Cellular basis of drug induced heart failure: role of stem cells

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Background: Several drugs provoke cardiovascular effects involving on-target and off-target mechanisms. Due to the inevitable shortcomings of the processes of drug development, phase I-III clinical trials and approval procedures, the adverse effects are detected only by post-marketing pharmacosurveillance studies. The life-saving therapies with several anti-tumor agents is hampered by their cardiotoxicity. In addition to well known effects of anthracyclines (ANT), new drugs that target pathways implicated in cell death and growth can be cardiotoxic. Because of the cytotoxicity of chemotherapy, bone marrow, that is provided with an active population of stem cells, does (like any other system) fail under toxic injury.

ANT cardiotoxicity is characterized by a dilated cardiomyopathy followed by congestive heart failure [Singal, Iliskovic. N Engl J Med 1998] suggesting that myocardial damage progresses with time. The mechanisms of ANT-induced cardiomyopathy are not fully elucidated but our understanding of this disease has been significantly evolving. Major side effects of tyrosine kinase inhibitors, a relatively new anti-cancer options, involves cardiotoxicity [Force et al. Nat Rev Cancer 2007] that differs from that of ANT. Intriguingly, agents acting on pathways implicated in cardiac development [Lee et al. Nature 1995] damage the adult heart, suggesting the persistence of cardiogenic compartments within the mature myocardium.

Objective: To understand the role of resident and extracardiac progenitors in the pathogenesis of cardiomyopathies can provide not only a better comprehension of cardiac homeostasis but may also open new avenues for therapeutic interventions.

Results: In animals and humans doxorubicin (DOXO)-cardiotoxicity is not restricted to myocytes, but affects also resident cardiac progenitor cells (CPCs). DOXO impaires vascular development and reduces the number of CPCs resulting in a higher vulnerability of the heart [Huang et al. Circulation 2010]. DOXO decreases the number of functionally competent CPCs by inhibiting their proliferation, accumulation of oxidative DNA damage, activation of p53, apoptosis, progressive cellular aging and defective differentiation, indicating that one of the events responsible for the initiation and evolution of the cardiomyopathy occurs at the level of the CPC [De Angelis et al. Circulation 2010]. Although these phenomena may not directly lead to heart failure, they can transform the myocardium of an apparently healthy person to at-risk phenotype. Although cell therapy could represent an innovative approach, our results suggest that the use of hCPCs isolated from patients suffering from DOXO-induced heart failure may not be feasible [Piegari et al. BRC 2013]. In this regard, taking to account the nature of DOXO-induced damage to CPCs and the involvement of SIRT1 in these processes, it may be reasonable to propose SIRT1 as a target to rescue functional properties and to obtain autologous hCPCs of acceptable quality[De Angelis et al. Int J Cardiol 2015].

Perspective: Resident and extracardiac progenitors involved in cardiac repair represent new targets of cardioprotection. The systemic effects of cytotoxic drugs on stem cells may exert two negative consequences on the myocardium: 1) impairment of the ability of bone marrow stem cells to migrate, home and replenish the depleted primitive cell compartment of the heart; 2) depletion of the resident cardiac progenitors. As alternative to cell therapy, several approaches may be designed including administration of compounds interfering with the homing/engraftment of progenitor cells and administration of clinically used drugs whose cardiovascular beneficial effects may be due to an improvement in progenitor cell function. Finally, efforts should be made for the difficult task of protecting the heart from cardiotoxic drugs while maintaining their antitumor efficacy with minor potential interference on cancer growth.