MECHANISM REGULATING ENDOTHELIAL PROGENITOR CELL HOMING AND DIFFERENTIATION

Stefanie Dimmeler, PhD;
Molecular Cardiology, University of Frankfurt, Germany
dimmeler@em.uni-frankfurt.de

INTRODUCTION: Experimental studies and clinical trials indicate that bone marrow-derived progenitor cells may be useful as a therapeutic tool to improve neovascularization after ischemia (1). Particularly, endothelial progenitor cells, a subset of hematopoietic progenitor cells which co-express endothelial markers improved recovery of blood flow after ischemia. EPC home to sites of ischemia, release growth factors and physically contribute to new blood vessel formation. However, the mechanisms by which progenitor cells are attracted and home to sites of ischemia and differentiate are unclear. Therefore, we investigated the mechanisms underlying endothelial progenitor cell homing (EPC) and maturation.

RESULTS: Homing of EPC to ischemic tissue was documented in animal models. Additionally, we studied the fate of \textsuperscript{111}indium oxide-labelled EPCs, which were infused in patients with acute or chronic ischemia. In patients with acute myocardial infarction 8.2±4% of the infused cells were detected in the heart, whereas the incorporation was significantly reduced by 59 % when patients with chronic ischemia were studied (p<0.05). These clinical studies suggest that an acute ischemic event and presumably the following activation of homing signals enhance the incorporation of EPC in vivo.

Experimental studies further demonstrated that a variety of steps regulated EPC homing. EPC are attracted by the cytokine SDF-1, which activates the CXCR4 receptor expressed on EPC. Further homing steps required integrins, including the \(\beta_2\) integrin CD18 (2). Substances released by the necrotic tissue or by inflammatory cells such as the high mobility group box protein 1 (HMGB-1) additionally stimulates the polarity of integrin localization and integrin activity of EPC and promote their migration.

The next step of EPC recruitment, the invasion of EPC to the ischemic tissue, is dependent on the expression of the protease cathepsin L. Cathepsin L is highly expressed on EPC and degrades the extra-cellular matrix. In an in vitro assay, a cathepsin inhibitor prevented different progenitor cell populations from passing through a matrigel layer. Moreover, progenitor cells lacking cathepsin L had an impaired capacity to promote neovascularization in ischaemic mouse limbs compared with normal, wild type cells (3).
Finally, we characterised the molecular mechanisms regulating the maturation of EPC to an endothelial phenotype. Our recent studies suggested that endothelial commitment requires HDAC activity and depends on the expression of the homeobox transcription factors HoxA9 (4). HoxA9 was essential to maintain the expression of a variety of endothelial marker genes such as eNOS, the VEGF-receptor 2 and VE-cadherin in cultivated endothelial cells. Functionally, HoxA9 deficient mice showed a severe impairment of recovery after limb ischemia (100% toe/limb necrosis). This phenotype was partially rescued by the infusion of wt progenitor cells.

The lecture will provide an overview regarding the current mechanism by which bone marrow-derived and circulating endothelial progenitor cells home to the sites of ischemia, differentiate to endothelial cells and improve neovascularization.

ACKNOWLEDGEMENT: This research was supported by the DFG (SFB553; TR-SFB 23; FOR501), European Network of Excellence (EVGN), Leducq Foundation, EU-IP “Heart Repair”.

REFERENCES (RECENT PUBLICATIONS)