

Project title: Treatment of ischemic cardiomyopathy with novel anti-remodeling proteins and clinical grade exosomes derived from amniotic mesenchymal stromal cells

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Main Abstract:

Ischemic cardiomyopathy is a leading cause of death and long-term morbidity worldwide, heavily impacting the costs of public health systems. The therapies currently available can partially prevent the negative ventricular remodeling ensuing after non-reperfused myocardial infarction and improve its prognosis but still many patients develop post-ischemic heart failure. Heart transplant represents the only cure for this condition, but it is hampered by several limitations. Consequently, the identification of novel strategies to prevent or repair post-ischemic cardiac damage is urgently needed.

Recently, it has been demonstrated that mesenchymal stromal cells isolated from the amniotic membrane of human placenta (AMSC) produce high amounts of secreted factors exerting cardio-protective and cardio-reparative effects in animal models and are more effective than adult MSC of bone marrow origin that over the years tend to lose therapeutic power due to aging and depletion of many paracrine factors. These findings lead to hypothesize that extensive research to define the role of these active paracrine components may result in the identification of new therapies for the treatment of ischemic cardiomyopathy. Such an approach would certainly be more readily transferable to the clinical practice compared with cell therapies, which present several limitations: production, scalability, and regulatory issues, poor engraftment, need for complex routes of administration, and possible side effects if infused intravenously, lack of pharma industry support for the development of cell products and large clinical trials.

Accordingly, we propose to develop a clinical-grade protocol for the scale-up of AMSC and to dissect the active components of AMSC secretome, composed of soluble cardio-protective and anti-remodeling factors and exosomes (exo). The rationale for our proposal lies in data already available showing that MSC-derived exo can by themselves recapitulate the effects obtained by administering the whole cell-secretome. We propose to verify if this is the case also for AMSC by comparing the cardioprotective and cardio-reparative effects exerted by exo with respect to the conditioned medium of AMSC. The cardioprotective, anti-remodeling, pro-angiogenic, and pro-cardiogenic effects exerted by the exosomes will be tested by carrying out both in vitro potency assays and an in vivo study on a murine model of ischemic cardiomyopathy.

The success of the project would have important practical implications for the translation of cell-derived therapies for the treatment of ischemic heart disease.

Techniques: stem cell isolation and culture, isolation of cell secretome and microvesicles, immunocytochemistry, microscopy, main molecular biology techniques, GMP procedures.

GRAPHICAL ABSTRACT

PhD Project

