Annexin A1 induces a pro-angiogenic macrophage phenotype to promote myocardial repair

B. Ferraro[1,2], G. Leoni[1], D. Bongiovanni[3], M. Hristov[1], M. Horckmans[1], R. T. A. Megens[1], S. Steffens[1], C. Weber[1], C. Kupatt[3] , M. D'Amico [2], O. Soehnlein[1,4,5]

1 Institute for Cardiovascular Prevention (IPEK), Ludwig-Maximilians University Munich, 80336 Munich, Germany.

2 Department of Experimental Medicine, Second University of Naples, 80138 Naples, Italy.

3 Medizinische Klinik I, Technische Universität München, 81675 Munich, Germany.

4 German Centre for Cardiovascular Research, partner site Munich Heart Alliance, 80336 Munich, Germany.

5 Department of Pathology, Academic Medical Center, University of Amsterdam, 1105 Amsterdam, the Netherlands.

Significant interest in the field of cardiovascular medicine has focused on the search for new therapeutic approaches to promote tissue repair and vessel formation to resolve damage after myocardial infarction. As such, the anti-inflammatory pro-healing protein Annexin A1 might represent a candidate for induction of healing of injured myocardium. Thus, the aim of this study was to elucidate the role of Annexin A1 in myocardial infarction repair. Echocardiographic evaluations revealed in Annexin A1 null mice a significant reduction of the major cardiac parameters such as cardiac output and ejection fraction. Absence of Annexin A1 led to an enhanced macrophage content in the ischemic area, in particular of the pro-inflammatory macrophage phenotype. Moreover, Annexin A1 had a predominant role on cardiac angiogenesis, a highly regulated process of myocardial repair. Proteomic analysis of cardiac tissue homogenate revealed a global defect in the production of the major pro-angiogenetic factors such as VEGF, FGF-b, angiopoietin-1, and PDGF in Annexin A1 null mice. Interestingly, in the absence of Annexin A1, cardiac macrophages released less pro-angiogenetic factors after myocardial infarction compared to WT control macrophages. Daily i.p. injections of hrAnnexin A1 led to increased myocardial repair by enhanced cardiac function and angiogenesis. In summary, delivery of Annexin A1 may represent a novel therapeutic strategy beneficial for the treatment of ischemic heart disease.