IMMUNOBIOLOGY

Comment on Bartz et al, page 4102

Career choices of monocytes in dangerous times

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Monocytes can differentiate into a number of end-stage effector cells. In this issue of *Blood*, Bartz and colleagues show that danger signals via toll-like receptors (TLRs) drive monocytes to differentiate into macrophages and prevent them from becoming dendritic cells, through the up-regulation of suppressor of cytokine signaling (SOCS) proteins.

Cells of the innate immune system recognize infectious organisms through pattern recognition receptors that include members of the TLR family. Many hematopoietic progenitors, including hematopoietic stem cells, express TLRs, and their ligation can direct the differentiation of these cells into various lineages.[1] As precursor cells in the innate immune system, monocytes are of particular interest in this regard: they can differentiate into phagocytic macrophages, an important immediate defense against bacteria, or into dendritic cells (DCs), the most potent professional antigen-presenting cells that orchestrate adaptive immune responses. This switch may play an important role in host defense. For example, monocytes from patients with progressive, systemic leprosy become primarily macrophages, whereas monocytes from patients with limited disease become DCs as well as macrophages.[2]

Cytokines, particularly granulocyte-macrophage colony-stimulating factor (GM-CSF), are key drivers of the developmental switch of monocytes into DCs. The study by Bartz and colleagues offers mechanistic insights into this switch, showing that TLR signals override GM-CSF signaling and prevent DC maturation. This switch appears to operate through the induction of SOCS family proteins, which are increased after TLR ligation. Overexpression of SOCS1 also blocks GM-CSF signaling and prevents DC maturation.

There are a few important caveats to these conclusions. This work was performed in vitro, and there is no direct evidence yet that this mechanism pertains in vivo. Forced overexpression of SOCS proteins may have nonspecific effects that could limit the interpretation of these results. But the findings suggest a mechanism of how danger signals[3] influence the functional development of immune cells for short-term versus long-term defense. During an ongoing infection, microbial products alert the immune system to immediate danger, increasing the number of macrophages that can phagocytose the invaders, at the expense of DCs. This mechanism could help explain why patients with sepsis are immunodeficient, and may suggest differential strategies for modulating or amplifying immune responses depending on whether the immune system is responding to an active infection or preparing for a future one.

The author declares no competing financial interests. ■

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HEMOSTASIS

Comment on Pula et al, page 4035

Uncovering the dark side of PKCδ

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In this issue of *Blood*, Pula and colleagues provide a novel mechanism for the negative regulatory role of platelet protein kinase C δ (PKCδ) that is independent of inside-out signaling, granular secretion, or early steps of GPVI signaling.

The initial step of agonist-induced platelet activation is platelet shape change, which is associated with intracellular calcium rise, phosphorylation of pleckstrin by PKC, and myosin light chain (MLC) by MLC kinase, followed by cytoskeletal rearrangement. Human platelets predominantly express 4 of the 12 known PKC isoforms.[1] Although PKCα, β, and θ have been shown to positively regulate platelet activation, PKCδ is unique in that it plays a positive as well as a negative regulatory role.[2,3]

In this issue, Pula and colleagues provide convincing evidence regarding the negative role of PKCδ in platelet aggregation and reveal a novel mechanism for regulation of actin and filopodia. Filopodia are membranous protrusions formed and supported by bundles of actin filaments and are followed by lamellipodia formation leading to platelet spreading.[4] Vasodilator-stimulated phosphoprotein (VASP) regulates actin polymerization and hence filopodia formation primarily through its anticapping activity. VASP is a major substrate of protein kinase A, protein kinase G, and PKC, which phosphorylate it on Ser157, Ser239, and Thr278. Phosphorylation of VASP on Ser157 is required for its anticapping activity.[5]

In previous studies using pharmacological agents, it was suggested that PKCδ negatively regulates collagen-induced dense granule secretion.[3] Using PKCδ knockout mice, Pula and colleagues show that negative regulation of platelet aggregation by PKCδ is independent of inside-out signaling, dense granule secretion, and early GPVI signaling. They also provide evidence that PKCδ physically interacts with VASP and inhibits VASP phosphorylation on Ser157 by classical PKC (cPKC) isoforms, thus suppressing actin polymerization and filopodia formation. The fact that cPKCs' ability to phosphorylate other platelet proteins is unaffected by the inhibition or absence of PKCδ suggests that PKCδ does not directly inhibit the activity of these enzymes. This workundoubtedly provides provocative