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C5a and Fcγ receptors: a mutual admiration society

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Commentary

Phagocytosis is a key process in protection of the host against pathogens and in provision 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 Fcγ receptors (FcγRs) been defined. In this issue of the *JCI*, C5a is shown to signal, via its receptor, the upregulation of activating (proinflammatory-type) FcγRs. Moreover, engagement of FcγRs 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 FcγR expression and function are enhanced, a very desirable event in concert with an infection but potentially deleterious in autoimmunity.

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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 in provision 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 Fcγ receptors (FcγRs) been defined. In this issue of the *JCI*, C5a is shown to signal, via its receptor, the upregulation of activating (proinflammatory-type) FcγRs (see the related article beginning on page 512). Moreover, engagement of FcγRs 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 FcγR 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 Ig and complement (C). Specifically, IgG and C3b bind to a target where they serve as ligands for Fcγ 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 Fcγ 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, Igs, and their receptors (1).

Cross-talk between C5a and FcγRs

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 rbcs, immune complexes form that bind to FcγRs 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 FcγR mRNA expression; and then (d) the increased number of FcγRs on these macrophages facilitates elimination of the antibody-coated rbcs, thereby leading to a more severe hemolytic anemia. While this

Nonstandard abbreviations used: C, complement; C5aR, C5a anaphylatoxin receptor; FcγR, Fcγ receptor.

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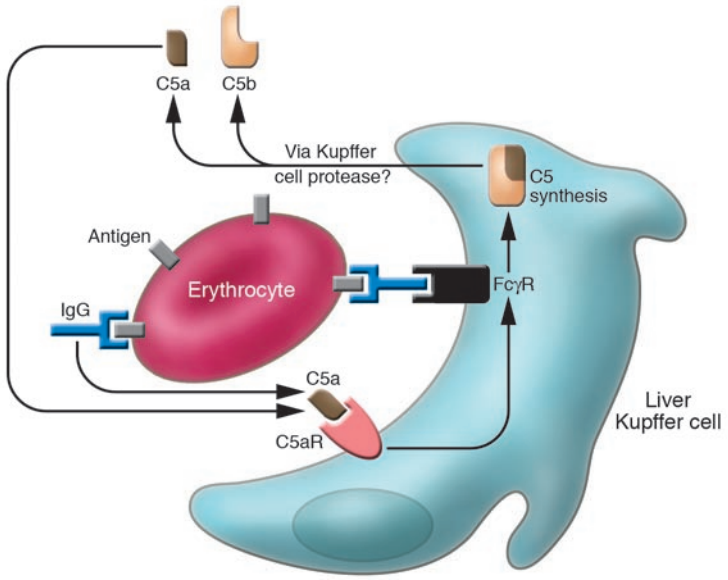

Figure 1
The interactions among C5a and IgG and their receptors. Humoral autoimmunity is illustrated. An IgG response has been made to an antigen on the surface of erythrocytes. IgG binds to this antigen to form immune complexes. Such immune complexes can both interact with FcγR and activate the complement 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.

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 FcγR. In 2 prior publications, including one in the *JCI*, this same group established that C5a initiates inflammation through its effects on FcγRs and through its more direct role as a cell activator and chemoattractant (2, 3). In the 2002 study, which used an acute immune complex pulmonary hypersensitivity model (2), C5aR engagement led to an increase in number and enhanced function of activating FcγRs (FcγRIII) versus the inhibitory FcγRs (FcγRII) on alveolar macrophages. If these changes did not occur, such as in C5aR-deficient animals, cytokine production and neutrophil recruitment were impaired. In the more recent report (3), which used a similar model, but this time in the peritoneum of mice, C5aR activation was necessary to initiate neutrophil recruitment and to instruct a proinflammatory FcγR response.

While immune models can be set up to demonstrate that certain immunopathologic conditions require only IgG and FcγR, or C and its receptors, most IgG-mediated events require FcγR engagement and complement activation. Moreover, these events are commonly additive, if not synergistic, and, in many cases, interdependent. The animal species, site of inflammation, antibody types mediating the response, cellular location of receptors, and many other factors contribute to such immune responses. The issue is not necessarily one of "my system is more important than yours," but rather one of an improved definition of the timing, interactions, and synergies that mediate a given response. This understanding has now been nicely demonstrated by Gessner and colleagues in the current study (1) and summarized by Gessner and Schmidt in a recent review (4).

