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IN A MULTI-MEDIATOR INFLAMMATORY ENVIRONMENT IL-1 SIGNALING ACTS AS PARAMOUNT DRIVER OF HUMAN CORONARY ARTERY ENDOTHELIAL ACTIVATION AND ENDOTHELIAL-TO-MESENCHYMAL TRANSITION

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Introduction: Kawasaki disease (KD) is an acute systemic vasculitis of unknown etiology that affects small- and medium-sized arteries of infants and children. Using biosamples from a phase II open-label study of the interleukin 1 (IL-1) receptor antagonist (IL-1Ra) anakinra in treating IVIG-resistant Kawasaki Disease (KD) patients, we recently identified leucin-rich-α2-glycoprotein-1 (LRG-1) as known trigger of endothelial activation and cardiac re-modelling to associate with IL-1β signaling in KD.
Objectives: In the present study we aimed to assess a potential role of LRG-1 in activation of human coronary artery endothelium in context of a complex inflammatory environment as in KD.
Methods: To mimic a multi-mediator inflammatory interplay, primary human coronary artery endothelial cells (HCAECs) were treated with patients' (KD (n=8), sJIA (n=4), MIS-C (n=3)) serum conditioned medium or an inflammatory matrix (IM) from stimulated healthy control whole blood, with or without IL-1R1 (anakinra), IL-6R (tocilizumab), TNFa (adalimumab) or LRG-1 (magacizumab) neutralizing drugs or IVIGs and were analyzed for inflammatory activation or endothelial-mesenchymal transition (EndoMT) on gene expression level. IM samples (n=8), treatment naïve KD (n=10) or HC sera (n=10) were subjected to proximity extension proteomic analysis for cardiovascular and/or inflammatory markers (n=184).
Results: Proteomic analysis of KD sera (n=10) and IM (n=8) revealed elevation of 32 versus 45 inflammatory proteins, respectively, and shared 19 significantly upregulated markers. HCAEC culture with IM or patient sera resulted in inflammatory endothelial activation, which differed between KD, MIS-C and sJIA. Upon exposure to IM this was most efficiently abrogated by IL-1R1 inhibition, while particularly IL-6R and LRG-1 targeting as well as IVIG-treatment revealed no effect. However, inflammatory endothelial activation is closely linked to endothelial-to-mesenchymal transition (EndoMT), which is supported by respective signatures in our proteomic analysis of cardiovascular activation in KD sera (n=10). Among others, EndoMT can be mediated by TGFβ1-signaling. Yet, inhibition of LRG-1 as a modulator of TGFβ1-signaling did not impact EndoMT of HCAECs. Instead, particularly on the level of transition as well as mesenchymal markers, EndoMT was most consistently abrogated by IL-1R1 inhibition compared to other drugs or combinations of those.
Conclusion: While targeted LRG-1 inhibition had no effect on inflammatory HCAEC activation or EndoMT, both processes were profoundly impacted by anakinra treatment. These observations highlight a superior role of IL-1 signaling in EndoMT, particularly in context of a high-dimensional inflammatory environment, and complement our understanding of the cytokine's prominent role in context of cardiovascular inflammation, arteriosclerosis, and myocardial fibrosis.
Patient Consent: Yes, I received consent
Disclosure of Interest: None declared