Beta-blocker treatment in heart failure patients correlates with successful isolation of resident cardiac progenitor cells and affects their phenotype through EMT modulation

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Background. Cardiovascular disease is a leading cause of mortality and morbidity, mostly due to myocardial infarction incidence and survival, and consequent epidemic heart failure (HF). Despite remarkable pharmacological efficacy and advancements, end-stage HF patients only have the option of transplantation, creating the urgent need for alternative therapies. Cardiac stem cell (CSC) therapy offers new promises for regenerative medicine approaches, based on successful pre-clinical and clinical data, and CSCs isolated as spontaneous 3D cardiospheres (CSs) represent the most promising resident population under clinical investigation. The impact of the patient's medical and pharmacological history on the biology of his/her own resident CSCs represents a key issue to be considered in the quality and potency of the final cell product for autologous protocols.

Aim. To investigate the influence of multiple clinical parameters on CSs isolation efficiency, and in particular the effects of beta-blockers on their biology.

Methods and results. Thirty adult HF patients undergoing elective cardiac surgery have been enrolled. Multiple medical parameters have been collected in a database, such as: sex, age, BMI, diagnosis, surgical intervention, cardiopulmonary bypass time, glicemia, cholesterol, AST, ALT, diabetes, smoking habits, IMA, drug prescriptions, etc. Corresponding biological data concerning CSs isolation timing and efficiency for each patient have been matched. We observed a positive statistical correlation between beta-blocker (BB) assumption by donors and both CS-forming cells yield and successful CS formation ($P<0.05$ for both) from cell cultures of corresponding bioptic samples. Considering that beta-blockers represent one of the elective HF pharmacological treatments, and that multiple evidences suggest a connection between mechanical/pharmacological stress reduction and CSC biology, we next investigated the effect of beta-blocking on CSs. CS yield was significantly higher for BB than not beta-blocked (NBB) patients. The overall balance among immunophenotype subsets inside the CS-derived cells (CDCs) population was different between BB and NBB patients. In fact, while the abundance of ckit+ cells was not affected, BB patients displayed a statistically significant lower percentage of CD90+ CDCs, associated to significantly lower expression levels of collagen I and higher levels of collagen III. Also, BB CDCs had significantly higher gene expression levels for MHC and Nkx2.5, suggesting for BB donors the presence of a resident CSC population enriched in cells with increased cardiomyogenic potential and reduced mesenchymal-like cells. Analysis of expression levels of selected mi-RNAs of interest confirmed a significant difference between CSCs profiles of BB versus NBB patients.

CONCLUSIONS. Overall our data suggest that BB treatment positively correlates with successful CSs isolation and with a more cardiomyogenic and less fibrotic phenotype of resident CSCs.

These results supports novel speculations on the mechanisms responsible for beta-blockers beneficial effects, and on the possible prognostic, predictive and adjuvant role of beta-blocker treatment in cardiac cell therapy applications.