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Role of exosomes in pericardial fluid-mediated cardiac regeneration

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Background: We recently demonstrated that epicardial stem cells participate to the regenerative response following myocardial infarction (MI) and factors released in the pericardial fluid (PF) may play a key role in this process. Exosomes are secreted microvesicles of endocytic origin, identified in most body fluids, which may contain proteins able to modulate cell functions. Here, we investigated whether exosomes are present in the PF and their role in epicardial stem cell-mediated cardiac repair.

Methods and Results: Exosomes were identified in PFs from non-infarcted patients (PFC) and patients with acute myocardial infarction (PFMI). A shotgun proteomics analysis of exosomes from PFC and PFMI was used to identify differentially expressed proteins in these microvesicles. We identified Clusterin in exosomes isolated from PFMI but not from PFC. Notably, clusterin is an important mediator of TGF β -induced epithelial-to-mesenchymal transition (EMT), a key process which regulates epicardial cell activation and differentiation. Both q-RTPCR and immunohistochemical studies showed cardiomyocytes expressing clusterin in the infarcted region 3 days following MI. The importance of EMT in PF-induced epicardial cells was confirmed by gene expressions studies on epicardial cells from infarcted mouse hearts in the presence and in the absence of PF. Three days following MI, the expression of genes related to EMT, i.e. Snai1 and Twist1 were increased in the presence of PF. Noteworthy, EMT genes were specifically upregulated in epicardial cells expressing the stem cell antigen c-kit as demonstrated by *in vitro* studies. *In vivo* studies are ongoing to demonstrate the involvement of clusterin in the PFMI induction of EMT and myocardial repair.

Conclusions: Exosomes are present in the PFs. Clusterin was identified only in PFMI and may account, at least in part, for epicardial EMT and myocardial regeneration following MI.

Biography

Federica Limana is working as a Post-doctoral fellow in the laboratory of Prof. Matteo A Russo at the University of Roma "Sapienza" (Dipartimento di Medicina Sperimentale). Her studies have led to several publications on aspects of cardiac regeneration in the injured heart. Specifically, in the last few years she studied the role of the adult epicardium in the physiologic process of myocardial regeneration and identified in this compartment a pool of cells that may represent a new source of CSCs.

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