Posner G, Miguez-Burbano MJ, Lu Y, Feaster D, Fletcher MA, Sauberlich H, Baum MK: Elevated IgE level in relationship to nutritional status and immune parameters in early human immunodeficiency virus-1 disease. *J Allergy Clin Immunol* 1995;95:886–892.
- 32 Paganelli R, Scala E, Mezzaroma I, Pinter E, D'Offizi G, Fanale-Belasio E, Rosso RM, Ansoategui JJ, Pandolfi F, Aiuti F: Immunologic aspects of hyperimmunoglobulinemia E-like syndrome in patients with AIDS. *J Allergy Clin Immunol* 1995;95:995–1003.
- 33 Rancinan C, Morlat P, Chêne G, Guez S, Baquay A, Beylot J, Salamon R: IgE serum level: A prognostic marker for AIDS in HIV-infected adults? *J Allergy Clin Immunol* 1998;102:329–330.
- 34 Kovacs JA, Hiemenz JW, Macher AM, Stover D, Murray HW, Shelhamer J, Lane HC, Urmacher C, Honig C, Longo DL, Parker MM, Natanson C, Parrillo JE, Fauci AS, Pizzo PA, Masur H: *Pneumocystis carinii* pneumonia: A comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. *Ann Intern Med* 1984;100:663–671.
- 35 Kaplan MH, Sadick N, McNutt NS, Meltzer M, Sarngadharan MG, Pahwa S: Dermatologic findings and manifestations of acquired immunodeficiency syndrome (AIDS). *J Am Acad Dermatol* 1987;16:485–506.
- 36 Coopman SA, Johnson RA, Platt R, Stern RS: Cutaneous disease and drug reactions in HIV infection. *N Engl J Med* 1993;328:1670–1674.
- 37 Pedersen M, Nielsen CM, Permin H: HIV antigen-induced release of histamine from basophils from HIV infected patients. Mechanism and relation to disease progression and immunodeficiency. *Allergy* 1991;46:206–212.
- 38 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.
- 39 Graziosi C, Pantaleo G, Gant KR, Fortin JP, Demarest JF, Cohen OJ, Sékaly RP, Fauci AS: Lack of evidence for the dichotomy of TH1 and TH2 predominance in HIV-infected individuals. *Science* 1994;265:248–252.
- 40 Maggi E, Mazzetti M, Ravina A, Annunziato F, De Carli M, Piccinni MP, Manetti R, Carbonari M, Pesce AM, Del Prete G, Romagnani S: Ability of HIV to promote a TH1 to TH0 shift and to replicate preferentially in TH2 and TH0 cells. *Science* 1994;265:244–248.
- 41 Fakoya A, Matear PM, Filley E, Rook GAW, Stanford J, Gilson RJC, Beecham N, Weller IVD, Vyakarnam A: HIV infection alters the production of both type 1 and 2 cytokines but does not induce a polarized type 1 or 2 state. *AIDS* 1997;11:1445–1452.
- 42 Israël-Biet D, Labrousse F, Tourani JM, Sors H, Andrieu JM, Even P: Elevation of IgE in HIV-infected subjects: A marker of poor prognosis. *J Allergy Clin Immunol* 1992;89:68–75.
- 43 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.
- 44 Lin RY, Smith JK Jr: Hyper-IgE and human immunodeficiency virus infection. *Ann Allergy* 1988;61:269–272.
- 45 Del Prete G, Maggi E, Parronchi P, Chretien I, Tiri A, Macchia D, Ricci M, Banchereau J, De Vries J, Romagnani S: IL-4 is an essential factor for the IgE synthesis induced in vitro by human T cell clones and their supernatants. *J Immunol* 1988;140:4193–4198.
- 46 Wills-Karp M, Luyimbazi J, Xu X, Schofield B, Neben TY, Karp CL, Donaldson DD: Interleukin-13: Central mediator of allergic asthma. *Science* 1998;282:2258–2261.

