Stem Cell Dysfunction in Diabetic Cardiomyopathy

F. Quaini[1], G. Graiani[1], D. Stilli[2], F. Ferraro[3], A. Falco[4], D. Madeddu[1], B. Lorusso[1], A. Gervasi[4], C. Lagrasta[4], C. Frati[1], L. Prezioso[1]

[1]Dipartimento di Medicina Clinica e Sperimentale, Università di Parma;[2]Dipartimento di Bioscienze, Università di Parma;[3]Center of Regenerative Medicine, Massachusetts General Hospital, Boston USA;[4]Dipartimento SBIBIT, Università di Parma

Diabetes Mellitus (DM) may represent a unique condition to establish whether organ pathology is primarily due to changes in the functional properties of stem cells (SC) or to the direct metabolic insult on parenchymal cells or both. The specific aim of this report is to provide an overview of the perturbance of tissue resident and circulating progenitors in DM. A significant literature exists on the functional impairment of Endothelial Progenitor Cells (EPC), cardiac primitive cells (CPC) and mesenchymal progenitors (MSCs) from Bone Marrow (BM) and non-BM sources as a feature of diabetes. Thus, premature cellular aging with increased expression of p16, telomere shortening and apoptotic death has been repeatedly documented with diabetes. In addition, a reduced ability of EPC to generate vessels in vitro has been shown. The deleterious effects of diabetes on the number and distribution of BMSC and on changes in BM microvasculature in humans has provided evidence that alterations of the complex cellular cross-talk regulating tissue homeostasis dictate a cascade of events ultimately leading to the clinical manifestations of the disease. Furthermore, we have identified diabetes-specific alterations in the expression of genes that regulate SC homing and migration, and endothelial cell-stem cell interactions, resulting in SC 'mobilopathy' and unspecific trans-endothelial migration. It is well established that the active regulation of stem cell number, fate and localization occurs within the niche through an orchestrated network of soluble signals and surface interactions. Supportive cells of the niche may represent an additional potential target for therapeutic intervention for several pathologic states, including diabetes, in which BM and tissue resident stem cells are involved. Emerging evidence suggests that CPC might be involved in the pathophysiology of diabetic cardiomyopathy (DCM). DM is an independent risk factor for left ventricular dysfunction and is associated with an increased risk to develop heart failure. In advanced phases of diabetes a progressive CPC damage and exhaustion associated with the loss of the physiological balance between cell death and regeneration, leads to the occurrence of overt ventricular dysfunction. Importantly, genetic and pharmacologic antioxidant interventions can prevent CPC depletion ameliorating diabetic cardiac dysfunction. These positive effects have been attributed to a decreased oxidative stress and to the reversal of the unfavourable myocardial pro-inflammatory 'milieu' affecting SC function in DM. Thus, both in BM and heart the interaction between resident stem cells and supportive elements of the niche may represent therapeutic target for the treatment of DM. In support of all of these contentions, more than 100 NIH approved clinical trials are ongoing on the use of cellular and growth factor therapy for diabetic patients affected by cardiac and peripheral vascular disorders.