TNF-α mediated monocyte adhesion: role of ephrinA1 as potential link to atherosclerosis

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Eph-receptors represent the largest family of receptor tyrosine kinases. Eph-receptors and their cognate ephrin-ligands are cell-surface proteins, which are able to generate bidirectional signaling. Eph/ephrin interactions are essential in a variety of processes like tumor biology and inflammation. However, the impact of Eph/ephrin-interactions in the pathophysiology of atherosclerosis is still not well understood. The aim of the present study was to investigate the involvement of the Eph/ephrin-system in the TNF-α mediated monocyte adhesion.

Human umbilical vein endothelial cells (HUVEC) were treated with TNF-α and the expression of different ephrin-ligands and Eph-receptors was analyzed on mRNA and protein level. EphrinA1 was found to be highly induced by TNF-α stimulation. This induction is mediated by NFκB, as overexpression of a constitutive active IκB mutant completely abolished the ephrinA1 induction. Previous results of our group showed an involvement of ephrinA1 in the process of monocyte adhesion to endothelial cells.

Therefore, the impact of TNF-α mediated ephrinA1 induction in monocyte adhesion was studied. The siRNA-mediated silencing of ephrinA1 in endothelial cells, leads to a reduction of monocyte adhesion to TNF-α stimulated endothelial cells. Using a Single-Cell-Force-Spectroscopy approach we could confirm these results. The detachment forces of monocytes from endothelial cells increase after TNF-α stimulation and more importantly were decreased in ephrinA1-silenced endothelial cells. The decrease in monocyte adhesion was accompanied by reduced cell-surface expression of VCAM-1 and ICAM-1 in TNF-α-stimulated and ephrinA1-silenced cells compared to control-transfected cells. Interestingly, the overall expression of VCAM-1 and ICAM-1 on mRNA and protein level was not influenced by ephrinA1 silencing. In contrast, the overexpression of ephrinA1 in endothelial cells shows contrary effects. Ephrin-A1 overexpression enhances the TNF-α mediated monocyte adhesion to endothelial cells as well as the detachment forces.

In conclusion, these data demonstrate that endothelial ephrinA1 is induced by TNF-α in a NFκB dependent manner. This induction of ephrinA1 by TNF-α in endothelial cells represents a crucial part of the proadhesive effect of TNF-α on monocytes. Mechanistically it can be shown, that ephrinA1 regulates the trafficking of adhesion molecules and therefore the presentation on the cell surface of endothelial cells. These results might open perspectives by defining a new role of ephrinA1 in TNF-α induced inflammatory processes like monocyte adhesion in atherosclerotic plaques.