required for the homing of T progenitors. The longer-term increase observed in ETPs in KGF-treated mice may reflect an increase in the TEC niches that bind ETPs, resulting in a sustained increase in thymic productivity after the initial "wave" of thymopoiesis had passed.

Finally, the authors have begun to explore the pathways of KGF signaling in TECs. KGF increased expression of transcripts of Wnt glycoproteins and bone morphogenic proteins (BMPs) in TECs. Furthermore, in mice with knock outs of Smad4, which blocks the BMP signaling pathway, KGF did not produce an increase in thymic cellularity. These studies hold the promise of a deeper understanding of the mechanisms of KGF action on thymopoiesis.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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Comment on Nedvetzki et al, page 3776

Control LPS or get killed

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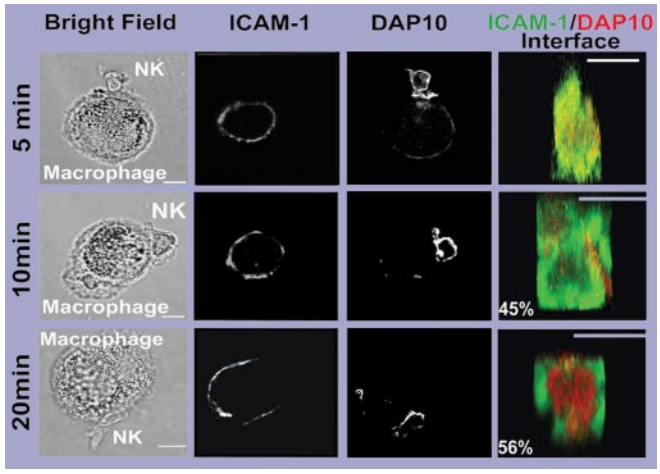
In this issue of *Blood,* Nedvetzki and colleagues demonstrate functional crosstalk between NK cells and macrophages; the outcome of these interactions is dependent on the extent of LPS stimulation.

Initially, natural killer (NK) cells were considered to be innate immune effectors capable of eliminating tumors or virus-infected cells. The detection of malignant or virus-infected cells is mediated by a range of different surface NK receptors that either inhibit or activate NK-cell functions.[1] Recently, emerging evidence also attributed to NK cells an important function in the initiation and modulation of immune responses.[2] In this context, the cellular crosstalk between NK cells and myeloid cells is of considerable interest, as it potentially shapes subsequent immune responses. Several studies have shown evidence for NK-cell–dendritic-cell (DC) crosstalk resulting in activation, cytokine production, NK-cell proliferation, and DC maturation.[2] Of interest, in vitro, NK cells also kill autologous immature, but not mature, DCs, and this might maximize the efficiency of antigen presentation.

Nedvetzki and colleagues, in the current issue of *Blood,* further extend the possible immune-regulatory role of human NK cells by examining their interactions with macrophages. They show, using a series of elegant experiments, that macrophages, via the engagement of 2B4, activate NK-cell proliferation and cytokine secretion and increase NK-cell cytotoxicity against susceptible target cells. On the other hand, the authors demonstrate that NK cells control macrophage activity, by NKG2D-dependent killing of macrophages stimulated by high doses of LPS. In this regard, it will be interesting to test whether other TLR stimulations will induce human NKG2D ligand expression and, consequently, killing by NK cells. Finally, using macrophages or macrophages stimulated with LPS, the authors demonstrate that the distinct functions of NK-cell–macrophage interactions are translated into different structures of immune synapses (see figure).

Nedvetzki and colleagues demonstrate functional interactions between NK cells and macrophages. Where, in vivo, could such interactions occur? One possible place is the site of inflammation, where cytokines and chemokines produced by resident macrophages or other cell types could attract NK cells. In such a case, the interactions between NK cells and macrophages could prime NK-cell effector functions in the inflamed tissue. It is also possible that macrophages play a role in recruiting NK cells to lymph nodes, as previously demonstrated for DCs.[2] Developing in vivo techniques to image NK-cell–macrophage interaction will probably lead to a better understanding of the importance of NK-cell–macrophage crosstalk.

Another issue to consider is when macrophages need to be killed. It is tempting to speculate that NK-cell–mediated killing of macrophages is important during chronic inflammatory reaction when the macrophage activity needs to be stopped, to prevent, for example, septic shock. The macrophage-mediated killing by NK cells might also be important in eliminating macrophages infected with pathogens such as *Mycobacterium tuberculosis.* In those situations, LPS-induced expression of NK-cell–activating ligands may aid in the elimination of macrophages exposed to, or infected by, the pathogens.



Two distinct NK-cell–activating immune synapses. See the complete figure in the article beginning on page 3776.

