The role of complement activation in IL-1 production has a long history; the role of complement products function as danger signals, inflammatory cytokines, and chemotactic molecules for innate immune response activation. The article also considers a role for C3a in interleukin-1β (IL-1β) processing and release via caspase-1 activation. In this issue of Blood, Asgari et al report that engagement of the C3a receptor triggers interleukin-1β (IL-1β) processing and release via caspase-1 activation. The role of complement activation in IL-1 production has a long history; complement products function as “alarmins” during innate responses. For many years before the term “innate immune response” was coined, it was fully understood that a highly nonspecific event such as activation of complement would induce a highly nonspecific molecule such as IL-1; these 2 linked processes would then affect a highly specific event such antigen-driven lymphocyte activation, for example, polarization to a T helper 1 (Th1) or a Th17 response. In this issue, investigators link the generation of C3a to playing a role in the activation of caspase-1. A unique and unexpected finding of the study is that engagement of the C3a receptor results in phosphorylation of extracellular signal-regulated kinase-1 and 2 (ERK-1/2), which promotes the efflux of adenosine triphosphate (ATP) from the macrophage. Release of ATP is a rate-limiting step for activating caspase-1, as extracellular ATP triggers the P2X7 purinergic receptor to initiate oligomerization of NLRP3.1

In the present study, the authors study IL-1β as a cofactor in immune responses, very much as IL-1 was studied as a cofactor for the production of IL-2. Engagement of the C3a receptor enhances the production of IL-17; that IL-1β enhances the production of IL-17 is hardly a new finding. If C3a enhances lipopolysaccharide (LPS)-induced secretion of IL-1β, it is no surprise that IL-17 is similarly increased by C3aR engagement. The production of IL-1β was studied from fresh human blood monocytes stimulated with LPS, and the authors correctly point out that fresh human monocytes will release IL-1β when stimulated with LPS whereas macrophages and dendritic cells require a second signal such as a high concentration of ATP. This important difference between circulating blood monocytes and a monocyte-derived macrophage or dendritic cells was first reported in a previous issue of Blood.5 So what is new?

The study then turns to a clinical issue: acute rejection of renal transplants. Successful kidney transplants change the lives of many with end-stage kidney disease, liberating them from the yoke of chronic hemodialysis. As with all transplanted organs, suppression needs to be carefully adjusted and increased with the early signs of rejection. The study compared the presence of C3a using immunohistochemistry of paraffin sections of kidney biopsies from healthy subjects with those from transplants. Indeed, they found large numbers of CD4+ lymphocytes expressing IL-17 in the vicinity of macrophages and tubular epithelial cells expressing C3a. The study concludes that “all the players” are present in acute renal rejection and, moreover, that C3a is an alarmin as a danger-associated molecular pattern.

The article also considers a role for C3a in the generation of ATP; indeed, oxidized ATP reduced IL-1β secretion by 50%. Is this new? In terms of a role for C3aR engagement, yes, but not unexpected as nearly all studies in which one adds oxidized ATP to human monocytes stimulated with LPS reduce IL-1β secretion.5 However, the present study does make an unexpected observation and that is the role of the pannexin-1 hemichannel for the efflux of ATP by engagement of C3aR. One may recall another role for this channel in macrophages that produce IL-1β upon

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stimulation with LPS in the absence of Toll-like receptor 4 (TLR4). However, in additional experiments, the study demonstrates that C3a activation in macrophages and dendritic cells results in phosphorylation of the ERK-1/2 and that efflux of ATP is dependent on phosphorylation of ERK-1/2 but which is independent of pannexin-1.

What is missing? Complement activation is unquestionably one of the first steps in sterile inflammation. Although demonstrating that the role of C3a is a welcomed contribution to understanding the inflammatory component of acute rejection, why use LPS as the activator of the monocyte/macrophage or the dendritic cell when there is no LPS involved in rejection? Whereas deletion of TLR4 in mice reduces disease severity, all TLRs share with IL-1 receptors is the intracellular Toll–IL-1 receptor domain, which activates MyD88 for the TLRs as well as the IL-1 receptor. The Asgari study would have had a greater and broader relevance if the authors had used IL-1α as the stimulant for IL-1β production rather than LPS, as the precursor of IL-1α is released readily at the same time of complement activation, is active as a precursor, and causes sterile inflammation in the absence of TLR signaling.

Moreover, there is no dearth of the IL-1α precursor in renal epithelial cells. In fact, the relevant “cocktail” for induction of IL-17 would be anti-CD3/CD28 in the presence of IL-1α and engagement of C3aR. The evidence that “autoinflammation” means IL-1 induction of IL-1 can be found in the downregulation of caspase-1 in monocytes of patients treated with anakinra. Anakinra, which blocks both IL-1α and IL-1β, would be the clinical lesson from the Asgari study in order to reduce renal allograft rejection.

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Comment on Monnereau et al, page 3492

Shedding light on UVR and Hodgkin lymphoma

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In this issue of Blood, Monnereau and colleagues pool 4 retrospective (case-control), observational epidemiologic studies to demonstrate an inverse association between UV radiation (UVR) exposure and risk of developing Hodgkin lymphoma (HL).

In recent years there has been considerable interest in the investigation of UVR and lymphoid malignancies. Most of the research has focused on non-HL, with initially conflicting data ultimately yielding to generally consistent inverse associations, although the biological mechanism underlying the relation is unclear. Fewer investigations have considered a potential association between UVR and HL, likely due in part to the relative rarity of the disease. However, in this issue of Blood, Monnereau et al advance the field by pooling data from 4 case-control studies of HL conducted in Europe, reporting that UVR is associated with reduced risk of HL, particularly Epstein-Barr virus (EBV)-positive HL (pooled odds ratio = 0.56, 95% confidence interval 0.35-0.91 for the highest vs lowest UVR exposure).

Pooling data across epidemiologic studies has key strengths and weaknesses that merit discussion. The main advantage lies in the large sample size, particularly for investigation of disease or patient subgroups. Additionally, pooled studies use individual-level data, which, unlike meta-analyses, allow exposure variables in each study to be redefined to a common scale. On the other hand, as Monnereau et al acknowledge, these harmonized variables may in fact obscure variability in exposure definitions arising from differences in the wording and structure of study questionnaires. More importantly, the detailed exposure characterization that may make an individual study so valuable is unlikely to be similar across studies, so the range of exposure variables that can be considered in a pooled analysis is often limited.

Monnereau et al leveraged the strengths of a pooled analysis to provide the first investigation of personal history of UVR exposure and HL according to disease subtype, taking into account HL histology as well as tumor EBV status. Interestingly, the data suggest that the inverse association may be stronger for EBV-positive than EBV-negative tumors. Although the finding requires confirmation, evidence for etiologic heterogeneity within HL has accumulated.
The C3a receptor, caspase-1, and release of IL-1β

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