Asweet spot to control complement-induced inflammation

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Complement is intricately involved in inflammatory processes, yet the mechanisms that modulate the actions of its key mediator C5a are poorly understood. A new study uncovers a molecular partnership between three neutrophil receptors in the recognition of differentially glycated immune complexes and sheds light on regulatory processes in autoimmune and inflammatory disorders (pages 1401–1406).

The immune system often walks a thin line between the efficient elimination of danger and debris (for example, microbial intruders or apoptotic cells) and an unintentional attack on host cells and tissues that can lead to severe inflammatory conditions. Perhaps the best illustrations of such attacks are immune complex–induced autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis, which affect ~50 million Americans and cancer, often only limited and/or expensive treatment options. Consequently, they impose a large burden on the affected individuals and the healthcare system1. In their search for underlying disease mechanisms and therapeutic options, researchers have increasingly discovered regulatory crosstalk between various branches of the immune system that shape the overall inflammatory response and have implications for biomedical research.

One intriguing example of such cooperative modulation occurs between two systems that act upstream of inflammatory responses and represent important bridges between innate and adaptive immunity: complement and Fcγ receptors (FcγRs). The importance of complement in antimicrobial defense, immune surveillance and homeostasis is well appreciated2; danger-sensing molecules recognize pathogens and damage-associated molecular patterns and trigger complement activation, with subsequent tagging and elimination of microorganisms, damaged cells, or immune complexes (ICs). In the course of such events, complement activation fragments are generated that, in intense crosstalk with other bodily systems, orchestrate an array of biological functions, ranging from homeostasis, metabolism and tissue regeneration to inflammation and modulation of adaptive immune responses2.

C5a, the anaphylatoxin fragment released from the C5 protein upon complement activation, plays an essential part in these immunomodulatory processes. By binding the C5a receptor (C5aR; CD88) on immune cells such as macrophages and neutrophils, C5a triggers intracellular signaling pathways that induce proinflammatory mechanisms such as cell migration and release of inflammatory mediators3 (Fig. 1). Thus, C5aR-mediated cell activation has a crucial role in the outcome of inflammatory disorders such as sepsis, asthma, rheumatoid arthritis, transplant rejection, cancer and neurodegenerative and periodontal disorders3,4,5. Although the role of C5a and C5aR in the promotion of inflammation is well understood, our knowledge is comparatively scarce regarding the mechanisms that circumvent C5a-induced damage and excessive activation of the immune system.

ICs can induce strong complement activation via different routes, and this activation is key to their solubilization and elimination. ICs also bind and co-aggregate various FcγRs expressed on immune cells, which can similarly initiate phagocytosis and the release of inflammatory mediators. Although crosstalk between C5aR and FcγRs has long been recognized, only recently have the extent of this crosstalk and its implications for health and disease begun to emerge. IC-induced complement activation generates C5a6, which binds C5aR and lowers the threshold for FcyR activation by inducing the expression of activating FcγRs (FcγRI and FcγRII) and decreasing the expression of the inhibitory FcγRIIB (Fig. 1). This step is crucial, as the proportion of activating versus inhibitory FcγRs (A/I ratio) determines the magnitude of IC-induced inflammatory responses. Conversely, FcγR activation can enhance the synthesis of C5 through the binding of IgG autoantibodies and, consequently, promote the generation of C5 that further increases the A/I ratio (Fig. 1). Although this positive-feedback loop allows for more efficient clearance through the phagocytosis of complement- and IgG-opsonized microbes, it may also lead to pathology, because the combined signaling from activating FcγRs and C5aR exacerbates inflammation via the production of cytokines and recruitment of inflammatory cells (Fig. 1).

However, the factors that tip this balance between physiological and pathophysiological effects have remained elusive.

