POSTER SESSION 1

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P173 Vascular endothelial fibrosis induced by endotoxin: characteristics, mechanism and therapeutic perspectives

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Purpose: Pathogenesis of vascular inflammatory diseases is characterized by endothelial dysfunction, including the endotoxemia-derived systemic inflammatory syndrome. Although interactions between the endotoxin and endothelial cells (ECs) evoke EC death, a significant portion of ECs are resistant to endotoxin challenge by means of the conversion of ECs into activated fibroblasts. However, the underlying mechanism that promotes the endotoxin-induced vascular endothelial fibrosis (EVEF) and its implications are not known. The activation of fibroblasts are dependent on intracellular Ca2+ concentration increases through the participation of calcium channels. However, the molecular identity of the calcium channel that mediates the Ca2+ influx during EVEF is unknown. Transient receptor potential melastatin 7 (TRPM7) is a calcium channel expressed in ECs. TRPM7 promotes fibroblasts activation inducing their characteristics. However, the role of TRPM7 in EVEF is unknown. Thus, our aim was to investigate the features of EVEF and study the role of TRPM7 as a new pharmacological target to avoid EVEF.

Methods: Primary cultures of ECs and whole blood vessels were isolated from umbilical cords from normal pregnancies, after patient’s informed consent conforms with the principles outlined in the Declaration of Helsinki.

Results: Endotoxin-challenged ECs showed an upregulation of both, fibroblast-specific proteins expression and extracellular matrix (ECM) proteins secretion, as well as a downregulation of endothelial markers, through a mechanism dependent on: ALK5/Smad2/3 and TLR4/NF-κB/NOX intracellular pathways. Furthermore, TRPM7 suppression protected ECs from the endotoxin-induced fibrogenesis. TRPM7 downregulation prevented the endotoxin-induced endothelial markers decrease and fibrotic genes increase. In addition, TRPM7 suppression abolished the endotoxin-induced increase in ECM proteins. Furthermore, the intracellular Ca2+ levels were greatly increased upon endotoxin challenge in a mechanism dependent on TRPM7 expression.

Conclusions: Endotoxin exposition is a crucial factor for inducing vascular endothelial fibrosis which perpetuates endothelial dysfunction as a maladaptive process rather than a survival mechanism for protection against LPS. Noteworthy, TRPM7 appears as a key protein involved in the mechanism underlying EVEF, emerging as a novel target for pharmacological design useful in improving current treatment against endotoxemia-derived systemic inflammation and other vascular inflammatory diseases.