The authors then put their crystal back on the x-ray diffractometer and obtained the x-ray crystal structure of the 1:1 calixarene–vinyl bromide complex. It is worth remarking on their clever choice of vinyl bromide as the guest molecule: In x-ray crystallographic terms, the electron-rich bromine atom of the guest is easy to resolve in the presence of only carbon, hydrogen, and oxygen, and vinyl bromide is therefore easy to locate (*9*).

This simple experiment with well-known materials has tremendous implications for solid-state dynamics. Protein crystallographers have of course been using a similar methodology for years. The method of isomorphous replacement involves soaking protein crystals in solutions containing heavy metal ions. The metals diffuse into the protein crystal and help crystallographers to solve the crystal structure of the original metal-free protein.

But protein crystals are not close-packed solids. They are as porous as inorganic zeolites. Crystals of biomolecules are usually awash with large water-filled channels, which facilitate the diffusion of the metal ions. In contrast, diffusion of a molecule as large as vinyl bromide through a nonporous, close-packed solid without disrupting the regular crystalline structure is difficult to picture. Sulfur dioxide can accomplish a similar feat, but it binds to its platinum-containing host by a strong coordination interaction (*10*). In the study of Atwood *et al.*, the binding only involves van der Waals forces. If nonporous solid-state diffusion can happen with calixarenes, the implication is that it can happen with many other materials. The beauty of the calixarene is that its ability to form complexes with the diffusing guest enables researchers to readily observe the process.

Atwood *et al.* propose a mechanism for this apparent tunneling of the guest involving "a highly synchronized process whereby neighboring host molecules at the advancing phase boundary cooperate with one another, not only to relay the guest through the lattice, but also to maintain continuity of the material such that the crystal does not fracture." This explanation must still be considered speculative, but it seems much more plausible than thinking of the vinyl bromide as a molecular "ghost" that can glide like an ethereal specter through the calixarene walls.

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PERSPECTIVES: IMMUNOLOGY

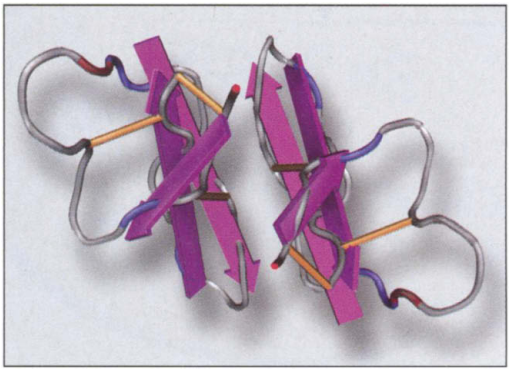
Versatile Defensins

Tomas Ganz

Defensins (see the figure) are a family of antimicrobial peptides abundant in immune cells—white blood cells (specifically neutrophils), intestinal Paneth cells, and barrier epithelial cells—that engage in host defense. There is increasing evidence that in these settings defensins (and other antimicrobial substances) directly contribute to the killing of microbes (*1*). Now, two reports in this issue, by Zhang *et al.* (page 995) and Biragyn *et al.* (page 1025), implicate defensins in a new set of specific activities (*2*, *3*). These investigators show that defensins are important for the anti-HIV activity of human $CD8^+$ T lymphocytes (*2*) and for the induction of cell-mediated antitumor immunity in mice (*3*).

Zhang *et al.* (*2*) propose that defensins are the solution to a puzzle that has challenged AIDS researchers since the early days of the epidemic. $CD8^+$ T lymphocytes from some HIV-infected patients secrete a substance (CD8 antiviral factor or CAF) that interferes with the ability of HIV to infect cells (*4*). This factor is particularly abundant in AIDS patients who are doing well clinically and in those HIV-infected patients (nonprogressors) who do not develop the symptoms of the disease for many years after the initial infection (*5*). Zhang *et al.* now show that $CD8^+$ T cells from long-term nonprogressor HIV patients secrete α-defensins-1, -2, and -3 when stimulated. These α-defensins account for much of the antiviral activity of CAF. The authors used neutralizing antibodies to human α-defensins-1, -2, and -3, and to the β-chemokines MIP-1α, MIP-1β, and RANTES in order to calculate the specific contributions of α-defensins and β-chemokines to CAF activity. These experiments demonstrate that HIV strains using the CXCR4 chemokine receptor for entry into host target cells are predominantly blocked by the α-defensins in CAF. In contrast, HIV strains that use the CCR5 chemokine receptor are only partially inhibited by α-defensins, with most of the remaining CAF activity attributable to β-chemokines. Both purified and synthetic α-defensins inhibited HIV replication in vitro. The authors show that unstimulated human $CD8^+$ T cells contain little defensin, whereas, after stimulation for 2 days with antibodies against their CD3 and CD28 receptors, α-defensin-1, -2, and -3 were readily detected in the cytoplasmic granules of these cells by immunostaining.

The activity of defensins as a component of CAF has important implications. The most optimistic interpretation is that α-defensins and β-chemokines are causally involved in slowing the progression of HIV infection in patients favored by specific environmental or genetic factors. If so, improved understanding of the regulation of defensin production in $CD8^+$ T lymphocytes could potentially extend these benefits to other HIV patients, and eventually a pharmacological substitute for these natural defensins could be developed. Alternatively, defensins may be markers of nonprogression, perhaps by indicating that despite HIV infection of the host, $CD8^+$ T cells



Defensins to the rescue. Human neutrophils secrete the antimicrobial peptides α-defensin-1, -2, and -3 in response to bacterial infection. These peptides form dimeric structures that contain a total of six β-strands (purple arrows). The positively charged side chains of α-defensin-3 are shown in blue, negative charges in red, and disulfide bonds in orange. [Protein structure coordinates from (*12*)]

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are appropriately stimulated and remain sufficiently functional to generate these antimicrobial peptides. If so, defensin measurements could be useful in determining the optimal timing of antiviral therapy (*6*). The mechanism of the anti-HIV activity of defensins is of great interest, and may be mediated by defensins' effects on the viral particles, the host cells, or both.

