Journal of Controlled Release 249 (2017) 196

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Cover story

Adipose-derived stem cells combined with neuregulin microparticles for efficient cardiac repair

Cardiovascular diseases remain the number one cause of death. Tissue engineering approaches can be used in heart repair, but there are still significant challenges in the design of cardiac scaffolds, controlled release of bioactive growth factors over the tissue regeneration period, and the improvement of cell engraftment. Most of the strategies developed to date for myocardial regeneration have used scaffolds loaded with either proteins or cells [1]. Only a few studies have investigated the effect of the simultaneous delivery of both protein and cell. Furthermore, macrophage responses toward implanted protein/cell scaffolds in the context of cardiac regeneration have not been investigated in detail [2,3].

A paper by Professor Blanco-Prieto and her colleagues in this issue [4] investigates a method to deliver adult stem cells to the infarcted myocardium after adhering them to poly(lactic-co-glycolic acid) (PLGA) microparticles (MPs) loaded with neuregulin (NRG). The rationale for this study is that this combination could increase regeneration of the damaged tissue as compared with delivery of protein or cell alone. The novelty of this work also resides in harnessing the stem cell paracrine secretion to obtain a multiple growth factor system capable of responding to the damaged tissue. NRG, a cardiovascular protein with capacity to restore cardiac function after myocardial infarction, was encapsulated into PLGA MPs. MPs were then covered with poly(D-lysine)/collagen type I for adhesion of adipose-derived stem cells (ADSCs). The reparative activity of the ADSC-coated NRG-loaded MPs (ADSC-NRG-MPs) were tested in a rat myocardial infarction model. This study analyzed the mechanisms by which ADSCs improved cardiac function, and the macrophage response to the implanted tissue engineering strategy.

The pioneering approach of the Blanco-Prieto team represents a step forward in the use of drug delivery systems loaded with proangiogenic and myogenic proteins such as NRG in combination with stem cells for cardiac repair. This study shows that the therapeutic value of ADSCs was significantly increased when the cells are delivered along with NRG encapsulated in sustained release MPs. This is probably a result of increasing stem cell survival and paracrine secretion of pro-survival and/or anti-inflammatory molecules. ADSC-NRG-MPs were able to induce longer cell survival, as ADSCs were detectable in the heart tissue three months following cell transplantation. Furthermore, the increase in cell survival, promoted by NRG and the attachment of ADSCs to the MPs, favored a synergy for inducing a greater and more complete improvement in heart regeneration mediated by tissue revascularization. In addition, the study also shows that ADSC-NRG-MPs promoted macrophage polarization towards a M2 anti-inflammatory phenotype, demonstrating active induction of the immune response. This important finding elucidates the role of macrophages in tissue healing following the delivery of both ADSC NRG in the myocardium. It will aid the design of new tissue engineering approaches that elicit a favorable response upon implantation in the heart.

The work by the Blanco-Prieto group has shown that the combination of ADSCs, MPs and NRG results in a synergy for inducing a greater and more complete improvement in heart regeneration and positive interactions with the immune system to achieve successful tissue integration. The approach taken in this study can be easily applied to other organs such as the kidney, liver or brain. With further improvement in the ADSC-NRG-MP formulation, such as increased loading of NRG, this work can significantly advance the heart tissue engineering field for translation of the ADSC-NRG-MP strategy to clinical practice.

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http://dx.doi.org/10.1016/j.jconrel.2017.02.014
0168-3659/