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The human amniotic fluid stem cell secretome as new promising tool to restore cardiac regeneration by paracrine therapy

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Introduction. Heart failure is related to inefficient cardioprotection, defective repair and lack of myocardial renewal following injury. Yet, the adult mammalian heart retains some regenerative capability, based on cardiac progenitor cell (CPC) activation and cardiomyocyte proliferation, although not efficiently responsive when facing pathological situations. We previously reported that human amniotic fluid-derived stem cells (hAFS) mediate acute cardioprotection on rodent ischemic myocardium and on cardiac cells experiencing cardiotoxicity.

Purpose. Here we aim at analysing the hAFS secretome to: i) enhance cardiac repair and ii) provide cardiac restoration by triggering endogenous regenerative mechanisms.

Methods. c-KIT+ hAFS were isolated from leftover samples of amniotic fluid from prenatal screening, following written informed consent and stimulated for 24h to enrich their conditioned medium (hAFS-CM) with cardioactive paracrine factors under 1% O2 (hAFS-CMHypo) versus control condition (hAFS-CMNormo). The anti-apoptotic, angiogenic, and proliferative effects were evaluated on mouse and rat neonatal ventricular cardiomyocytes (m/rNVCM), human endothelial colony forming cells (hECFC) and human CPC (hCPC) in vitro. To pinpoint the therapeutic role of the whole secretome versus the extracellular vesicle (EV) component, a mouse model of myocardial infarction (MI) was treated with total hAFS-CM, with hAFS-CM depleted by EV (hAFS-DM), and with hAFS-EV. All animal experiments were performed under specific authorisation from local ethical committee and the Italian Ministry of Health.

Results. hAFS-CM increased cell viability of mNVCM undergoing oxidative and hypoxic stress by about 46% and 25%, respectively. hAFS-CM was also able to induce remarkable intracellular Ca2+ signals in hECFC. EdU+ rNVCM were significantly increased by 4.6-fold, following hAFS-CM priming. Likewise, human epicardial CPC showed enhanced proliferation up to 70% more, when stimulated with hAFS-CM, compared to untreated cells. Single intra-myocardial administration of hAFS-CMHypo soon after MI provided substantial cardioprotection and significantly curbed down infiltrating neutrophils and macrophages by 46% and 32% in the short term, while sustaining angiogenesis at 4 weeks post-MI, compared to control animals. Notably, the whole hAFS secretome remarkably triggered resident surviving cardiomyocyte proliferation by 3-fold, almost doubled the amount of endogenous re-activated epicardial CPC a week after MI and improved cardiac function by 1.8-fold at 1 and 4 weeks post MI, with a possible key role played by hAFS-EV.
Conclusions. These encouraging findings substantiate the concept of paracrine-based approach via cell-free delivery of bioactive factors to prevent heart failure. In such scenario, the hAFS secretome may offer an easily obtainable and appealing source of cardioactive molecules as an advanced medicinal product for new cardiac regeneration strategies.