In this issue of Nature Medicine, Karsten et al.7 offer new insight into the regulation of this complement-FcγR crosstalk by uncovering a new mechanism by which galactosylated IgG1 ICs, FcγRIIB and the C-type lectin receptor dectin-1 cooperate to suppress C5aR-derived inflammatory functions (Fig. 1). They found that FcR γ-chain–deficient (FcγRIIb−/−) mice, which express only inhibitory and no activating FcγRs, are protected from IC-mediated injury despite the presence of C5aR. Furthermore, injection of mouse IgG1–ICs blocked the intracellular signaling pathways employed by C5aR and, consequently, the release of intracellular calcium. These results led the authors to hypothesize that ICs and FcγRIIB have an inhibitory role and suppress C5a-induced inflammation. In line with this concept, IgG1–ICs that preferentially bound FcγRIIB inhibited C5a-mediated recruitment and adhesion of neutrophils and upregulation of CD11b expression in neutrophils from wild-type and FcγRIIb−/− mice but not FcγRIIb−/− mice (which lack FcγRIIB) (Fig. 1). These effects were independent of activating FcγRs, which are usually regulated via pairing of the immunoreceptor tyrosine-based inhibitory motif (ITIM) of the FcγRIIB with the immunoreceptor tyrosine-based activation motif (ITAM) of activating FcγRs8. In their search for an alternative binding partner for ITIM in the absence of activating FcγRs, the authors identified a suitable candidate in dectin-1, which harbors an ITAM-like motif2. Consistent with a role for dectin-1 in the IC-mediated inhibition of C5a-induced inflammation, inhibition of dectin-1 or the use of dectin-1–deficient cells counteracted the inhibitory effects of ICs on C5a. Mechanistically, Karsten et al.7 found that tyrosine and Syk phosphorylation downstream of dectin-1 is linked to the tyrosine phosphorylation of the ITIM motifs within FcγRIIB. Subsequent phosphorylation of SHP-1–containing 5′-inositol phosphatase (SHIP) inhibits the signaling pathways downstream of C5aR that are crucial for the proinflammatory functions triggered by C5a (Fig. 1).

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One question still remained: what triggers dectin-1 to cooperate with FcγRIIB? The authors found the answer in the glycan composition of the IgG1-ICs: IgG molecules contain a branched N-glycan in their Fc portion that shows high heterogeneity, is subject to dynamic changes beyond IC-mediated autoimmune diseases and may contain terminal sialic acid, galactose or N-acetyl-glucosamine residues. Although the glycan composition of IgG is known to affect binding to FcγRs and complement sensor proteins, it also seems to drastically influence this newly discovered dectin-1–mediated regulation pathway. Notably, Karsten et al. showed that agalactosylated or low-galactosylated ICs completely lost the ability to inhibit C5a-induced inflammation both in vitro and in vivo mouse models of autoimmune disease. Furthermore, high galactosylated ICs had no inhibitory effect in dectin-1–deficient mice. This finding is particularly surprising, as dectin-1 has not been associated with binding of Fc glycans. Also, this mechanism is apparently highly cooperative, as IgG1-ICs did not bind dectin-1 in the absence of FcγRIIB, yet dectin-1 seems to be decisive to distinguishing between galactosylation states and essential for inhibiting C5aR signaling. Although the processes defining glycan composition and remodeling are not yet fully resolved, it is evident that they are important in pathophysiological processes. Under physiological conditions, 25–30% of Fc glycans are agalactosylated, but this percentage substantially increases in autoimmune conditions such as rheumatoid arthritis or systemic lupus erythematosus. The presence of galactose residues may evoke a regulatory loop that brakes C5a-induced inflammation before a switch to an agalactosylated form. It would be interesting to explore whether complement–humoral immunity crosstalk is involved in this process, which controls glycation in the Golgi during IgG secretion. An additional regulatory mechanism dependent on Fc-glycan composition implicates an interaction between sialylated IgG and another C-type lectin receptor, SIGNR-1, which culminates in an upregulation of the inhibitory FcγRIIB on effector macrophages. Notably, whereas an inflammatory microenvironment is associated with the induction of desialylated IgG, tolerogenic conditions result in the production of immunosuppressive sialylated IgGs by plasma cells. Together, these distinct mechanisms may partially explain the anti-inflammatory effect of intravenous immunoglobulin (IVIG) used as treatment for inflammation in several autoimmune disorders.

The findings of Karsten et al. impressively illustrate the complexity of crosstalk mechanisms between complement and other systems; they also offer new mechanistic insights into the regulation of inflammatory diseases that reach beyond IC-mediated autoimmune diseases and may also apply to other disorders. Finally, they offer valuable information to be considered in the development of new therapeutic approaches using glycol-engineered IVIG.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.