Injured myocardiocytes prompt dental pulp stem cells migration and early homing in ischemic hearts

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Although almost all mammalian tissues have been demonstrated to possess stem cells, the majority of them are unable to guarantee its partial or total regeneration after injury. A significant example is represented by the heart, where myocardial infarction results in adverse ventricular remodeling and heart failure. Thus, the possibility to intervene for replenishing the dying myocardiocytes with adult stem cell and avoiding/repairing the occurring lesions could greatly enhance both expectancy and quality of patients' life. On this basis, cell-based therapies have been already performed with a wide spectrum of different stem cells populations. Nevertheless, appropriateness and efficacy still remain elusive or debated.
In the present study, we try to unravel some aspects prompting stem cells' migration and heart homing after ischemic lesion, in both in-vitro and ex-vivo experiment. We employ an our already characterized rodent stem line (MUR-1) [1] expressing early cardiac pre-commitment genes as Nkx2.5, Gata4 and Mef2c and phenotypically resembling those neural crest cells (NCC) able to drive cardiogenesis during the embryo development.
Our results demonstrated that cardiac myoblast H9c2 cells, injured in-vitro by means of serum deprivation and/or hypoxia, are able to prompt MUR-1 migration. As MUR-1 are responsive to myocardial cells injury, we evaluated their homing and behavior in an ex-vivo models of ischemic heart. Here, we clearly demonstrated that dental pulp stem cells are able to roll in damaged tissues leaving from healthy ones. In our experiments MUR-1 had enhanced migration volume if implanted in infarcted hearts, reaching predominantly dying tissues, as evinced by the co-localization of implanted cells and trypan blue stain. The homing specificity was confirmed by the low MUR-1 migration observed in controls. Such migratory differences are due to organization of CX43 cell-cell interactions and selective vWB factor-mediated adhesiveness, In control hearts CX43 still remained predominantly placed amidst MUR-1 while it is pinpointed between MUR-1 and cardiac cells following ischemic injuries. Thus, the enhanced presence of vWB factor in ischemic tissues mediates the MUR-1 retention into the damaged area, as evinced by the localization of MUR-1 cells which are found onto or surrounded by vWB spots in infarcted hearts, but not in control ones. Finally, we identified chemotactic factors involved in MUR-1 migration by means of Boyden chambers. As demonstrated by our results, MUR-1 cells express cognate receptors for SDF-1 (CXCR4), FGF-2 (FGFR1), HGF (c-MET) and VEGF (Flt-1, other than Flk-1, as previously reported [1]). Nevertheless, motility depends on SDF-1, FGF-2 and HGF, similarly to what occurs for NCC migration during the cardiogenesis. Otherwise, VEGF appears not involved in MUR-1 migration.
Noteworthy, the same factors are implied into the post-ischemic attempt to recovery the heart functionality. Indeed, myocardial injuries lead to a transient release of SDF-1, FGF-2, HGF and VEGF, in order to mediate post-ischemic salvage and/or revascularization.
In conclusion, we demonstrated for the first time, that dental pulp stem cells are sensitive to those stimuli involved during both heart organogenesis and ischemic pathology. Moreover, they migrated within the lesion sites and likely kept contact with myocardiocytes by means of CX43, as well as cardiac NCC moved and condensed in the developing embryo. Although far still remains the identification of the most suitable stem population to solve cardiac ischemia, here we propose some features and behaviors that should become mandatory for the future attempting at ischemic heart recovery.

1. Sprio AE, F Di Scipio, S Raimondo, P Salamone, F Pagliari, S Pagliari, A Folino, G Forte, S Geuna, P Di Nardo and GN Berta. (2012). Self-Renewal and Multipotency Coexist in a Long-Term Cultured Adult Rat Dental Pulp Stem Cell Line: An Exception to the Rule? Stem Cells Dev. 21:3278-3288.