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Ecto-5'-Nucleotidase (CD73) Inhibits Vascular Inflammation During Vein Graft Remodeling

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The degeneration of human vein grafts after bypass surgery is mediated by multiple biological pathways including those governing atherosclerosis and vascular remodeling. Adenosine has been shown to play a critical role in vascular homeostasis and regulation of inflammatory processes and therefore has been considered a promising candidate to regulate vein graft remodeling following bypass implantation. Using a murine model jugular veins were transplanted into femoral arteries in mice lacking the adenosine producing enzyme CD73 and in controls using the cross-over design; both species serving either as graft donors or graft recipients. The main finding was that the grafts with $CD73^{-/-}$ mice exhibited a striking cell hyperplasia due to pro-inflammatory cell infiltration, accompanied by outward vascular remodeling. To investigate the underlying biological principle vSMCs were isolated from $CD73^{-/-}$ mice and assessed for their chemoattractive competence in lymphocyte migration assays. The chemoattractive power of $CD73^{-/-}$ vSMCs was roughly doubled as compared to WT vSMCs; an effect that was reversible following adenosine treatment. Using a qPCR array a set of 34 pro-inflammatory gene products that were up regulated in $CD73^{-/-}$ vSMCs was identified, including TRAIL, IL-33, CCL20, CCL17, CCL11 and CXCL10. TRAIL and CCL20 expression was suppressed in $CD73^{-/-}$ vSMCs upon adenosine treatment. This thesis postulates that (i) CD73 is a powerful suppressor of proinflammatory pathways in vein grafts, that (ii) $CD73^{-/-}$ vSMCs can contribute to the maintenance of inflammation by expressing pro-inflammatory genes and attracting lymphocytes, and (iii) that the anti-inflammatory effect of CD73 is in part mediated by adenosine. Taken into consideration that the extent and nature of early vein graft inflammation exerts great impact on vein graft remodeling and failure, adenosine signaling is introduced here as a possible target to control vein graft remodeling and thus to improve the low patency rate after venous bypass operation in humans. Until now there were no information available about the impact of adenosine produced by CD73 during vein graft remodeling and therefore this thesis could serve as a guide for future research adressing the improvement of human vein graft patency.