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Pillars of Immunology

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The Unexpected Pleiotropic Activities of RANTES

Jay A. Levy[1]

The field of chemokines represented by the β-chemokine RANTES began just 20 years ago (1). Several of these small basic proteins were discovered about the same time and defined the process of chemotaxis, which today is an important component of our understanding of immune responses to infection and injury, as well as immunologic communication (1).

The authors of this issue's *Pillars of Immunology* article made use of a relatively new technology at the time to identify RANTES, subtraction cDNA libraries, which help to distinguish genes expressed in one cell and not in another (2). This genetic approach has since led to the uncovering of close to 50 other chemokines and chemokine receptors (1). The authors named this new protein for its characteristics: *R*egulated (increased production) upon *A*ctivation, expressed by *N*ormal *T* c*E*lls (as well as other cells), and presumably (now confirmed) *S*ecreted. This initial report on RANTES placed further attention on a new family of chemotactic proteins that proved to be important in influencing many other biologic processes (1, 3).

The chemotactic activity of RANTES, now given the immunologic designation CCL5, brings T cells, dendritic cells, eosinophils, NK cells, mast cells, and basophils to sites of inflammation and infection (3). Whereas this cytokine was initially considered a T cell-specific protein, it has since been found to be produced by many cells in the body including platelets, macrophages, eosinophils, and fibroblasts, as well as endothelial, epithelial, and endometrial cells (3).

Through its location and production, RANTES has beneficial activity by bringing immune cells to areas of infection and injury. It can also be involved in direct antimicrobial (antitrypanosomal) activity by inducing NO in macrophages (4). However, RANTES can have detrimental effects via the recruitment of immune cells that enhance inflammatory processes such as arthritis, atopic dermatitis, nephritis, colitis, and other disorders (e.g., arteriosclerosis, pulmonary hypertension, asthma, nasal polyps, endometriosis, nephropathy, and perhaps Alzheimer's disease) (1, 3). This cytokine has been associated as well with the induction or promotion of cancer (e.g., prostate and breast) (3, 5, 6). In this latter situation, RANTES can be angiogenic and also increase the metastatic potential of cancer cells by encouraging cellular migration to sites of its production (3).

In the field of HIV/AIDS, RANTES took on particular relevance when it was found about a decade ago to have anti-HIV activity (7). This antiviral role of RANTES was noted during studies directed at determining the nature of an unidentified $CD8^+$ anti-HIV cell protein that suppressed HIV replication at transcription: the $CD8^+$ cell antiviral factor (CAF)[2] (8).

From the culture supernatant of an established T cell line, three β-chemokines were recovered with anti-HIV activity, particularly in combination: RANTES, MIP-1α, and MIP-1β (7). That observation led to the recognition that one of the β-chemokine receptors, CCR5, was a secondary binding site for nonsyncytium-inducing, macrophage-tropic HIV isolates (now called R5 viruses) (9). The discovery of this chemokine coreceptor for HIV followed an earlier observation that the receptor for the chemokine SDF1, CXCR4, was a major binding site for the X4 HIV types (10). These latter syncytium-inducing viruses, distinct from the R5 viruses, are highly cytopathic and replicate well in established T cell lines as well as $CD4^+$ lymphocytes, but not in macrophages (9, 10).

The β-chemokines were not CAF, but their identification encouraged additional research directed at evaluating their role in HIV pathogenesis. The observations have been controversial. In some in vitro studies the β-chemokines blocked HIV infection of cells (7–9, 11) and were associated in vivo with a delay in disease progression (12–14). Binding of RANTES to glycosaminoglycans on the cell surface can be involved in this antiviral activity (15). In other studies, these cytokines did not appear to have antiviral activity or they increased HIV infection (16–19). This enhancement in HIV replication could reflect increased binding to or activation of T cells, particularly by aggregated forms of RANTES (20, 21).

The amount of chemokines required for anti-HIV activity appears to be much higher than the physiologic amount generally found in HIV-infected people (11). It is also curious that R5 viruses induce a greater production of β-chemokines than do the X4 viruses (22). These findings suggest that in vivo the chemotactic activity of RANTES, bringing immune target cells to the site of infection, plays a more prominent role in HIV pathogenesis than its antiviral function. Nevertheless, certain RANTES genetic alleles have been associated with a reduced progression to AIDS (23, 24).

An important observation following the connection of β-chemokines with HIV was their relationship to individuals who remained uninfected despite multiple exposures to HIV. These people had a mutation in both alleles of the CCR5 gene, which blocked expression of this receptor on the cell surface (9). A natural protective mechanism existed against R5 viruses. This type of mutation is found in 1–3% of the Caucasian population (9). Because an absence of CCR5 expression did not appear to

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[2] Abbreviations used in this paper: CAF, $CD8^+$ cell antiviral factor; AML, acute myelogenous leukemia.

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be detrimental to people, therapeutic approaches to block CCR5 via entry inhibitors such as RANTES analogues have been considered (25). At the same time, antagonists for RANTES are being explored as therapy for the inflammatory and allergic conditions associated with its production (26). It would appear that the ideal drug derived from the RANTES structure would be one that has selective anti-HIV activity and very low inflammatory activity, aside from the ability to recruit sufficient cells for controlling infection and injury.

Most recently, a bone marrow transplant using stem cells from a CCR5-negative donor was used to treat an HIV-infected individual with acute myelogenous leukemia (AML) (27). In nearly 2 years the AML has not recurred and, notably, the dominant R5 virus has not been detected in the blood stream. Although not a cure, this finding encourages the use of other approaches to control HIV replication, namely by reducing CCR5 expression. The manipulation of stem cells by gene therapy to lack CCR5 and the use of vectors carrying anti-CCR5 activities (e.g., small interfering RNA, ribozymes, antisense RNA, and anti-splicing RNA components) are directions being tested (28). They may prove helpful in providing long-term control of HIV infection without drug toxicities. One caveat for any manipulation of CCR5 expression is the observation that individuals with the CCR5 mutation have a greater risk of serious West Nile virus infections (29).

Thus, it is intriguing that RANTES has a similar but contrasting history to that of the IFNs. These latter cytokines, named for their initial antiviral activity, were later found to have pleiotropic immunologic effects. Conversely, the β-chemokine RANTES, named for its initial immunologic effect, is now, two decades later, known to have multiple effects in virology and pathology as well as immunology. This current knowledge of RANTES can provide valuable directions for the therapy of inflammatory and virologic medical conditions.

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