Finally, several reports have recently demonstrated that NK cells, themselves, might also serve as antigen-presenting cells (APCs).[3] These observations, together with the results of Nedvetzki and colleagues and the accumulating evidence demonstrating interactions between NK cells and DCs,[4] suggest a possible APC network communication. Such a communication might be used, for example, to transfer peptides from one APC to another, for presentation to T cells. It will be interesting to test whether B cells, which can also serve as APCs, might directly interact with NK cells.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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Comment on Florey et al, page 3881

FcγRs join in the cascade

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A growing body of evidence indicates that neutrophil FcγRs support adhesion to immune complexes (ICs) under shear flow conditions. In this issue of *Blood,* Florey and colleagues report that both FcγRIIA (CD32) and FcγRIIIB (CD16) on human neutrophils can mediate adhesion to human IgG–coated vascular endothelial cells under in vitro shear flow conditions and exhibit differential requirements for endothelial accessory molecules of the classical multistep adhesion cascade.

Neutrophil recruitment to sites of infection or injury is widely held to occur by a multistep adhesion cascade leading to stable leukocyte adhesion to endothelium. Treatment of cultured endothelium with inflammatory cytokines (eg, TNF-α, IL-1β, LPS) triggers expression of adhesion molecules and chemokines that promote significant leukocyte adhesion and transmigration. The first step in adhesion (initial attachment and rolling) is mediated by members of the selectin family of adhesion molecules (E-, P-, and L-selectin).[1] The second step, firm adhesion, requires activation of leukocyte β2 integrins and their engagement of endothelial-cell counterreceptors ICAM-1 and ICAM-2.[2] The β2 integrins also contribute to the deceleration of leukocyte rolling, which may facilitate firm adhesion. Integrin activation is mediated by chemoattractants and chemokines presented on the endothelial-cell surface. Transmigration is the final step and involves multiple adhesion molecules including β2-integrin, ICAM-1, PECAM-1, and CD99.[3]

In systemic immunologic diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis, high levels of circulating self-reacting antibodies form ICs, deposit in tissues and organs, and trigger sustained recruitment of neutrophils (reviewed in Firestein[4]). Accordingly, effort has been placed on elucidating the mechanisms underlying IC-mediated neutrophil recruitment in order to create effective therapeutics, which begs the question whether IC-dependent mechanism(s) share components of the multistep cascade. Neutrophil interaction with ICs is mediated by 2 low-affinity receptors, FcγRIIA and FcγRIIIB. Coxon et al were the first to demonstrate a primary role for FcγRIIIB in capture and adhesion of human neutrophils to immobilized rabbit IgG containing ICs (2.0 dynes/cm^2) in the absence of adhesion molecules that mediate attachment (ie, selectins).[5] They further found that β2 integrins mediated shear-resistant adhesion to ICs. Recently, Skilbeck et al reported that human neutrophil adhesion and subsequent spreading on immobilized human IgG required FcγRIIIB, with a lesser role by FcγRIIA for adhesion, and that stable adhesion and spreading was β2 integrin dependent[6]; however adhesion occurred only at very low shear stress (0.5 dynes/cm^2). These authors also suggested that the role of FcγRIIIB versus FcγRIIA was due to species differences in the IgG because adhesion to human IgG was FcγRIIA and FcγRIIIB dependent, whereas adhesion to rabbit IgG was solely FcγRIIIB dependent. In vivo, IC deposition within the vasculature resulted in rapid FcγRIII-dependent neutrophil recruitment in mice[5,7]; albeit the relative contribution of the human receptors in vivo is not clear because murine neutrophils express a transmembrane form of FcγRIIIB that requires a signaling gamma subunit (FcγRIIIB), while human neutrophils express a GPI-linked FcγRIIIB and the single subunit FcγRIIA. FcγRs were also required for slow rolling through P-selectin and enhanced adhesion in the context of P-selectin and intravascular IC deposition.[7] On the other hand, IC formation primarily in tissues resulted in endothelial-cell activation, which led to neutrophil recruitment that was dependent on many of the traditional players in neutrophil trafficking, including endothelial selectins and VCAM-1.[8]

The current report by Florey and colleagues extends the field by introducing a new model that contains endothelial monolayers coated with SLE patient IgG or ICs in an in vitro flow model. The key observation was that SLE patient IgG-coated human microvascular endothelial cells (HMECs) supported neutrophil adhesion and that adhesion depended on (1) the HMEC activation status (ie, TNF-α activation), and (2) whether HMECs were coated with IgG or ICs. The authors report that the IgG-coated HMECs provoked enhanced neutrophil adhesion under shear flow only if HMECs were preactivated with TNF-α, and that this augmented adhesion was dependent solely on FcγRIIA and not FcγRIIIB, and required E-selectin, leukocyte β2 integrin, and CXCL1/2 (IL-8R). A role for FcγRIIIB-dependent neutrophil adhesion was detected for IC-coated unstimulated HMECs expressing E-selectin, suggesting a prerequisite for selectin-mediated capture. High-density immobilized ICs also supported neutrophil adhesion as previously described.[5] The take-home message is that both FcγRIIA and FcγRIIIB can mediate adhesion to ICs under flow but that FcγRIIA has a specialized nonredundant ability to augment neutrophil adhesion to monomeric IgG-coated HMECs and to promote stable adhesion by β2 integrins under shear flow, while FcγRIIIB predominates in