In 1986, just about two years after the identification of HIV-1 as the causative agent of AIDS, a research team led by J.A. Levy demonstrated that CD8+ T cells are capable of preventing in vitro HIV-1 infection of susceptible cells by secreting soluble factors. However, the exact nature of these factors remained unknown until a research team led by P. Lusso demonstrated that three inflammatory CC chemokines, RANTES (CC-chemokine ligand 5 or CCL5), macrophage inflammatory protein 1α (MIP-1α or CCL3) and MIP 1β (CCL4) were the major components of the HIV-suppressive factor(s) released by CD8+ T cells. Joon Feng and colleagues identified CXCR4, a receptor for the CXC chemokine stromal cell-derived factor 1 (SDF-1), as the long sought coreceptor for T-tropic HIV-1 strains. It is well known that the expression of human CD4, the high-affinity receptor for HIV-1, was necessary but not sufficient for viral entry and a species-specific cofactor was required. These discoveries led within a few months to another milestone of the HIV research, i.e., the identification of CCR5, a receptor for CC chemokines, as the main coreceptor for primary M-tropic HIV-1 strains. It is well known that the expression of human CD4, the high-affinity receptor for HIV-1, was necessary but not sufficient for viral entry and a species-specific cofactor was required. These discoveries led within a few months to another milestone of the HIV research, i.e., the identification of CCR5, a receptor for CC chemokines, as the main coreceptor for primary M-tropic HIV-1 strains. Although other chemokine receptors have been identified that can facilitate HIV infection in vitro, it is now well recognized that only CCR5 and CXCR4 are the critical coreceptors for HIV infection in vivo.

Chemokines are small proteins in the cytokine family that bind to chemokine receptors promoting a large number of functions among which, more importantly, the development and homeostasis of the immune system, the cellular movement by chemotaxis, the stem cell survival, the angiogenesis. They are divided into four subfamilies based on structure and primary amino acid sequence: CXC, CC, C, and CX3C. To date, approximately 50 human chemokines and 20 receptors have been discovered. In addition to HIV infection, chemokines and their receptors are found associated with many pathologies including transplant rejection, cancer, autoimmune, pulmonary and vascular diseases (for a comprehensive review see).

Chemokine receptors are G protein-coupled receptors that are best known for their involvement in providing leukocyte trafficking in response to chemokine gradients. Many types of inflammatory and immunoregulatory cells are strongly influenced by the interplay between secreted chemokines and receptors expressed on their surfaces. The functions of these receptors have received, in the recent years, intense scrutiny because of their fundamental role in immunity and particularly in cell penetration by HIV-1.

Variations in the promoter and coding regions of CCR5 have been found altering the susceptibility of HIV-1 infection in several populations. Most attention has been given to a deletion in the region coding for a portion of the 1 transmembrane domain of the receptor. This deletion of 32 base pairs (CCR5Δ32) results in a truncated dysfunctional protein that does not get expressed on the cell surface. This allele is common in the white population with a prevalence of 10 to 14 per cent and individuals carrying 2 copies of this mutant gene are virtually protected against transmission by HIV-1 strains that use CCR5 for viral entry. With regard to chemokines, recent studies indicate that polymorphisms in CCL5 may alter the likelihood and the course of HIV-1 infection. There are three haplotypes, i.e., AC, GC, and AG, that differentially modulate CCL5 expression and its interference with virus replication. Homozygosity for the AC haplotype associates with an increased risk of acquiring HIV-1 as well as an accelerated disease progression in European Americans, but not in African Americans. Conversely, the AG haplotype, which is found much more frequently in Asian individuals, seems to contribute favourably to the prognosis for infected persons. However, polymorphisms in CCL5 are only a part of the picture.
Gallo and colleagues have argued persuasively that the levels of CC chemokines are consistent and reproducible parameters associated with both HIV-1 transmission and disease progression\textsuperscript{14}. These chemokines exhibit strong anti-HIV-1 properties \textit{in vitro}, and \textit{in vivo} studies have unequivocally demonstrated that their expression levels affect susceptibility to HIV-1 infection. Data from HIV vaccine studies also indicate that CC chemokine production is a true correlate of protection. Recently, vaccine studies also indicate that CC chemokine inhibitor of HIV-1 binding and entry, a potent natural chemokine inhibitor of HIV-1 binding and entry, significantly influence HIV-1/AIDS susceptibility\textsuperscript{15}. It has been demonstrated that some ethnic groups possess a significantly greater number of \textit{CCL3L1} gene copies than others. However, it does not seem the absolute number of \textit{CCL3L1} gene copies to be important for HIV-1 susceptibility, rather the gene dosage relative to the average copy number in a given population. A lower \textit{CCL3L1} copy number compared with the population average is associated with markedly enhanced HIV/AIDS susceptibility\textsuperscript{15}.

