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GUEST COMMENTARY

Chemokines Meet Defensins: the Merging Concepts of Chemoattractants and Antimicrobial Peptides in Host Defense

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The capacity of the immune system to respond appropriately and eradicate microbial infections depends on the production of peptide and small protein mediators with diverse structures and functions, many of which are induced by contact with pathogens or inflammatory stimuli. Based on their activities and, in part, structural features, several of the mediators have been classified as chemokines that recruit and activate leukocytes (for recent reviews, see references 12 and 31) and as cationic antimicrobial peptides (CAMPs) that inactivate invading bacterial, fungal, or viral pathogens (recently reviewed in references 6 and 30). These two groups have been studied separately until recently, when it became apparent that several mediators from both groups have overlapping functions and contribute to both recruitment of immune cells and direct inactivation of pathogens. The article by Tang et al. (21) in this issue provides new important evidence showing that the two classes of mediators have many features in common. It has been known for a long time that platelets from rabbits and humans store several chemokines (1) and also contain potent antimicrobial molecules (28). Now, in this issue, Tang et al. demonstrate that antimicrobial activity is exerted by platelet chemokines, thereby combining features of both chemoattractants and CAMPs (21).

The more than 40 human chemokines identified to date are produced by diverse cell types, including monocytes, granulocytes, lymphocytes, epithelial cells, and endothelial cells, and act primarily on certain classes of leukocytes, allowing the cells to migrate in a chemotactic fashion along a gradient of a particular chemokine. In addition to their role in cell positioning, chemokines also stimulate activation of target cells, leading to leukocyte degranulation, angiostasis, or angiogenesis. Chemokines probably evolved at the beginning of the vertebrate lineage when the various leukocyte types diverged (13). Based on amino-terminal patterns of cysteine residues, the various chemokines have been classified into four families: the CC, CXC, C, and CX3C chemokines (31). A few years ago, CXC and CC chemokines, representing the largest families, were regarded as potent attractants for neutrophils and monocytes, respectively. However, this classification was too simplified since some CXC chemokines were later shown to act also on monocytes and since members from both groups are now known to be highly specific for lymphocytes and dendritic cells, thereby controling adaptive immune responses. The various chemokine-specific receptors are related to each other and belong to the class of G-protein-coupled serpentine receptors (12).

CAMPs are more diverse in structure and seem to be more-ancient molecules (8). Although the phylogenetic relationships are uncertain, peptides with similar structures and functions are found in virtually all branches of multicellular organisms (30). In many cases, CAMPs have been shown to damage bacterial cytoplasmic membranes; however, the actual antimicrobial mechanisms are incompletely understood. The best-studied class of human CAMPs are the defensins, which have β-sheet structures and three disulfide bridges (11). Based on bridging patterns, two defensin subgroups, α- and β-defensins, can be distinguished and are produced mainly by neutrophils or by intestinal Paneth cells and epithelial cells, respectively. Cathelicidins are released from precursor proteins bearing an amino-terminal cathepsin L inhibitor (cathelin) domain (10). Humans produce only one cathelicidin, α-helical LL-37, which is found on various epithelia and in neutrophils. Antimicrobial peptides of a third class, thrombocidins (also termed platelet microbicidal proteins [PMPs]), are found in platelets; PMPs are released upon contact with pathogens or stimulation with thrombin (9, 28). Yeaman and Bayer (29) have demonstrated that PMPs from rabbit platelets contribute significantly to the prevention of endovascular staphylococcal, streptococcal, and fungal infections and have provided a large body of evidence for an active role of platelets in host defense.

More recently, Krijgsveld et al. (9) have characterized two antimicrobial peptides from human platelets; these two peptides are truncated derivatives of the CXC chemokines CXCL7 (NAP-2) and CTAP-3. Tang et al. (21) have characterized a larger set of antimicrobial molecules from human platelets and have demonstrated that several platelet chemokines, including CXCL4 (PF-4), CCL5 (RANTES), and full-length CTAP-3, along with the CTAP-3 precursor platelet basic protein, have potent antimicrobial activity for *Escherichia coli, Staphylococcus aureus, Cryptococcus neoformans,* and, with the exception of CTAP-3 and PBP, *Candida albicans* (Table 1) (21). Moreover, antimicrobial activity has been assigned to additional platelet peptides with chemotactic properties, such as fibrinopeptide B and thymosin β-4. Together with recent data from

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TABLE 1. Antimicrobial properties of human chemokines

Chemokine	Microorganisms reported to be susceptible	Reference
CXC family		
CXCL4 (PF-4)	*Escherichia coli*, *Staphylococcus aureus*, *Cryptococcus neoformans*, *Candida albicans*	21
CXCL9 (MIG)	*Escherichia coli*, *Listeria monocytogenes*	4
CXCL10 (IP-10)	*Escherichia coli*, *Listeria monocytogenes*	4
CXCL11 (I-TAC)	*Escherichia coli*, *Listeria monocytogenes*	4
CTAP-3	*Escherichia coli*, *Staphylococcus aureus*, *Cryptococcus neoformans*	21
CC family		
CCL5 (RANTES)	*Escherichia coli*, *Staphylococcus aureus*, *Cryptococcus neoformans*, *Candida albicans*	21

