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C5a and Fcγ receptors: A mutual admiration society

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Phagocytosis is a key process in protection of the host against pathogens and is created in proportion of antigens for the immune response. Synergism between C3b and IgG and their receptors in promoting adherence to and then ingestion of an antigen has been recognized for decades. Only more recently, however, has cross-talk between another complement activation fragment, the anaphylatoxin C5a, and FeγR receptors (FcγRs) been defined. In this issue of the JCI, C5a is shown to signal, via its receptor, the upregulation of activating (proinflammatory-type) FeγR (see the related article beginning on page S12). Moreover, engagement of FeγR by the IgG-bearing immune complex instructs the cell to synthesize more C5, from which C5a is derived. Thus, this work establishes a feedback loop whereby FeγR expression and function are enhanced, a very desirable event in concert with an infection but potentially deleterious in autoimmunity.

**Opsonization: helping phagocytes to eat**

Opsonins attach to invading microorganisms and other antigens in order to enhance the uptake of foreign particles by phagocytes. The 2 most important opsonins in blood are IgG and complement (C). Specifically, IgG and C3b bind to a target where they serve as ligands for FeγR and C receptors, respectively. This reaction can be conveniently split into 2 sequential steps; namely, immune adherence followed by internalization. Early on, it was recognized that C3b and C receptors most effectively mediated the adherence step, while FeγR receptors (FcγRs) most effectively mediated the internalization step. This combination of “talents” ensures efficient phagocytosis of an infectious particle. As the humoral immune response rapidly matures, it deposits more and more IgG on particles, which subsequently elicits complement activation.

Many types of in vivo and in vitro experiments have demonstrated how much more proficient C3b and IgG are as partners than either is alone in promoting phagocytosis. C3b can mediate internalization but requires a relatively large ligand load and activated monocytes/macrophages. IgG can mediate adherence, but again, a heavy dose of ligand is necessary. However, a combination of C3b and IgG is synergistic in mediating the phagocytic process. Thus, this cooperation between the receptors for these 2 ligands enhances this time-honored immune phenomenon that is critical to survival. In this issue of the JCI, Kumar, Gessner, and colleagues provide further evidence for another remarkable interaction among complement-derived ligands, IgGs, and their receptors (1).

**Cross-talk between C5a and FeγRs**

Kumar et al. (1) report a clear demonstration of cross-talk between the C and Ig receptors (Figure 1 and Table 1). In a mouse model of a so-called antibody-dependent, type II autoimmune reaction, the authors convincingly demonstrate the following interesting sequence of events: (a) upon injection of an autoantibody to mouse rbc, immune complexes form that bind to FeγRs on liver macrophages (Kupffer cells); (b) these cells in turn secrete C5 and possibly a protease (yet to be clearly defined) that cleaves C5 into the anaphylatoxin C5a and the initiator of membrane attack complex, C5b; (c) C5a binds to its receptor (C5aR) on Kupffer cells, which upregulates FeγR mRNA expression; and then (d) the increased number of FeγRs on these macrophages facilitates elimination of the antibody-coated rbc, thereby leading to a more severe hemolytic anemia. While this...
process is designed to “rev up” immune clearance in the setting of an infection by splenic and hepatic macrophages (once known as the reticuloendothelial system), it will of course also play out in immunopathologic syndromes.

These data (1) are not the first to suggest this intriguing connection between C5a and FcyR. In 2 prior publications, including one in the JCI, this same group established that C5a initiates inflammation through its effects on FcyRs and through its more direct role as a cell activator and chemoattractant (2, 3). In the 2002 study, which used an acute immune complex clearance model, C5aR engagement led to an increase in FcγR and activate the complement system. The FcγR signals the cell to increase C5 synthesis, resulting in more C5a, which in turn feeds back through its receptor to upregulate FcγR expression.

Figure 1
The interactions among C5a and IgG and their receptors. Humoral autoimmunity is illustrated. An IgG response has been made to an antigen on the surface of erythrocytes. IgG binds to this antigen to form immune complexes. Such immune complexes can both interact with FcγR and activate the complement system. The FcγR signals the cell to increase C5 synthesis, resulting in more C5a, which in turn feeds back through its receptor to upregulate FcγR expression.

Table 1
Consequences of C5aR engagement for FcγRs

<table>
<thead>
<tr>
<th></th>
<th>Activating or proinflammatory receptors</th>
<th>Inhibitory receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>↑ in FcγRI expression</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>↑ in FcγRIII expression</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>No change or ↓ in FcγRIII expression</td>
<td></td>
</tr>
</tbody>
</table>

Results: Augmented FcγR number and function, which is desirable in infections but undesirable in humoral autoimmunity.

Commentaries

Specifically, the 3 reports from the Gessner group establish a feedback loop via cross-talk between 2 receptors (Figure 1). The early engagement of FcγRI sends a signal to macrophages to provide a source of C5 from which C5a can be generated. C5a, through its receptor, in turn signals the cell to synthesize more FcγRs. The signal has specificity, as expression of the activating (proinflammatory) FcγRI and FcγRIII receptors is upregulated, while expression of the inhibitory FcγRII receptor is either down-modulated or unchanged. Many investigators have previously shown that “activated” macrophages, with their increased supply of FcγRs and other accoutrements, are more efficient at immune clearance and phagocytosis than resting cells (6). So, in many respects, these studies re-establish the importance of macrophage activation in the destruction of antibody- and C-targeted antigens. While this feedback event was established in an animal model of passive transfer of an autoantibody, its physiological role is to more efficiently eliminate bacteria and viruses from the bloodstream. There is much yet to be learned about the intracellular pathways in these signaling events and the control of this process.

A few caveats about the authors’ model system (1) should be mentioned. The inves-
mucosal barrier, antibodies may also activate C5a (8). C5a is a potent chemoattractant for neutrophils and monocytes, and it also enhances the adhesion and chemotactic migration of eosinophils. C5a is generated by the enzymatic cleavage of C5 by C5 convertase, which is a complex of Cl r-forming enzymes (C1r/C1s, C4b2a, and C3b) and complement factor B. C5a can also be generated by the action of serine proteases such as kallikrein or mast cell tryptase and by the action of metalloproteinases on membrane-anchored C5. C5a is a potent chemoattractant for neutrophils and monocytes, and it also enhances the adhesion and chemotactic migration of eosinophils. C5a is generated by the enzymatic cleavage of C5 by C5 convertase, which is a complex of Cl r-forming enzymes (C1r/C1s, C4b2a, and C3b) and complement factor B. C5a can also be generated by the action of serine proteases such as kallikrein or mast cell tryptase and by the action of metalloproteinases on membrane-anchored C5. C5a is a potent chemoattractant for neutrophils and monocytes, and it also enhances the adhesion and chemotactic migration of eosinophils. C5a is generated by the enzymatic cleavage of C5 by C5 convertase, which is a complex of Cl r-forming enzymes (C1r/C1s, C4b2a, and C3b) and complement factor B. C5a can also be generated by the action of serine proteases such as kallikrein or mast cell tryptase and by the action of metalloproteinases on membrane-anchored C5. C5a is a potent chemoattractant for neutrophils and monocytes, and it also enhances the adhesion and chemotactic migration of eosinophils. C5a is generated by the enzymatic cleavage of C5 by C5 convertase, which is a complex of Cl r-forming enzymes (C1r/C1s, C4b2a, and C3b) and complement factor B. C5a can also be generated by the action of serine proteases such as kallikrein or mast cell tryptase and by the action of metalloproteinases on membrane-anchored C5.