An important point is that the use of C3-deficient mice would not have been sufficient to rule out a role for complement in the studies by Kumar et al. (1). The reason for this is straightforward but not appreciated or commented upon by most investigators. C5, like many complement components, may be synthesized locally by monocytes/macrophages and other cell types, where it can be cleaved by proteases to produce C5a. This type of complement activation does not rely on any 1 of 3 pathways (classical, lectin, or alternative). A lack of appreciation for this possibility has led other investigators to mistakenly rule out an effect of the complement system, including those mediated by the upregulation of FcγRs following C5aR engagement (4, 5). C5 and C5aR knockout animals must be examined before a role for the complement system can be excluded.

Feedback loop to enhance Fcγ expression

Specifically, the 3 reports from the Gessner group establish a feedback loop via cross-talk between 2 receptors (Figure 1). The early engagement of FcγR 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 downmodulated 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-

Table 1
Consequences of C5aR engagement for FcγRs

1. ↑ in FcγRI expression 2. ↑ in FcγRIII expression	Activating or proinflammatory receptors
3. No change or ↓ in FcγRII expression	Inhibitory receptor

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

tigators injected a single, large dose of an autoantibody that recognizes mouse rbcs to generate their cross-talk model system. The quantity of antibody used decreased the hematocrit from 50% to 25% in 4 days, even in FcγR$^{-/-}$ animals. Thus, C activation and rbc destruction took place via intravascular lysis and receptor-mediated extravascular sequestration (7). Complement activation occurs rapidly (within seconds) in this model and would provide another source of C5a to enhance FcγR mRNA expression; this may be the most likely C5a source in vivo. Second, the authors do not establish the mechanism for generating C5a. They hypothesize that a protease cleaves C5. Third, while they demonstrate upregulation of FcγRI and FcγRIII mRNA expression, they do not document an increased number of FcγRs on Kupffer cells in vitro or in vivo. Fourth, the authors nicely establish that FcγRII (the FcγR that sends a negative or antiinflammatory signal) plays no role in their observations. The reason here is simple: Kupffer cells do not express this receptor, although FcγRII was expressed on sinusoidal cells.

Immunopathologic reactions

As a final comment, in their study, Kumar et al. (1) refer to their model as an antibody-dependent type II autoimmune reaction. Antibodies of this type are directed at cell-bound targets (in the case of autoimmune hemolytic anemia) or matrix proteins (in the case of Goodpasture syndrome). The most up-to-date immunology textbooks still all have tables showing the Gell and Coombs classification system of immunopathologic reactions (8). I first learned about this system, as did many aspiring immunologists of my generation, at the NIH, where we were so fortunate to have Bill Paul as our teacher in the immunology course. I have now been teaching this same classification system for 30-plus years to students at Washington University School of Medicine. Students and senior immunologists still find it a useful scheme to classify immune reactions that we would like to be able to better control. Hopefully, insights provided by studies like those of Gessner's group will eventually provide us with the tools to accomplish this goal.

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Mucus in chronic airway diseases: sorting out the sticky details

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Mucous hypersecretion is a major cause of airway obstruction in asthma, chronic obstructive pulmonary disease, and cystic fibrosis. EGFR ligands and IL-13 are known to stimulate mucous induction, but the detailed mechanisms of epithelial mucous regulation have not been well defined. In this issue of the *JCI*, Tyner et al. show, in a mouse model of chronic mucous hypersecretion, that ciliated epithelial cell apoptosis is inhibited by EGFR activation, allowing IL-13 to stimulate the differentiation of these cells into goblet cells, which secrete mucus (see the related article beginning on page 309). In defining this coordinated, 2-step process, we can consider the therapeutic effects of blocking mucous production. This begs the question, Is it possible to reduce airway obstruction in chronic lung disease by inhibiting EGFR activation and/or by inhibiting IL-13?

In the respiratory tract, mucus is a critical component of the innate host defense system. On the airway epithelial cell surface, the sticky gel layer traps particles and the sol layer, which is predominantly water, contacts the surface of ciliated cells and permits moving of the gel out of the lower airways like an escalator so that it can ultimately be cleared by coughing or swallowing. Mucus also contains antibacterial agents to aid in its defense function. Pathogens and harmless proteins we inhale are thus removed from the respiratory tract and have a limited encounter with other immune components. In the bronchial airways, mucus is produced by surface epithelial cells with secretory features and a classical goblet shape, called goblet cells. Goblet cells produce mucins that are complexed with water in secretory granules and are released into the airway lumen. In the large airways, mucus is also produced by mucous glands. Under basal conditions, the columnar epithelial surface comprises a small percentage of goblet cells and a majority of ciliated cells. This struc-

Nonstandard abbreviations used: COPD, chronic obstructive pulmonary disease.

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