Chemerin reveals its chimeric nature

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Chemerin is a proinflammatory plasma protein that binds to the GPCR ChemR23/CMCLR1 on macrophages and plasmacytoid dendritic cells, and promotes chemotaxis. An orphan GPCR, CCRL2, has now been identified as an additional receptor for chemerin, providing a unique mechanism by which chemerin enhances inflammation. Furthermore, because recent data shows that chemerin-derived peptides possess antinflammatory properties, chemerin may be involved in both the initiation and resolution of inflammation.

As the authors hypothesized, peptides released upon C-terminal processing might be responsible for the inhibition.

To test this hypothesis, Cash et al. synthesized several peptides from the C-terminal end of mouse chemerin and tested them for inhibitory effects. One peptide, chemerin 15, possessed potent antinflammatory effects at surprisingly low picomolar concentrations. Intraperitoneal administration of chemerin 15 to mice before zymosan challenge suppressed the recruitment of neutrophils and monocytes with a concomitant reduction in the expression of proinflammatory mediators. Chemerin 15 also appeared to signal through ChemR23, as it had no inhibitory effect in ChemR23-deficient mice.

Administration of neutralizing antibody against chemerin to mice before zymosan challenge markedly enhanced intraperitoneal infiltration by inflammatory cells. Because zymosan normally activates resident macrophages, chemerin-derived inhibitory peptides are presumably generated at the site of inflammation and appear to play an important role in down-regulating inflammatory responses. Thus, depending on the class of protease that processes pro–chemerin or chemerin, ChemR23 binding peptides with either pro- or anti-inflammatory effects are produced.

Because the chemerin-derived inhibitory peptide acts via the same receptor as the proinflammatory chemerin, these structurally related agonistic and inhibitory peptides may compete at the level of receptor binding. In fact, picomolar levels of the inhibitory peptides are active, whereas nanomolar concentrations are required for agonistic effects by chemerin. Other GPCR ligands demonstrate similar competition. For example, an N-terminal deletion

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The Rockefeller University Press

Published September 22, 2008

variant of the chemokine MCP-1 (called 7ND) inhibits MCP-1–mediated monocyte chemotaxis (15). Extension of the human chemokine RANTES by a single residue at the N-terminus (Met-RANTES) creates a potent and selective RANTES antagonist (16). Met-RANTES also inhibits the effects of MIP-1α, a chemokine that shares its receptors with RANTES, raising the possibility that chemerin 15 may also inhibit the effect of other ChemR23 ligands, such as the antiinflammatory lipid resolvin E1. Like chemerin 15, resolvin E1 suppresses zymosan-induced peritoni-
sus and sulfonic acid–induced colitis in mice (17, 18). It remains a mystery how the different Chem23R ligands can induce opposing effects through the same receptor. Future studies may identify other receptors that participate and are trans–activated by this GPCR.

**Chemerin finds a new partner**

Chemerin’s complex functions have been amplified by two more reports. The first identified the orphan GPCR GPR1, which is closely related to ChemR23, as a second chemerin receptor (19). In this issue, Zabel et al. (14) unexpectedly identify a third chemerin–binding GPCR, CCRL2. The authors show that mouse CCRL2 (mCCRL2, the presumptive orthologue of human CCRL2 [20]) is constitutively expressed on mast cells. To examine whether CCRL2 plays a role in the inflammatory response, they used mice lacking the receptor. The absence of mCCRL2 ligation normally amplifies the inflammatory response. The amplified response was caused by mCCRL2 expression on mast cells, as mast cell–deficient mice engrafted with mCCRL2-deficient bone marrow progenitor cells had less ear swelling than did those engrafted with WT cells.

In an attempt to identify the ligand of mCCRL2, the authors screened known chemokines, but none of them stimulated chemotaxis of mCCRL2–transfected cells. To the authors’ surprise, however, chemerin blocked the binding of anti-mCCRL2 antibody to mouse peritoneal mast cells. Despite binding to mCCRL2 with high affinity, chemerin elicited no functional response from mCCRL2–expressing cells. Binding failed to trigger intracellular calcium mobilization, chemotaxis, or mCCRL2 internalization. Instead, incubating mCCRL2–transfected cells with chemerin resulted in a time–dependent increase in surface–bound chemerin. These chemerin–loaded cells then triggered calcium flux in responder cells expressing ChemR23. Thus, CCRL2 seems to concentrate bioactive chemerin and facilitate its presentation to ChemR23 on adjacent cells.

A wide variety of soluble proinflammatory mediators are produced and released at inflammatory sites, and mechanisms have been developed to retain or concentrate those mediators by preventing their diffusion. Chemokines, for example, bind to glycosaminoglycans, resulting in the formation of leukocyte-attracting chemokine gradients in tissues (21). Bacterial LPS binds to LPS-binding protein, which enhances the subsequent binding of LPS to MD-2 in the TLR4–MD-2 receptor complex, thus initiating the TLR4 intracellular signaling cascade (22). Some ligands, such as TNF, are present in both soluble and cell membrane–bound form. In its membrane–bound form, the receptor binding domain of TNF is exposed, which may explain why DC activation by neutrophil–derived TNF requires cell–cell contact (23). Because neutrophils generally produce cytokines at much
There are now three known types of functionally distinct receptors in the chemokine GPCR family. The first are functional, signal-transducing chemokine receptors. The second are so-called decoy receptors that bind to and signal chemokines from the environment, but do not transduce signals or activate cells. Finally, the newly identified type of receptor reported by Zabel et al. neither internalizes its ligands nor transduces signals. Instead, it plays a proinflammatory role by presenting bound ligands to functional signaling receptors expressed on neighboring cells.

The recent papers in JEM provide us with two novel insights. First, as reported by Cash et al., enzymatic proteolysis of precursor proteins, such as pro-chemerin, can result in the generation of both activating and inhibitory peptides. These opposing molecules with opposing activities can be generated by different classes of proteases, such as serine or cysteine proteases. Whereas serine proteases capable of producing activating peptides are released from neutrophils (29), cysteine proteases that generate inhibitory peptides are released from activated elicited macrophages (11). As neutrophils are typically the first cells to arrive at sites of inflammation, it is likely that the generation of proinflammatory peptides precedes the generation of anti-inflammatory peptides, which may then help control the severity of inflammatory responses.

Second, the findings of Zabel et al. reveal the existence of a new class of silent chemokine receptor–like GPCRs, which binds its ligand(s) and presents it to signaling receptors expressed on neighboring cells. Thus, soluble chemerin is a truly multifunctional protein with both stimulatory and inhibitory signaling capabilities, whereas cell-bound chemerin sends proinflammatory signals by bridging cells that express the silent receptor with those expressing the ChemR23 receptor.

REFERENCES


