ADVANCING THE KNOWLEDGE ON IMMUNOMODULATORY PROPERTIES OF HUMAN CARDIAC STEM CELLS

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Transplantation of allogeneic human cardiac/stem progenitor cells (hCSC) is currently being tested in several phase I/II clinical trials as a novel and promising therapy for restauration of myocardial tissue function in acute myocardial infarction (AMI) patients. Previous findings demonstrate that these cells have an immune suppressive profile, interacting with different populations from the immune system, resulting in overall attenuation of myocardium inflammation. However, transplanted hCSCs are still recognized and cleared from the injured site impairing long retention times in the tissue that could be translated into a higher clinical benefit. In this work, different models of allogeneic hCSC/ T-lymphocyte interaction *in vitro* were explored, using the same hCSCs employed in the allogenous hCSCs transplantation phase I/II clinical trial CARE-MI, NCT02439398. T lymphocytes were cultured either in direct contact with hCSCs, or using transwell inserts or with hCSC conditioned medium.

In our results, we show that IFN-γ activation is correlated with an increase in hCSC indoleamine 2,3-dioxygenase (IDO) enzyme expression. We also show a significant inhibition of T lymphocyte inhibition when cultivating human peripheral blood mononuclear cells (hPBMCs) in direct cell-cell contact, using transwells or with activated hCSC conditioned medium, combined with tryptophan depletion and kyurenine (a tryptophan metabolite) accumulation in activated hCSCs conditioned medium.

These findings provide evidence, that although playing a role in the process, PDL-1 cell contact dependent T-regulatory cell modulation is not the exclusive neither the central mechanism involved in T-lymphocyte proliferation inhibition. This finding further supports the prominent paracrine-based beneficial CSC activities in the host tissue.

Our results demonstrate for the first time that hCSCs exert an immune-suppressive effect on T lymphocyte proliferation through a paracrine mechanism associated with IDO enzyme mediated tryptophan metabolism. The knowledge generated contributes not only to a better understanding on hCSC immunomodulatory mechanisms, but also open new avenues in the development of new hCSC transplantation strategies in allogeneic settings.