partially inhibited adhesion whereas β2 integrin–mediated adhesion to intercellular cell adhesion molecule 1 (ICAM-1) or fibrinogen was strongly inhibited.4 Talin-1 knockout strongly inhibited adhesion on all 3 ligands. Assessing integrin activation state with conformation–specific antibodies supports the adhesion assay results. Thus, although both β1 and β2 integrin–mediated neutrophil adhesion is talin dependent, only β2 integrin adhesion is strongly RIAM dependent. Likewise, T-cell adhesion to VCAM-1 is largely independent of RIAM. This may be due to compensation for RIAM deficiency due to impaired platelet function or on activation of the platelet integrin αIIbβ3 as assessed using reporter antibodies.3 Thus, there is considerable integrin and cell-type specificity in the requirement of RIAM for integrin activation and, even when expressed in the same cell, β2 integrins are more dependent on RIAM than β1 integrins. This latter result, along with expression profiling, shows that the differential responses are not due to compensation for RIAM deficiency by expression of the related family member lamellipodin.

The work of Klapproth et al10 and Su et al8 highlights areas requiring further study to provide a complete understanding of control of integrin activation. Their data strongly suggest that RIAM-independent talin activation occurs in many or most adherent cell types (supporting normal development in the RIAM-null mouse) and in platelets. The existence of alternative talin activation methods was already appreciated11; indeed, vinculin competes with RIAM for binding to talin rod and is implicated as an alternative talin activator in mature adhesions.7 However, it is notable that Rap1-null platelets exhibit adhesion defects under conditions where none are evident in RIAM-deficient platelets.5,8,10 Another Rap1 effector, RAPL, has been implicated in integrin function but, like RIAM-null mice, RAPL–null mice exhibit leukocyte adhesion deficiencies and no platelet defects have been reported.13 This suggests that additional Rap-dependent talin activation pathways remain to be discovered. Furthermore, how RAPL– and RIAM-mediated signals are integrated in leukocytes is currently unclear. Another major question is the mechanism of specificity in integrin activation. Most integrins require talin but RIAM is selectively important for β2 integrins and to a lesser extent for β1 integrins. The basis for this is unknown although Klapproth et al10 suggest the possibility of differential integrin localization in specific membrane compartments. Altogether, these recent findings validate the in vivo role of Rap1–RIAM in talin-mediated β2 integrin activation. Moreover, they illustrate that although talin is a common final step in integrin activation, pathways upstream of talin appear to be integrin specific, allowing for the fine tissue-specific tuning of integrin-mediated adhesion.

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Comment on Bagaitkar et al, page 2724

To stimulate the phagocytes

Niels Borregaard University of Copenhagen

“There is at bottom only one genuinely scientific treatment for all diseases, and that is to stimulate the phagocytes.” We have come a long way since this declaration by Sir Ralph Bloomfield Bonington in George Bernard Shaw’s 1906 play, The Doctor’s Dilemma. Stimulation of phagocytes is even more relevant for understanding the process of inflammation now, over 100 years later, as knowledge of pro-and anti-inflammatory cytokines and macrophage polarization in infectious and inflammatory diseases and cancer has expanded. In this issue of Blood, Bagaitkar et al add further to the understanding of how inflammation is controlled.1

Inflammation is the body’s response to infection and may cause extensive destruction of tissue whether evoked by infection (such as by Mycobacterium tuberculosis) or whether no infectious organism has (yet) been identified as inducing inflammation.
MSU crystals injected i.p. are taken up by macrophages and induce secretion of IL-1α. IL-1α stimulates production of G-CSF (here by fibroblasts and endothelial cells), which causes release of neutrophils from bone marrow to blood and further to tissue. NADPH oxidase (Phox), a normal constituent of macrophages (and neutrophils), reduces the amount of IL-1α secreted from macrophages; consequently, it reduces the production of G-CSF and the mobilization of neutrophils from bone marrow and their recruitment to the site of inflammation, where they may activate macrophages further. Professional illustration by Patrick Lane, ScEyEnce Studios.

(such as in rheumatoid arthritis and inflammatory bowel diseases).

Chronic granulomatous disease (CGD) is a severe inherited immunodeficiency that in its classic forms is caused by mutations in 1 of 4 components that together with a fifth component, p47phox, constitute the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase of activated phagocytes.2 NADPH oxidase consumes oxygen for the delivery of 1 electron to reduce molecular oxygen to the superoxide anion; from this, other reactive oxygen derivatives are formed depending on cell type. In CGD, NADPH oxidase cannot be assembled. The clinical picture is characterized by a profound, but quite narrow, deficiency of microbial killing and by an exaggerated inflammatory response in the form of granuloma and inflammatory bowel disease. Recently, an important aspect of how inflammation is controlled by NADPH oxidase activity was discovered by Campbell et al, who demonstrated that the mere consumption of oxygen by NADPH oxidase causes activation of hypoxia-inducible factor 1 in epithelial cells during inflammation of the gut. This drives a protective response that dampens inflammation and tissue destruction.3

