Unravelling molecular and biochemical dysfunction by Shiga toxin: implication for thrombotic microangiopathy in Hemolytic Uremic Syndrome

STELLINGEN

behorende bij het proefschrift

Unravelling molecular and biochemical dysfunction by Shiga toxin: implication for thrombotic microangiopathy in Hemolytic Uremic Syndrome.

Marina Morigi

- Infection with Verotoxin/ Shiga toxin-producing *E. coli* is the most common causative agent of the epidemic form of Hemolytic Uremic Syndrome, the major cause of acute renal failure in children. Endothelial injury has been recognized as the trigger event in the development of microangiopathic process.

  (This thesis)

- Shiga toxin-1 modulates *in vitro* leukocyte - endothelium interaction under flow conditions by increasing leukocyte adhesion and upregulating adhesive molecules on endothelial surface.

  (This thesis)

- Microvascular endothelial cells change their normal thromboresistant phenotype in response to Shiga toxin-1 and become thrombogenic under high shear stress, via the upregulation of endothelial adhesive proteins.

  (This thesis)

- Shiga toxin-2 via transcriptional activation mechanism mediated by NF-kB induces endothelial MCP-1 and IL-8, chemokines involved in leukocyte adhesion and transmigration.

  (This thesis)

- In response to plasma protein load glomerular podocytes reorganize actin cytoskeleton network and modulate endothelin-1 gene expression.

(This thesis)

- Podocyte is a functionally relevant target of Shiga toxin-2 that via the upregulation of endothelin gene, induces podocyte activation and cytoskeletal derangement. These changes may contribute to glomerular dysfunction in epidemic form of Hemolytic Uremic Syndrome.

(This thesis)

- Abnormal traffic of proteins through the glomerular capillary barrier has an intrinsic renal toxicity linked to their over-reabsorption by proximal tubular epithelial cells and activation of tubular-dependent pathways of interstitial inflammation.

- Stem cells from adult and embryonic sources have great therapeutic potential, but much research is still needed before their clinical use becomes commonplace.

- Bone marrow-derived mesenchymal stem cells, by virtue of their renotropic properties and tubular regenerative potential may have a role in the treatment of acute renal failure.

- Scientists of developed world may help in shaping scientific institution and training a new generation of health professional in developing countries.

THE WALL STREET JOURNAL