Septic shock: Pathophysiology

Sepsis occurs when the release of proinflammatory mediators in response to an infection exceeds the boundaries of the local environment, leading to a more generalized response. The cause is likely multifactorial and may include the direct effects of invading microorganisms or their toxic products, release of large quantities of proinflammatory mediators, and complement activation. In this context, an anti-inflammatory response may reduce the toxic effects of the excessive inflammatory response, but may also compromise effective host protection from the infection. Some individuals may be genetically susceptible to developing sepsis.

Widespread cellular injury may occur when the immune response spreads beyond the site of infection causing sepsis. Cellular injury is the precursor to organ dysfunction. The cellular injury, accompanied by the release of proinflammatory and antiinflammatory mediators, often progresses to organ dysfunction.

Pearl: Activation of **Toll-like receptor 4 (TLR4) has been postulated to be responsible for the pathogenesis of SIRS**. The pathogenesis of sepsis involves complex interaction between the host and the infecting microorganism. The innate immune system provides an immediate response against toxic insults, mediated by phagocytic cells and host-defense molecules, including pattern recognition receptors. An important pattern recognition receptor is Toll-like receptor 4 (TLR4), a transmembrane receptor that recognizes a range of ligands, including lipopolysaccharide (LPS), which is found in the cell wall of gram-negative bacteria. Activation of TLR4 has been postulated to be responsible for the pathogenesis of SIRS. Through the activation of TLR4 receptors, inflammatory cytokines are released that cause tissue damage and microvascular injury.

Question:

A 45-year-old man is intubated and mechanically ventilated because of hypoxic respiratory failure two days after undergoing open laparotomy for treatment of a ruptured appendix. Postoperatively the patient is febrile, hypotensive, tachycardic, and oliguric. Activation of which of the following receptors is the MOST likely cause of these findings?

a. β-2 adrenergic receptor
b. Endothelial protein C receptor (EPCR)
c. Protease-activated receptor 1 (PAR1)
d. Toll-like receptor 4 (TLR4)

Answer: D - Activation of Toll-like receptor 4 (TLR4) has been postulated to be responsible for the pathogenesis of SIRS