ImmunoTools *special* Award 2014

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Protection of mesenchymal stem cell and cardiac progenitor cells from oxidative-stress induced apoptosis

Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality in the industrialized countries. Mesenchymal stem cells and Cardiac Progenitor Cells (CPCs) transplantation has been proposed as an alternative strategy to improve the current therapeutic arsenal against CVD. CPCs therapy has been identified as a promising approach to CVD for their potential of differentiation into cardiomyocytes and ability of secreting growth factors and cytokines to nourish myocardium. However, because of the poor cell engraftment and paracrine activity due to the adverse cardiac microenvironment, mechanical injury and maladaptation, stem cells transplantation could only yield marginal benefits, which severely restrict the clinical potential of this therapeutic approach. Physical stimulation, pharmacological agents treatments, genetic manipulation by over-expression of pro-survival genes were shown to enhance differentiation potential and paracrine activity of stem cells. Therefore, preconditioning of stem cells before transplantation was proposed good strategy to enhance their resistance to adverse environment and their therapeutic efficacy for cardiac repair.

Cell treatment with growth factors and cytokines could induce an autocrine loop, which could be advantageous, once cells are transplanted, also for regulating endogenous processes which would be otherwise insufficient. Paracrine mechanisms have been shown to influence cell contractility. These findings suggest the existence of a complex crosstalk between transplanted and endogenous stem cells, which may be the basis of successful cell-based therapies.

In our laboratory we have two cell models to test the activity of growth factors and cytokines in the prospect of analyzing their anti-apoptotic activity. Indeed, oxidative stress mediated by ROS is an essential mechanism causing cardiomyocyte apoptosis in pathological conditions such as infarct/reperfusion (I/R) injury,

myocardium remodeling after myocardial infarction, and heart failure. Susceptibility to oxidative stress is higher in the heart than in other organs because of low levels of antioxidant enzymes. Increased endogenous antioxidants could protect hearts from oxidative stress associated with I/R injury. Therefore, either exogenous administration of antioxidants or upregulation of endogenous antioxidants is an important therapeutic strategy to prevent cardiac I/R injury by ROS.

In particular we have shown that an agonist monoclonal antibody against the HGF receptor is able to protect a rat cardiomyoblast cell line from oxidative stress induced apoptosis. Similarly the polyphenolic compound Clovamide present in the cacao was found to protect these cells. The laboratory has also established a mesenchymal stem cell line from adipose tissue of fvb strain mouse (m17.ASC). Indeed this cell line espresses many stemness markers, and show constant doubling time for more than 180 generation, probably because of the stability in telomere length. In parallel, this cell line has a normal karyotype, and it does not display in vitro transforming or in vivo tumorigenic activities. It has the multipotency expected for bona fide stem cells, since it can be driven to osteogenic, chondrogenic and adipogenic phenotypes, when stimulated with appropriate differentiating media. Moreover, when co-cultivated in the presence of neonatal cardiomyocytes, it acquires traits of cardiomyogenic differentiation. These cell lines thus represent valuable cell models to study the differentiation mechanisms involved in tissue repair as well as models for pharmacological/toxicological studies. We would like to investigate in vitro if other factors, such as EGF, FGF, IGF-1, VEGF-A, can enhance the effects induced by these molecules. The results obtained with these cell lines could then be translated to hCPCs isolated from human auricula fragments obtained by the cardiosurgery department.