In a companion paper by Biragyn *et al.* (*3*), we are introduced to yet another aspect of defensins: their ability to signal to the cells involved in adaptive immunity. In response to infection, defensins are produced within minutes to hours by neutrophils or specialized epithelial cells. Some defensins act as chemoattractants for immature dendritic cells (*7*) that present antigen to T cells when stimulated to mature. Biragyn and colleagues now show that murine β-defensin-2, in addition to being a chemoattractant that binds to and signals through the CCR6 chemokine receptor, also induces dendritic cells to mature by binding to Toll-like receptor-4. This receptor is essential for the host response to bacterial lipopolysaccharide (*8*). When the authors linked murine β-defensin-2 to nonimmunogenic tumor antigens, they obtained a potent cell-mediated immune response and antitumor activity in mice (*5*).

In this setting, defensins act as a potent immunological adjuvant, suggesting that they may be useful in the formulation of therapeutic antitumor vaccines for use in human cancer patients. However, defensin sequences vary considerably between humans, mice, and other animals, and it is not certain that a human defensin with similar properties will be found, or that the murine defensin will retain its activity in humans. More than 20 human defensin gene products remain uncharacterized and could provide useful leads in the search for functional homologs of murine β-defensin-2 (*9*).

We must assume (as the investigators do) that murine β-defensin-2 is not simply a highly efficient carrier for otherwise undetectable amounts of bacterial lipopolysaccharide. If we assume this, then we can infer that the defensin peptide exerts its effects through at least two unrelated receptors. The two main families of antimicrobial peptides found in humans, defensins and cathelicidins, are encoded by genes that have undergone rapid evolution, and there is little of the sequence conservation typically seen in peptides that are high-affinity ligands. Accordingly, the interactions of antimicrobial peptides with receptors are weaker than those of the primary ligands. Even though many antimicrobial peptides reach high concentrations in tissues and blood, it remains to be shown that their receptor-mediated activities take place naturally and are biologically important in vivo.

One possibility is that these highly variable cationic amphipathic peptides bind promiscuously to complementary pockets in other proteins, sometimes mimicking receptor ligands (*10*). Alternatively, the preferred targets of antimicrobial peptides in both microbes and host cells may be the lipid domains that surround membrane-associated proteins, including various mammalian receptors (*11*). Perhaps certain cationic amphipathic peptides mimic the combination of hydrophobic and polybasic motifs that anchor some receptors to anionic phospholipids in these lipid domains. The disruptive effects of murine β-defensin-2 on these lipid domains could produce an immunoadjuvant effect through the CCR6 and TLR-4 receptors. Better understanding of the interactions of antimicrobial peptides with different mammalian receptors may shed light on how these receptors operate, leading to new immunization strategies for preventing and treating cancer and other diseases.

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PERSPECTIVES: AURORAL AND SPACE PHYSICS

The Heavens in a Pile of Sand

Mervyn P. Freeman and Nicholas W. Watkins

Dramatic auroral displays over Earth's polar regions reveal a range of intricate patterns. Auroral spirals, westward-traveling surges, auroral curls, and many other phenomena have been identified on time scales from seconds to hours and spatial scales from 100 meters to thousands of kilometers (see the figure, panel A) (*1*). Recently, attention has begun to focus on whether there may be universal aspects to auroral structure, of the type observed in many complex natural systems (*2*).

One universal footprint seen in many complex systems is self-affinity. An object is self-affine if it is the same when viewed on any scale. In the early 1990s, the self-affinity of the aurora began to be noticed (3). Takalo *et al.* investigated this by analyzing the auroral electrojet (AE) index—a time series of the peak magnetic perturbation on the ground caused by electrical currents in the aurora, 100 km overhead (*4*). They found that the average squared difference between equally spaced points of the AE index time series doubled when the spacing was quadrupled, for any resolution between 1 and 100 min (*4*).

This fractional power law relationship is a classic definition of a self-affine structure—a "fractal." The fractal behavior was broken for time scales longer than 100 min, a feature thought to correspond to sporadic interruptions of the time series by a global auroral disturbance known as the substorm. Other measures of the AE index were also found to have power law relationships. For example, the probability distribution of the time for which the AE index exceeded a given fixed threshold followed a power law distribution from 1 to 1000 min. Superposed on the power law was another distribution centered on a fixed scale of ~100 min, corresponding to the substorm (*5*, *6*, *7*).

A similar measure was used to investigate the spatial structure of the aurora. In ultraviolet images of the aurora from NASA's Polar spacecraft, Lui *et al.* (*8*) identified auroral bright spots where the auroral emission intensity exceeded some fixed threshold, during both quiet and substorm intervals. They found a power law relationship between the number of bright spots and their area between 3000 and 1 million km^2. An additional population was found to be centered on a fixed scale of ~2 million km^2, corresponding to the substorm disturbance.

Because auroral bright spots evolve in space and time, a bright spot counted in one image at one time may be the same as another bright spot counted at an earlier or later time. Thus, the Lui *et al.* method overestimates the number of evolving spots. Uritsky *et al.* (*9*) reanalyzed Polar spacecraft auroral images, taking this spatiotemporal evolution into account (see the figure, panel B). The probability distribution of maximum bright spot area, and of area integrated over bright spot lifetime, now both followed a power law distribution over the entire observable range (three to five orders

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