- 47 Grünig G, Warnock M, Wakil AE, Venkayya R, Brombacher F, Rennick DM, Sheppard D, Mohrs M, Donaldson DD, Locksley RM, Corry DB: Requirement for IL-13 independently of IL-4 in experimental asthma. *Science* 1998; 282:2261–2263.
- 48 Gauchat J-F, Henchoz S, Mazzei G, Aubry J-P, Brunner T, Blasey H, Life P, Talabot D, Flores-Romo L, Thompson J, Kishi K, Butterfield J, Dahinden C, Bonnefoy JY: Induction of human IgE synthesis in B cells by mast cells and basophils. *Nature* 1993;365:340–343.
- 49 Schroeder JT, Howard BP, Jenkins MK, Kagey-Sobotka A, Lichtenstein LM, MacGlashan DW Jr: IL-4 secretion and histamine release by human basophils are differentially regulated by protein kinase C activation. *J Leukoc Biol* 1998;63:692–698.
- 50 Devouassoux G, Foster B, Scott LM, Metcalfe DD, Prussin C: Frequency and characterization of antigen-specific IL-4- and IL-13-producing basophils and T cells in peripheral blood of healthy and asthmatic subjects. *J Allergy Clin Immunol* 1999;104:811–819.
- 51 Bradding P, Feather IH, Howarth PH, Mueller R, Roberts JA, Britte K, Bews JPA, Hunt TC, Okayama Y, Heusser CH, Bullock GR, Church MK, Holgate ST: Interleukin 4 is localized to and released by human mast cells. *J Exp Med* 1992;176:1381–1386.
- 52 Okayama Y, Petit-Frère C, Kassel O, Semper A, Quint D, Tunon-de-Lara MJ, Bradding P, Holgate ST, Church MK: IgE-dependent expression of mRNA for IL-4 and IL-5 in human lung mast cells. *J Immunol* 1995;155:1796–1808.
- 53 Burd PR, Thompson WC, Max EE, Mills FC: Activated mast cells produce interleukin 13. *J Exp Med* 1995;181:1373–1380.
- 54 Pawankar R, Okuda M, Yssel H, Okumura K, Ra C: Nasal mast cells in perennial allergic rhinitis exhibit increased expression of the FcεRI, CD40L, IL-4, and IL-13, and can induce IgE synthesis in B cells. *J Clin Invest* 1997;99:1492–1499.
- 55 Moore JP: Coreceptors: Implications for HIV pathogenesis and therapy. *Science* 1997;276: 51–52.
- 56 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.
- 57 Ugucioni M, Mackay CR, Ochsenberger B, Loetscher P, Rhis S, LaRosa GJ, Rao P, Ponath PD, Baggiolini M, Dahinden CA: High expression of the chemokine receptor CCR3 in human blood basophils. Role in activation by eotaxin, MCP-4, and other chemokines. *J Clin Invest* 1997;100:1137–1143.
- 58 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.
- 59 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.
- 60 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 β-chemokine receptors CCR3 and CCR5 facilitate infection by primary HIV-1 isolates. *Cell* 1996;85:1135–1148.
- 61 Doranz BJ, Rucker J, Yi Y, Smyth RJ, Samson M, Peiper SC, Parmentier M, Collman RG, Doms RW: A dual-tropic primary HIV-1 isolate that uses fusin and the β-chemokine receptors CKR-5, CKR-3, and CKR-2b as fusion cofactors. *Cell* 1996;85:1149–1158.
- 62 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.
- 63 Ghorpade A, Xia MQ, Hyman BT, Persidsky Y, Nukuna A, Bock P, Che M, Limoges J, Gendelman HE, Mackay CR: Role of the β-chemokine receptors CCR3 and CCR5 in human immunodeficiency virus type 1 infection of monocytes and microglia. *J Virol* 1998;72: 3351–3361.
- 64 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.
