

Protecting the Endothelial Cell Barrier

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Editorial

Endothelial barrier dysfunction (EBD) is a major cause of various vascular diseases such as sepsis, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [1,2]. Current therapeutic strategies to mitigate these vascular pathologies involve administration of broad-spectrum antibiotics [3,4] and anti-cytokine antibodies [5,6] providing limited alleviation of symptoms and are clearly insufficient.

A single layer of endothelial cells (EC) lines the lumen of blood vessels forming a physical barrier between blood and tissues. This endothelial barrier regulates selective passage of various micro- and macro-molecules via either transcellular or paracellular pathways [7,8]. The paracellular pathway is regulated by a network of intercellular junction proteins and disruption of these intercellular interactions causes vascular leakage and EBD [9]. Various agonists, such as lipopolysaccharide (LPS), thrombin, cytokines, TGF β and VEGF, bind to the EC membrane and induce a complex network of signaling pathways that ultimately cause cytoskeletal remodeling, reactive oxygen and nitrogen species formation and release of pro-inflammatory cytokines leading to EBD [10,11].

Heat Shock Protein 90 (Hsp90) is an abundant molecular chaperone, essential for cell growth and survival, that regulates maturation and stability of various proteins that include several protein kinases, and transcription factors [12]. Inhibition of Hsp90 using small-molecule inhibitors have been extensively studied for their therapeutic potential in targeting cancer cells and promoting apoptosis [13-15]. Targeting Hsp90 results in destabilization and ubiquitin-mediated degradation of many client proteins thereby mimicking a multi-targeted effect on cellular signaling [16,17]. Hsp90 inhibition attenuates LPS-induced phosphorylation and activation of PI3k/Akt, ERK, Src and Rho-ROCK pathway [18-20] and also blocks NF κ B-mediated pro-inflammatory gene expression [21]. Also, Hsp90 inhibitors prolong survival, attenuated inflammation and reduced lung injury in a murine model of LPS-induced ALI/ARDS [22].

The histone deacetylases (HDAC) family consists of 18 characterized enzymes that are involved in epigenetic and non-epigenetic regulation of diverse cellular functions including transcription, cytoskeletal polymerization and signaling [23-25]. In endothelial cells, HDAC3, a class I HDAC, deacetylates and inactivates cytoplasmic endothelial nitric oxide synthase (eNOS), thus decreasing vascular function [26]. In contrast, SIRT1, a class III HDAC, deacetylates and activates eNOS, thus improving endothelium-dependent vascular function [27]. Two deacetylases, HDAC6 and SIRT2, regulate cytoskeletal microtubule disassembly [28,29]. Similar to Hsp90 inhibitors, HDAC inhibitors also reduce disease severity in animal models of inflammatory and autoimmune disease and are already used clinically in cancer [30-32]. HDAC inhibitors suppress LPS-mediated TLR4 signaling [33], eNOS mRNA and protein levels

[34,35], induce angiogenesis [36] and suppress thrombin-induced EBD [37].

Therapeutic strategies targeted against EBD have involved blocking agonist-receptor interaction, signal transduction or inflammation [38]. However, combined data from previous two decades strongly suggests that pharmacological intervention of any single target is only partly successful and a more multi-targeted and broad-spectrum approach is needed. Hsp90 and HDAC inhibitors might provide an effective way to protect the endothelial cell barrier and EBD.

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