In this issue, Bagaitkar et al demonstrate that the NADPH oxidase inhibits macrophage activation and recruitment of neutrophils in a mouse model of sterile inflammation elicited by intraperitoneal (i.p.) injection of monosodium urate (MSU) crystals, well known to cause painful inflammation in gout.1 Activation of macrophages is driven by recognition of pathogen-associated molecular patterns (PAMPs) or damage (or danger)-associated molecular patterns (DAMPs). PAMPs are structures shared by classes of pathogens, an archetype of which is lipopolysaccharide from gram-negative bacteria, and are recognized largely by Toll-like receptors. DAMPs are structures liberated by tissue damage, such as adenosine triphosphate, DNA, and, as here, uric acid, and sensed by intracellular NLRP3. This leads to formation of a structure called the inflammasome. As the name implies, this is central to inflammation. An intracellular protease, caspase-1, is recruited to the inflammasome, is activated, and converts proinflammatory cytokines, primarily interleukins 1β and 18 (IL-1β and IL-18), from inactive to active proteins that are then secreted and are central activators of inflammation.5

IL-1β has a cousin, IL-1α. They both bind the same receptor on the surface of cells, but in contrast to IL-1β, IL-1α also works intracellularly in the nucleus to control gene expression and does not need processing by caspase-1 to be active.5 It is well established that IL-1α mediates recruitment of neutrophils to sites where DAMPs are generated (eg, from necrotic cells injected i.p.).6

Bagaitkar et al make a very fruitful connection between the exaggerated inflammation in CGD and DAMP-induced inflammation and ask whether NADPH oxidase controls DAMP-induced inflammation. Indeed it does. A CGD mouse has an exaggerated inflammatory response to uric acid crystals or necrotic cells injected into the peritoneum, recruiting double the number of neutrophils into blood and from there into the peritoneum, compared with wild-type (WT) mice. The increased influx of neutrophils is solely a consequence of enhanced mobilization of neutrophils from the bone marrow by elevated levels of granulocyte colony-stimulating factor (G-CSF); this is caused by elevated levels of IL-1α and could be eliminated by antibody preventing IL-1α from binding to its receptor (see figure). In contrast to IL-1β, IL-1α is expressed by many cells in addition to macrophages, but the elevated levels of IL-1α in the CGD mouse originate from macrophages, as nicely demonstrated by studies of chimeric mice, that is, WT mice transplanted with bone marrow from CGD mice and allowed to repopulate tissue with macrophages from the CGD bone marrow. An important additional observation made was that depletion of CGD neutrophils (antibody mediated) reduced the number of activated macrophages in the peritoneum after DAMP challenge. This demonstrates that a cycle exists between macrophages and neutrophils to propagate inflammation if not dampened by NADPH oxidase.

This study makes us reexamine the control of inflammation, especially in CGD patients. It raises the question of why the inability to assemble NADPH oxidase leads to more secretion of IL-1α.

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Comment on Kapur et al, page 2747

TRALI: hit by CRP

Karina Yazdanbakhsh NEW YORK BLOOD CENTER

In this issue of Blood, Kapur et al identify the acute-phase protein C-reactive protein (CRP), a general biomarker for infection and inflammation, as a potent mediator of antibody-dependent transfusion-related acute lung injury (TRALI). This study provides a novel and direct link between inflammation and TRALI, opening doors for possible new approaches in targeting TRALI.

TRALI is a syndrome characterized by acute respiratory distress resulting in acute lung injury within 6 hours upon blood transfusion. In the majority of the cases, antibodies against HLA and/or human neutrophil antigen (HNA) present in the transfused product are thought to be responsible for initiating TRALI. The implementation of TRALI mitigating strategies, such as the use of male-only transfused blood products, has decreased the incidence of antibody-mediated TRALI, however, TRALI still remains the leading cause of transfusion-related mortality and is thus an important clinical problem. Generally, TRALI is assumed to result from 2 hits, the first hit being caused by the underlying clinical condition of the patient, whereas the second hit occurs when the antibodies or factors are transferred to the recipient during the transfusion. The pathogenesis is still poorly understood but several cellular processes have been described such as neutrophil activation, pulmonary endothelial barrier function disruption, and the involvement of monocytes.

In addition, several TRALI risk factors have been described in recipients which include increased levels of interleukin-8 (IL-8), liver surgery, chronic alcohol abuse, shock, higher peak airway pressure while being mechanically ventilated, smoking, and positive intravascular fluid balance. In a prepost study, IL-6 and IL-8 were found to be elevated before and after transfusion in patients with TRALI. These studies clearly identify systemic inflammation as a major risk factor for developing TRALI.

In the current study, Kapur et al provide further support for inflammation as a prerequisite for antibody-mediated TRALI and offer novel insights into TRALI pathogenesis by linking CRP to increased risk of antibody-mediated TRALI induction. CRP is an acute-phase protein, produced in the liver, and is clinically regarded as a general biomarker for acute inflammation and infections. As CRP levels increase rapidly during inflammation, and because inflammation is a risk factor for TRALI, the role of CRP in antibody-mediated TRALI was investigated. The authors used a BALB/c mouse model for TRALI which is based on injection of the anti-major histocompatibility complex (MHC) class I antibody, 34-1-2s; BALB/c mice are known to be resistant to TRALI, unless primed with the gram-negative bacterial endotoxin lipopolysaccharide (LPS). The authors did