Cole et al. (4) on anti-*E. coli* and antilisterial activities of the gamma interferon-inducible chemokines CXCL9 (MIG), CXCL10 (IP-10), and CXCL11 (I-TAC) (4) (Table 1), these data shed a new light on the role of chemokines in host defense and indicate a considerable overlap of chemokine and CAMP functions.

This new concept is further supported by recent reports on an obverse phenomenon, the chemokine-like activities of mammalian CAMPs, including LL-37, and several defensins. Representatives of α- and β-defensins are chemotactic for human monocytes, mast cells, and subsets of dendritic and T cells (2, 14, 27), while LL-37 is capable of recruiting human neutrophils, monocytes, T cells, and mast cells (2, 15, 26) (Table 2), thereby providing a link between innate and adaptive immune responses. Moreover, human β-defensin 2 even shares the CCR6 receptor for triggering chemotactic responses in dendritic cells and T cells with the chemokine CCL20 (LARC) (27).

TABLE 2. Chemotactic properties of human antimicrobial peptides

Peptide	Leukocyte(s) reported to be attracted	Chemotaxis receptor	Reference(s)
α-Defensins			
HNP1	Monocytes, T cells, dendritic cells	Unknown	2, 22, 25
HNP2	Monocytes, T cells, dendritic cells	Unknown	2, 22, 25
β-Defensins			
hBD1[a]	Dendritic cells	CCR6	24, 27
hBD2	T cells, dendritic cells, mast cells	CCR6	14, 24, 27
hBD3	Monocytes, dendritic cells	CCR6	24
hBD4	Monocytes	Unknown	7
Cathelicidins			
LL-37	Neutrophils, monocytes, T cells, mast cells	FPRL1	2, 15, 26

[a] hBD, human β-defensin.

Defensins and certain chemokines share similar characteristics, including size, disulfide bonding, interferon inducibility, and cationic charge. The amino acid sequences exhibit no obvious similarities, but the α-defensins HNP1 and HNP2 contain a CXC motif close to the N terminus. Moreover, elucidation of nuclear magnetic resonance solution structures of human β-defensin 2 and murine CCL20 have recently revealed a surprising similarity in the three-dimensional structure of the two molecules (see Fig. 6 in reference 17) (17), which provides an explanation for the capacity of both to trigger the CCR6 receptor.

Toxic activity for microorganisms and chemotactic activity for leukocytes require different concentrations of a particular peptide and may be relevant in different situations during infection. At local sites of microbial infections, neutrophils, macrophages, or platelets release large amounts of the various peptides. Concentrations of defensins, cathelicidins, and certain chemokines sufficient to kill microorganisms have been detected or calculated for relevant in vivo settings (3, 4). Once these peptides are diluted by diffusion, they lose their antimicrobial capacity, but they may be responsible for recruiting more and additional types of leukocytes to infected tissues. The antimicrobial and chemotactic properties of defensins can be controlled separately, as shown for the human α-defensin HNP1. ADP ribosylation by arginine-specific ribosyltransferases from airway epithelia resulted in inhibition of the antimicrobial activiy of HNP1 while the chemotactic and leukocyte-stimulating activities were retained (16).

Sophisticated studies will be necessary to confirm that both antimicrobial and leukocyte-attracting activities of chemokines and CAMPs are relevant for the optimal function of mammalian immune systems. It should be noted that the overlap of chemokine and CAMP functions is only partial and that several chemokines, such as CXCL8 (interleukin-8), have been shown not to be antimicrobial (4). Nevertheless, it is tempting to assume that the two types of mediators have coevolved in order to ensure appropriate immune responses and to keep up with the equally quickly evolving immune system escape mechanisms of microbes. Interestingly, bacteria such as *S. aureus* have found efficient ways to counteract both the antimicrobial and the chemotactic mechanisms of human leukocytes. Resistance to CAMPs is achieved by staphylococci and many other bacterial pathogens by modulation of their cell envelopes through modification of teichoic acid polymers with D-alanine (20) and of phospholipids with L-lysine (19), which result in repulsion of CAMPs and considerably increased capacity of the bacteria to colonize host tissues (5, 18). In addition, *S. aureus* has recently been shown to produce a novel inhibitor of leukocyte chemotaxis (23), which most probably is another key factor in staphylococcal virulence.

The merging concepts of chemokines and CAMPs and the increasing knowledge of microbial countermeasures will stimulate new research strategies and a better understanding of host-pathogen interactions.

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