Toll-like receptor signaling mechanisms in hostile neutrophils. Focus on “Bone marrow MyD88 signaling modulates neutrophil function and ischemic myocardial injury”

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More than three decades of research have demonstrated that circulating leukocytes can be trapped under a variety of conditions in the microcirculation, including the myocardial microcirculation. Such entrapment may occur as a consequence of the activation of the innate immune reaction to an infection and it can also occur in the absence of overt infections. When activated, leukocytes can be readily trapped in the capillary network and also, though less frequently, can attach to endothelium in the arterioles. For example, when leukocytes or endothelial cells form pseudopods, when they express membrane adhesion molecules, or when platelets may adhere to capillary endothelium (e.g., at cell junctions), or when the pressure drop across the capillary network is reduced, leukocytes can become trapped in capillaries. In the process, leukocytes obstruct such capillaries (“capillary plugging”), giving rise to the capillary “no-reflow” phenomenon. In addition, one of the most frequent forms of leukocytes entrapment in the microcirculation is attachment to post-capillary venules, e.g., via a P-selectin rolling mechanisms and/or an ICAM-1-CD11/CD18 membrane attachment and activation mechanism. Multiple regulatory mechanisms have been identified that control the initial attachment of the leukocytes to the endothelium as well as the subsequent steps that lead to the spreading on the endothelium and the migration across the endothelial cells and basement membrane into the interstitial space.

One of these regulatory mechanisms is the family of Toll-like receptors (TLR). For example, TLR-4-deficient mice have reduced neutrophil infiltration into the myocardial microcirculation after ischemia and reperfusion and are partially protected from myocardial injury (1). Myeloid differentiation factor 88 (MyD88) is one of four known adapter molecules (in addition to Trif, TIRAP, and TRAM) that signal NF-κB activation and therefore have a direct effect on several neutrophil responses to bacterial infection and inflammatory responses. MyD88 is critical for neutrophil migration and chemokine receptor expression. The study by Dr. Feng (5) and her colleagues in this issue of American Journal of Physiology-Cell Physiology continues their fascinating line of investigations (4) that have focused predominantly on MyD88 signaling, and in particular bone marrow-derived circulating cells expressing MyD88. Using a combination of MyD88−/− mice and chimeric mice deficient of MyD88 in their bone marrow-derived circulating cells but with normal MyD88 expression in the heart, the authors demonstrate that this signaling pathway has a direct effect on infarct size in acute ischemia-reperfusion. MyD88−/− mice exhibit reduced migration into the peritoneum together with reduced CXCR2 levels in vivo (less in vitro), chemokine KC (a ligand for CXCR2) and IL-6 cytokine levels in lavage fluid, but otherwise a mixed picture. MyD88 deficiency leads to a reduction in neutrophil chemokine receptor (CXCR2) expression and impaired neutrophil migratory function. MyD88 signaling controls neutrophil migration by maintaining neutrophil CXCR2 expression. In contrast, Toll-interleukin-1 receptor (TIR)-domain-containing adaptor protein-inducing interferon-β-mediated transcription factor (Trif), another innate immune adaptor also capable of inducing chemokine release, had no effect on the CXCR2 downregulation or on myocardial neutrophil recruitment in this ischemic model (Fig. 1). Figure 1. Schematic diagram of cardiac infarct size (blue region) after acute ischemia and reperfusion (I/R) and neutrophil downregulation by deletion of the Toll-like receptor 4 (TLR-4) adapter myeloid differentiation factor 88 (MyD88) globally (right top) and targeted to leukocytes only (right bottom).
reduction of myocardial injury in the ischemic heart is comparable to that seen with alternative approaches that downregulate MyD88 expression (8).

The evidence is not isolated to the ischemic heart. Blockade of MyD88 signaling is also protective in the ischemic intestine (7), the brain (13), and the liver (14). But in the kidney, both MyD88-dependent and -independent signaling pathways have been observed (11). MyD88 signaling plays a role in sepsis (3, 9, 10). In polymicrobial sepsis (by cecal ligation), renal injury depends in part on MyD88 signaling while liver injury is MyD88 independent (2). This may well have to do with the mechanism by which neutrophils become trapped in the microcirculation. Besides cytokine- or chemokine-mediated pathways, biophysical mechanisms due to reduced fluid shear stress can lead to entrapment in the microcirculation (6), endothelial reactions, and in part even specific interactions with platelets (12) that will determine to what degree leukocytes become trapped in the microcirculation. The level of proteases responsible for detachment of leukocytes from the endothelium by integrin receptor cleavage, and thus the state of leukocyte granulation and degradation, may thus contribute to the mechanisms by which MyD88 signals the entrapment and migration in ischemic tissue.

Where does this evidence stand with regard to possible future clinical utility of the translocon-associated protein (TRAP)-like protein (TLP)-MyD88 signaling pathway? Despite the double-edge action of neutrophils in acute ischemia and reperfusion, in chronic heart disease these cells are participants among perhaps more important mechanisms. But interventions directed against leukocytes in more acute situations (e.g., filtering of leukocytes from the endolymph by integrin receptor cleavage, and thus the state of leukocyte granulation and degradation, may thus contribute to the mechanisms by which MyD88 signals the entrapment and migration in ischemic tissue.

REFERENCES

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