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Sepsis and Coagulation

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The host response to infection is a highly complex yet well-orchestrated process that involves an elaborate array of soluble mediators (eg, components of the inflammatory and clotting cascades) and cells (eg, monocytes, neutrophils, endothelial cells, and platelets). Normally, the host response prevails in containing and eliminating the pathogenic threat. When excessive or sustained, however, the host response may ''turn on its bearer'' and lead to organ dysfunction.

Severe sepsis is invariably associated with activation of primary hemostasis (platelet response) and secondary hemostasis (soluble clotting factors). This article describes sepsis-associated changes in coagulation, discusses the putative role for these changes in pathogenesis of the sepsis syndrome, and outlines current diagnostic and therapeutic strategies.

General principles

Sepsis

Sepsis represents the systemic inflammatory response to infection. Severe sepsis is defined as sepsis associated with organ dysfunction. Severe sepsis is associated with the concomitant activation of the inflammatory and coagulation cascades. The monocyte-tissue macrophage initiates the abnormal host response. The endothelium serves to perpetuate and amplify the process. Monocytes and endothelial cells function together to defend the host against pathogen, and in the process may inflict collateral damage on the host (organ dysfunction), resulting in pathology that is not diffuse, but rather remarkably focal in its distribution.

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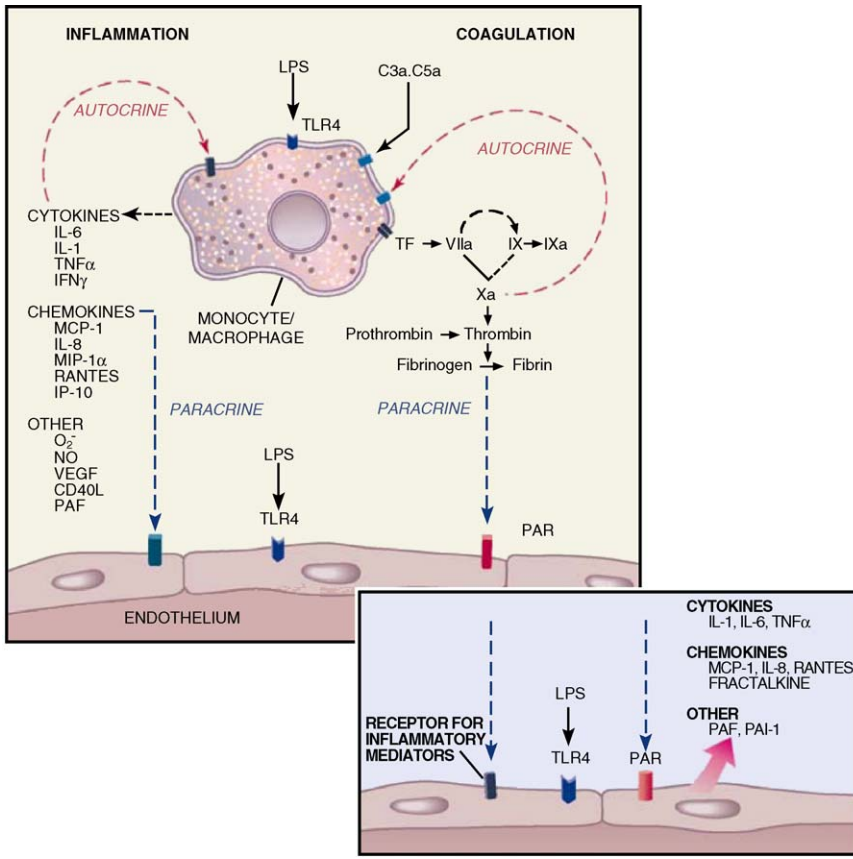

Fig. 1. The host (innate immune) response to infection. Circulating monocyte or tissue macrophage binds to LPS by TLR4, resulting in activation of inflammatory and coagulation pathways. Components of each pathway (only some of which are listed) participate in autocrine or paracrine loops to further activate the monocyte and endothelial cell, respectively. For purposes of illustration, the many receptors for the inflammatory mediators are depicted as a single generic receptor. From the perspective of the endothelium (inset), input may arrive directly by way of LPS or indirectly through monocyte-macrophage–derived paracrine signals. Endothelial output includes a variety of phenotypic changes including alterations in hemostatic balance; leukocyte trafficking; permeability; or inflammation (shown is the release of certain inflammatory mediators). IFN-ϒ, interferon-ϒ; IL, interleukin; IP-10, interferon-ϒ–inducible protein-10; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein-1α; NO, nitric oxide; PAF, platelet activating factor; PAI-1, plasminogen activator inhibitor; PAR, protease-activated receptor; RANTES, regulated on activation, normal T-cell expressed and secreted; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor. (*From* Aird WC. Targeting the endothelium in sepsis and multiorgan dysfunction. Sci Med (Phila) 2003;9:108–19; with permission.)