- 65 Silverman GJ: B-cell superantigens. *Immunol Today* 1997;18:379–386.
- 66 Karray S, Zouali M: Identification of the B cell superantigen-binding site of HIV-1 gp120. *Proc Natl Acad Sci USA* 1997;94:1356–1360.
- 67 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.
- 68 Gelderblom HR, Hausmann EHS, Özel M, Pauli G, Koch MA: Fine structure of human immunodeficiency virus (HIV) and immunolocalization of structural proteins. *Virology* 1987; 156:171–176.
- 69 Andrew DP, Chang MS, McNinch J, Wathen ST, Rihaneck M, Tseng J, Spellberg JP, Elias CG III: STCP-1 (MDC) CC chemokine acts specifically on chronically activated Th2 lymphocytes and is produced by monocytes on stimulation with Th2 cytokines IL-4 and IL-13. *J Immunol* 1998;161:5027–5038.
- 70 Marone G (ed): *Human Basophils and Mast Cells: Biological Aspects*. Basel, Karger, 1995.
- 71 Marone G (ed): *Human Basophils and Mast Cells: Clinical Aspects*. Basel, Karger, 1995.
- 72 Galli G, Annunziato F, Mavilia C, Romagnani P, Cosmi L, Manetti R, Pupilli C, Maggi E, Romagnani S: Enhanced HIV expression during Th2-oriented responses explained by the opposite regulatory effect of IL-4 and IFN-γ on fusin/CXCR4. *Eur J Immunol* 1998;28:3280–3290.
- 73 Penn ML, Grivel J-C, 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.
- 74 Gaynor RB: Regulation of HIV-1 gene expression by the transactivator protein Tat. *Curr Top Microbiol Immunol* 1995;193:51–77.
- 75 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.
- 76 Helland DE, Welles JL, Caputo A, Haseltine WA: Transcendental transactivation by the human immunodeficiency virus type 1 tat protein. *J Virol* 1991;65:4547–4549.
- 77 Westendorp MO, Frank R, Ochsenbauer C, Stricker K, 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.
- 78 Frankel AD, Pabo CO: Cellular uptake of the tat protein from human immunodeficiency virus. *Cell* 1988;55:1189–1193.
- 79 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 β-chemokine homolog that promotes migration and up-regulates CCR3 expression on human FcεRI⁺ cells. *J Immunol* 2000;165:7171–7179.
- 80 Li Y, Li L, Waldey R, Reddel SW, Qi JC, Archis C, Collins A, Clark E, Cooley M, Kouts S, Hassan NM, Mohammed A, Cunningham A, Wong G, Stevens RL, Krilis SA: 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 (abstract). *J Allergy Clin Immunol* 2000;105: 586.
- 81 Paiva DD, Morais JC, Pilotto J, Veloso V, Duarte F, Lenzi HL: Spectrum of morphologic changes of lymph nodes in HIV infection. *Mem Inst Oswaldo Cruz* 1996;91:371–379.
- 82 Silver R, Silverman AJ, Vitkovic L, Lederhender II: Mast cells in the brain: Evidence and functional significance. *Trends Neurosci* 1996;19:25–31.
- 83 Juremalm M, Hjertson M, Olsson N, Harvima I, Nilsson K, Nilsson G: The chemokine receptor CXCR4 is expressed within the mast cell lineage and its ligand SDF-1α acts as a mast cell chemotaxin. *Eur J Immunol* 2000;30:3614–3622.
- 84 Jinquan T, Jacobi HH, Jing C, Reimert CM, Quan S, Dissing S, Poulsen LK, Skov PS: Chemokine stromal cell-derived factor 1α activates basophils by means of CXCR4. *J Allergy Clin Immunol* 2000;106:313–320.

Copyright: S. Karger AG, Basel 2001. Reproduced with the permission of S. Karger AG, Basel. Further reproduction or distribution (electronic or otherwise) is prohibited without permission from the copyright holder.