Unfriendly Fire From Neutrophils Promiscuously Potentiates Cardiovascular Inflammation

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Polymorphonuclear leukocytes (PMNs) comprise the vast majority of white blood cells and serve as the first responders during acute inflammatory responses. These cells constitute an essential component of the innate immune response, classically conceived of as antimicrobial stews that deliver their toxic payload at the site of injury. These cells contain granules, hence their membership in the granulocyte family of leukocytes. The granules contain enzymes such as myeloperoxidase, which generates the strong oxidant hypochlorous acid, and proteinases, which degrade foreign peptides, among other functions. PMNs also possess machinery that potently produces other reactive oxygen species (ROS) such as superoxide anion. Combined with phagocytosis, the mediators elaborated by PMNs provide a bulwark of defenses to combat foreign invaders and also to aid mop up operations in injured tissues.

Yet, friendly fire from PMNs can aggravate or cause disease when these cells undergo excessive or inappropriate activation. Cardiovascular and allied conditions provide examples of the adverse consequences of collateral damage because of the unleashing of PMNs’ potent actions (Figure). The dreaded mechanical complications of myocardial infarction such as rupture of the intraventricular septum, papillary muscles, or of the ventricle itself may result, in part, from excessive extracellular matrix dissolution and extensive cell damage wrought by PMN mediators. Coronary microvascular damage caused by PMN can contribute to no reflow situations. PMNs accumulate during ischemia reperfusion in the heart, liver, lung, kidneys, and gut within minutes. In myocardial tissue, the degree of PMN infiltration directly correlates with infarct size. Experimental neutropenia in animals reduced necrosis and myocardial injury after ischemia-reperfusion.

ROS generated by tissues during ischemia lower nitric oxide activity, impairing vasodilatation, and produce further endothelial damage that releases chemokines. These chemokines attract more PMNs during reperfusion, amplifying the local inflammatory response. Degranulation of recruited PMNs leads to production of additional ROS and other mediators that can activate cell surface receptors on endothelial cells (ECs) such as Toll-like receptors (TLRs). In the pulmonary circulation, PMNs can aggravate endothelial damage, potentiate capillary leak, and thus contribute to adult respiratory distress syndrome. In the kidneys, the accumulation of PMNs can cause direct damage to the nephron. This injury results from both the burst of ROS through myeloperoxidase and tubule destruction by released proteases. Accumulation of PMNs can also obstruct the glomerular capillaries, leading to further damage. PMN-mediated damage to micro- and larger vessels contribute to many vasculitides. Moreover, humoral immune reactions to PMN granular constituents such as myeloperoxidase and proteinase 3 mediated by antineutrophil cytoplasmic antibodies can also cause vasculitis. Each of these scenarios requires recruitment of PMNs to the particular place where they play their part in pathogenesis.

Products of PMN generate neutrophil extracellular traps (NETs) implicated in venous and in arterial thrombosis. NETs consist of strands of decondensed chromatin studded with histones and antimicrobial proteins and provide a primitive defense against bacteria. NETs can also bind circulating platelets, tissue factor procoagulant, and von Willebrand factor, forming a scaffold for clot formation. Peptidyl-arginine deiminase 4, an enzyme whose action permits the unraveling of the normally tightly wound PMN DNA from histones, contributes causally to NET formation. Administration of a peptidyl-arginine deiminase 4 inhibitor reportedly reduced atheroma size in hypercholesterolemic mice after 11 weeks. We have postulated a particular role for NETs in superficial erosion, a mechanism of coronary arterial thrombosis that may have increasing importance in the statin era. Neutrophils and the innate immune receptor TLR2 coexist within human superficial erosion plaques. Engagement of TLR2 in vitro increased ROS and caused EC apoptosis. Subsequent studies have shown that flow perturbation in mouse carotid arteries promoted neutrophil accumulation and EC death. These findings augmented with TLR2 agonism and diminished with TLR2 inhibition, suggesting an important link between TLR2 engagement and the neutrophil response. Ablation of PMNs abrogated these effects.

In this issue of Circulation Research, Mittal et al propose an intriguing mechanism by which neutrophils (PMNs) arriving at the site of inflammation facilitate their migration across ECs. They show that PMNs can trigger VE-cadherin phosphorylation and adherens junctions disassembly through transient membrane potential melanatin–2–mediated Ca²⁺ signaling on ECs. ROS produced by PMNs initiate this signal supporting a new role for these pro-oxidant mediators in inflammatory cascades.
These authors build on previous study by others that demonstrated that the interaction of PMNs with ECs can trigger Ca²⁺-dependent phosphorylation of myosin light chain in ECs, leading to inter-EC gap formation and PMN transmigration. Other studies have also suggested that PMNs can use their nuclear lobes to generate gaps between ECs. Thus, a theme has emerged, which suggests that PMNs trigger their own migration across EC layers through their interactions with ECs, an innovative proposal supported by recent study by Mittal et al.¹⁵

The current body of evidence supports PMNs as an important contributor to the immune response. The study of Mittal et al.¹⁵ shows that the PMNs can facilitate their own migration across ECs through the production of ROS and engagement of the transient membrane potential melastatin-2 receptor on ECs. This initial step in the inflammatory cascade opens the doors for the arrival of additional leukocytes, including monocytes, other granulocytes, and leukocytes including B and T lymphocytes. Thus, in some acute inflammatory situations, the early actions of PMNs can pave the way for more sustained inflammation by more chronic players in innate and adaptive immune responses.⁶

Neutrophils alone may account for more morbidity and mortality than any other single cell type. Our understanding of the complex role that PMNs play continues to grow and augment appreciation that these cells have an active role in the engagement of and migration across ECs. As we gain a greater appreciation of the role of inflammation in many forms of disease, understanding these pathways should pave the way to new therapeutic strategies.

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**References**


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