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**NEU1 increases monocyte and macrophage-mediated inflammation and may act as a potential modulator of atherosclerosis**

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**Topic(s):**
Basic Science - Vascular Biology and Physiology: Leukocytes, Inflammation, Immunity

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Background: Dysregulation of cholesterol trafficking and innate immunity are considered to play central roles in the initiation and progression of atherosclerosis. The CANTOS trial recently showed an important role for IL-1β in this disease suggesting beneficial effects of the IL-1β inhibitor Canakinumab. However, a higher incidence of fatal infections was reported. Sialic acids (SA) are terminally bound sugars on the cell surface glycocalyx and regulate intercellular and intermolecular interactions in inflammatory cells. Here, we investigated the expression of SA cleaving enzyme neuraminidase-1 (NEU1) in atherosclerotic plaques and its potential role in monocytes and macrophages.

Methods and Results: We observed increased expression of NEU1 in isolated peripheral blood mononuclear cells of patients with myocardial infarction 2-4 days after insult (MI patients: +91% compared to healthy controls; P<0.01). Double staining for NEU1 and the macrophage marker CD68 on atherectomies of carotid arteries from patients with atherosclerosis revealed high expression of NEU1 in macrophages present on the intima layer, within calcified regions and within the adventitia of the plaque region.

Stimulation with IL-1β (+27%; P<0.05) and LPS (+41%; P<0.01) but not with Angiotensin II induced the expression of NEU1 in the monocytic cell line THP-1. Lentiviral NEU1-overexpression in THP-1 monocytes/macrophages enhanced formation of multinuclear cells, phagocytosis, MCP-1-stimulated chemotaxis and the expression of CD80 all indicative for polarization towards the M1 phenotype. CRISPR/Cas9-mediated knock-out of NEU1 in THP-1 cells (NEU1-KO) did not affect differentiation of monocytes to macrophages. In NEU1-KO-macrophages LPS-induced TNFa and IL-1β expression was attenuated, while oxLDL-induced cytokine expression was not affected. siRNA-mediated knock-down of NEU1 in primary human CD14+ monocytes did not affect differentiation to M1 or M2 macrophages, but reduced the expression of TNFa and IL-1β in M1 macrophages.

Conclusion: Thus, NEU1 seems to be interconnected in a positive feedback loop with LPS and IL-1β that promotes an activated and pro-inflammatory phenotype in monocytes and macrophages. The increased expression of NEU1 in atherosclerotic lesions and in circulating monocytes of patients after MI suggests that NEU1 may act as a novel modulator of inflammation in atherosclerosis, which modulates IL-1β in a more moderate way compared to the IL-1β inhibitor Canakinumab.
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