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Neutrophil activation patterns in acute coronary syndrome with intact fibrous cap - results from the OPTICO-ACS study

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Background: In up to one third of all cases, acute coronary syndrome occurs without signs of plaque rupture. Instead endothelial cell erosion is considered to be the hallmark of acute coronary syndrome with intact fibrous cap (IFC-ACS), with matrix metalloproteinase 9 (MMP9) directly linked to this pathology. The main source of MMP9 immediately after ACS are the neutrophil granulocytes. Therefore, their molecular activation patterns and subsequent MMP9 production are the objectives of the ongoing, translational OPTICO-ACS-Study, aiming to compare the mechanisms and prognosis of IFC-ACS and ACS with ruptured fibrous cap (RFC-ACS).

Methods: Local and systemic blood samples were simultaneously obtained from the site of the ACS-causing culprit lesion (LOC) using an aspiration catheter and from the systemic circulation (SYS). Using optical coherence tomography (OCT) the ACS-causing culprit lesion was characterized and two patient groups, patients with ACS caused by intact (IFC-ACS) and by ruptured fibrous cap (RFC-ACS) were compared. Each group consists of twenty patients (n=20) matched by age, gender and diabetes. Neutrophil counts and expression of activation markers were immediately quantified by whole-blood flow cytometry. Release of active MMP9 into the plasma was assessed by fluorescence-based zymography. Activation profiles of freshly isolated neutrophils, including MMP9 activity and effect on endothelial cell death, in response to toll-like receptor 2 (TLR2) stimulation was studied.

Results: Local neutrophils of patients with IFC-ACS show significantly higher expression of TLR2 in comparison to RFC-ACS neutrophils (LOC: 1866±382.1 vs. 1498±426.9; IFC-ACS vs. RFC-ACS, p=0.03). MMP9 activity is significant higher (p=0.01) in plasma obtained from the culprit site of IFC-ACS (74.1 U/ml±4.1) compared to those of RFC-ACS patients (70.0 U/ml±5.1) indicating secretion and activation of the enzyme during IFC-ACS. Importantly, in patients with IFC-ACS, TLR2-stimulation using Pam3CSK4 triggers higher activity rates of MMP9 only in neutrophils isolated directly from the culprit site (LOC), but not systemically (+27%±17.2% IFC-LOC vs. IFC-SYS; p=0.003). This effect was not observed in RFC-derived neutrophils. Inhibiting TLR2 by a monoclonal antibody, strongly reduced secretion of activated MMP9 only in the local neutrophils from IFC-ACS-patients (–54.6%±6.5% in IFC-LOC-anti-TLR2 vs. IFC-LOC-vehicle; p=0.008), but not from systemic IFC-neutrophils, nor from RFC-neutrophils. Furthermore, LOC IFC-ACS neutrophils aggravate endothelial cell death upon TLR2-activation in comparison to LOC RFC-ACS neutrophils (58.4±4.96% vs. 20±1.89%, IFC-ACS vs. RFC-ACS; p=0.0023).

Conclusion: We newly describe differential kinetics of MMP9 release by neutrophils in ACS patients with IFC versus RFC. Our data support a role of a TLR-2 activated and neutrophil-MMP9-mediated mechanism leading to endothelial cell erosion in patients with IFC-ACS.