Correlations between microRNAs and their target genes in skeletal myoblasts cell therapy for myocardial infarction

Andrea Rognoni[1], Chiara Cavallino[1,2], Francesco Rametta[2], Angelo Sante Bongo[1]

[1]Coronary Care Unit and Catheterization Laboratory, "Maggiore della Carità Hospital", Novara, Italy; [2]Division of Cardiology, Sant'Andrew Hospital, Vercelli, Italy

Correspondence to: Andrea Rognoni, MD, FSCAI. Coronary Care Unit and Catheterization Laboratory, "Maggiore della Carità" Hospital, Corso Mazzini 18, 28100 Novara, Italy. Email: arognoni@hotmail.com.

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In the setting of ischemic heart disease in which revascularization therapies (both percutaneous and surgery) and pharmaceutical therapy are able to contribute to ventricular remodeling, nowadays we also have some indications about promising options to prevent or reverse the ventricular remodelling process and consequent heart failure. Stem cells provide an alternative curative intervention for the infarcted heart by compensating for the cardiomyocyte loss subsequent to myocardial injury. The presence of resident stem and progenitor cell populations in the heart, and nuclear reprogramming of somatic cells with genetic induction of pluripotency markers are the emerging new developments in stem cell-based regenerative medicine. However, until safety and feasibility of these cells are established by extensive experimentation in *in vitro* and *in vivo* experimental models, skeletal muscle-derived myoblasts, and bone marrow cells remain the most well-studied donor cell types for myocardial regeneration and repair (1,2). Furthermore in the literature we can find a lot of indications about microRNAs as novel and alternative cardiac biomarkers. These are 22-nucleotide-long non-coding RNAs that regulate gene expression at post-transcriptional level. Several recent studies have shown that miRNAs play a physiological role in cardiovascular homeostasis and in the pathogenesis of cardiovascular disease. Expression-pattern studies of myocardial tissue reveal that several miRNAs are up- or down-regulated during myocardial infarction (3,4). During nearly two decades of cell therapy research for treatment of ischemic heart disease, stem cell transplantation, either alone or in combination with the other therapeutic interventions, has demonstrated promise as a novel curative strategy (5). The prime advantage of the heart cell therapy using stem cells is its capability to replace the loss-of-functioning cardiomyocytes to preserve the deterioration of left ventricular function (6,7). Of all stem cells used, skeletal muscle-derived myoblasts have been investigated in experimental and clinical studies; in fact skeletal myoblasts and bone marrow derived stem cells remain the most well-characterized studied therapy for myocardial reparability in the patients with ischemic heart disease (8,9). Skeletal myoblasts constitute the renewable source of progenitor cells in skeletal muscle that participate in the repair process in the event of injury. The most important characteristics of skeletal myoblasts that make them suitable for use are their autologous availability, potential to expand *in vitro*, resistance to ischemia, low risk of tumorigenesis and myogenic differentiation potential (10,11). In the paper of Liu *et al*., published on *Journal of Transplantation Medicine* in 2015, the authors analyzed the correlations between microRNAs and their target genes in skeletal myoblasts cell therapy for myocardial infarction. Their final data showed that the down regulation of apoptosis-regulatory microRNAs and in turn up regulation of target genes may partially account for rescue effect of skeletal myoblasts therapy for myocardial infarction (12). Since the early 2000s we can find in the literature a lot of *in vitro* researches that have assessed the performance of skeletal myoblasts for the treatment of ischemic and non ischemic cardiomyopathies in animal models (13-16). All these studies showed that skeletal myoblasts prevented left ventricular remodeling, preserved ejection fraction, left ventricular pressure wall thickness and left ventricular pressure. Skeletal myoblasts were, also, used in post myocardial patients in some clinical settings (17,18). Even in these cases, results from heart function were

promising increasing in left ventricular ejection fraction and in segmental contractility on echocardiography. The interesting feature of the paper of Liu *et al*. (12) was to compare the expression of microRNAs in post myocardial infarction rats with or without skeletal myoblasts cell transplantation. The authors focused their research on new apoptosis-associated microRNAs and their target genes; in particular they showed that four microRNAs were down regulated in the skeletal myoblasts treated group compared with the untreated group. Some studies in the recent past showed the role of microRNAs; some of this have distinct roles in modulating skeletal and cardiac muscle proliferation and differentiation (19-21); other studies have, also, demonstrated that microRNA-206 and -1 directly down regulated gap junction coupling after the initiation of myoblast fusion *in vitro* and *in vivo* and inhibit Cx 43 expression during myoblast differentiation without altering Cx43 microRNA levels (22). The paper of Liu *et al*., (12) is the first comparative *in vitro* study of microRNA and microRNA expression in myocardial infarction heart treated with skeletal myoblasts transplantation using surgical route. We hope as interesting for the future skeletal myoblasts transplantation combined with transplantation of other cell types or growth factor; a combined therapy based on simultaneous delivery of skeletal myoblasts and bone marrow stem cells may be more effective with either cell type alone as partially demonstrated in the recent past (23). In-depth mechanistic studies, genetic reprogramming or pharmacological manipulation, and combinatorial approach involving skeletal myoblast transplantation with other relevant interventions, such as growth factor administration, can help safety and therapeutic efficacy; in fact simultaneous insertion of skeletal myoblasts with multiple growth factors promoted their ability to integrate with host myocytes. Skeletal myoblasts remain the most well-studied donor cell type.

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Footnote

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