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Heart Failure and Cardiomyopathies

MIGRATION, PROLIFERATION AND DIFFERENTIATION OF C-KIT+ POSTNATAL MYOCARDIAL PROGENITORS ARE REGULATED BY SCF/C-KIT AND SDF1/CXCR4 PATHWAYS

Poster Contributions
Hall C
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Background: c-Kit+ cardiac stem cells (CSCs) have the capacity for differentiation into cardiomyocytes and ex-vivo expanded CSCs hold promise to treat damaged hearts. Endogenous CSCs may be modulated by cell-cell interactions with mesenchymal stem cells, but the molecular mechanisms underpinning this effect are unknown. To address the basis of MSCs-CSCs interactions, we employed a tamoxifen-inducible cKitCreERT2/+ mouse to label endogenous CSCs. We hypothesized that Scf/c-Kit and Sdf1/Cxcr4 signaling pathways underlie the capacity of MSCs to regulate CSC activity.

Methods: Two-day old cKitCreERT2/+ mice and the dual-fluorescent Cre-reporter allele IRG (n=6) were administered tamoxifen (50µl of 20mg/ml) to induce Cre-mediated recombination in c-Kit+ cells, which irreversibly converts DsRed to EGFP expression. The next day, pups were euthanized, and myocardial explant cultures were established in the presence or absence of 2x10^5/ml mitomycin-C inactivated porcine MSCs and 100ng/ml recombinant murine SCF. Live-cell imaging was employed to monitor the emergence and responses of EGFP+ c-Kit CSCs.

Results: The presence of both MSCs and SCF, but not each factor alone, enhanced CSC proliferation (EGFP+ cells after 5 days in culture: 48.2±33.2 in control; 55.0±39.8 with SCF alone; 81.7±25.7 with MSCs alone; 171.3±65.4 in MSCs+SCF group; $p<0.0001$). EGFP+ clones migrated from the explant and expanded on MSCs-feeders, whereas in the absence of MSCs, EGFP+ cells were exclusively retained within the myocardial explant. Addition of the Sdf1/Cxcr4 antagonist AMD3100 blocked migration of EGFP+ cells on MSC feeders, while causing a ~28-fold ($p<0.0001$) increase in the number of spontaneously contracting EGFP+ cardiomyocytes. Neutralization of SCF/c-Kit with an anti-cKit antibody did not affect migration but significantly reduced proliferation from 173.5±30.4 to 102.2±23.1 EGFP+ CSCs/sample ($p<0.001$).

Conclusions: Together these findings reveal critical mechanisms underlying the capacity of MSCs to favorably interact and modulate key aspects of CSC biology. Scf/cKit signaling potentiates clonal expansion, while Sdf1/Cxcr4 mediates migration and differentiation of CSCs.