At least three hypotheses may be made to explain how high doses of \textit{CCL3L1} would contrast HIV-1 infection or disease progression. The first one takes into account the increased production of the \textit{CCL3L1} protein by individuals with increased copy numbers of \textit{CCL3L1}. It would sterically inhibit the HIV-1 gp120 binding thus limiting the entry through CCR5. The second one considers the reduced infectibility by M-tropic HIV-1 of T cells with reduced CCR5 expression due to the receptor internalization triggered by \textit{CCL3L1}. Finally, a possible consequence of the \textit{CCL3L1} production might be quantitative or qualitative changes in leukocyte recruitment, similarly to what recently reported for CX3CL1 and its receptor CX3CR1\textsuperscript{16}. In conclusion, a lot of genetic evidences exist supporting the concept that quantitative and qualitative variations in CC chemokines and their receptors have a relevant impact on susceptibility to HIV infection and disease progression. Unfortunately, non genetic attempts to establish a clear-cut correlation between CC chemokines production and HIV disease progression have brought contradictory results\textsuperscript{17}. An association between high CC chemokine production and slow progression or asymptomatic state has been consistently reported, but only when antigen- or mitogen-stimulated peripheral blood mononuclear cells (PBMCs) or T cell clones were examined. As opposite, in spite of intense investigations, the long sought-after predictive value of CC chemokine levels in serum or plasma has been never firmly demonstrated.

In this issue Ramalingam and colleagues report very interesting data about the CC chemokines plasma concentrations of a group of HIV-1-infected individuals from south India\textsuperscript{18}. The strength of this paper is certainly the study population. In fact, the patients enrolled in this study, naïve for antiretroviral treatments, came from the same geographic area and belonged, in a quite homogeneous manner, to the three CDC groups. They found increased levels of CC chemokines in HIV-1 infected individuals in comparison to controls. This increase was related to the CDC stage being major in patient with more advanced disease. Finally, a significant positive correlation was found between CCL31 and CCL4 (but not CCL5), on one hand, and CD4+ T cell count and plasma viral load, on the other hand. Consequently, the conclusion of the paper is that the CC chemokines may also exert an inhibitory activity against HIV-1, but only in the initial stages of the infection. This is undoubtedly one of the possible interpretations of the available results and certainly the increased production of CC chemokines in the advanced disease reflects the increased T cell activation. However, can we state that the rate of the disease progression would be the same in absence of the observed increased levels of CC chemokines? Unfortunately, an insurmountable problem with the interpretation of the results of the \textit{in vivo} studies on CC chemokines is that these latter are only one of the many factors determining the course of HIV-1 disease.

Some years ago we started evaluating the effect of highly active anti-retroviral therapy (HAART) at the level of CC chemokine production and chemokine receptor expression in a selected population of HIV-1 infected individuals showing a moderate immunodeficiency and mostly naïve for antiretroviral therapy\textsuperscript{19-22}. At enrolment we observed increased levels of CC chemokine in plasma of HIV-1 infected patients in comparison to controls that significantly reduced during the first months of HAART. However, after 12 months of HAART the levels of CC chemokines reascended to values that did not significantly differ from those detected before starting HAART. These results were consistent with, and have been subsequently confirmed by, different studies including the present study\textsuperscript{18}. 

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There are however other studies that are, apparently, at variance with the above mentioned results. However, a careful reading of the methods may allow to unveil a number of discrepancies accounting for the different results. A large part of the discrepancies observed in in vivo studies on CC chemokines in HIV-1 infected individuals could be explained in terms of differences, for instance, in the size of the study population, the stage of HIV disease, used drugs, methods of preparation of cell cultures and means of activation, the viral load and the virus tropism.

In conclusion, it is our opinion that in order to clearly demonstrate the role of CC chemokines in HIV-1 infection an extremely well defined population of subjects is needed in which the highest number of contributing factors could be standardized. In this context, this paper is an interesting piece of work that adds very useful information to the complex scenario of CC chemokines in HIV-1 infection.

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