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Relaxin, cardiac stem cells and heart regeneration

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Summary

The notion that the adult heart of mammals including humans contain a small population of resident cardiac progenitor/stem cells (CSCs) have questioned the traditional paradigm of the myocardium as a post-mitotic terminally differentiated tissue. These cells, however, are relatively scarce and unable to be recruited in large number at the site of tissue damage. This has sparkled novel interest in the identification of molecules capable of stimulating the regenerative potentials of CSCs in their microenvironment. In this context, the peptide hormone relaxin (RLX), recently validated as a cardiovascular hormone, deserves a key place. This article summarizes the most recent findings of our group on the ability of RLX to modulate growth and differentiation of mouse neonatal cardiomyocytes, suggesting that this hormone, for which the heart is both a source and target organ, may participate in the endogenous mechanisms of myocardial repair/regeneration. Moreover, we have recently observed that RLX, by a Notch-1-mediated mechanism, inhibits cardiac myofibroblast differentiation and function, suggesting that the known anti-fibrotic effects of RLX may be part of a complex network of actions whereby this hormone facilitates cardiac stem cell growth and improves myocardial regeneration.

Key words

Relaxin, heart, cardiac stem cells, mesenchymal stromal cells

Starting from the end of 20th century, the discoveries on the regenerative potential of stem cells and the possibility to use stem cell therapy as a treatment of heart failure has represented a field of intensive experimental and clinical research (Leri et al. 2008). Moreover, the paradigm that the adult heart represent a terminally differentiated organ has been recently challenged by the identification of resident cardiac stem cells (CSCs) which could be recruited to cardiac repair. Anyhow, even if few question are definitively addressed in the field of cardiac repair, it seems well accepted that a functionally significant myocardial regeneration, especially after massive muscle tissue loss as occurs upon myocardial infarction, cannot be achieved by either resident or transplanted stem cells (Formigli et al. 2010). Therefore, increasing the current knowledge on the factors and their mechanisms of action which may enhance the regenerative ability of cardiac stem cells represents a major research objective. In this scenario, relaxin (RLX) deserves a key place. In fact, the heart is both a source and specific target organ for RLX (Nistri et al 2007). In the last years, evidence has been offered that RLX, administered exogenously or secreted locally by genetically engineered stem cells grafted into the infarcted heart in experimental animals, reduces ischemic myocardial injury and dysfunction (Nistri et al 2007; Formigli et al. 2010).

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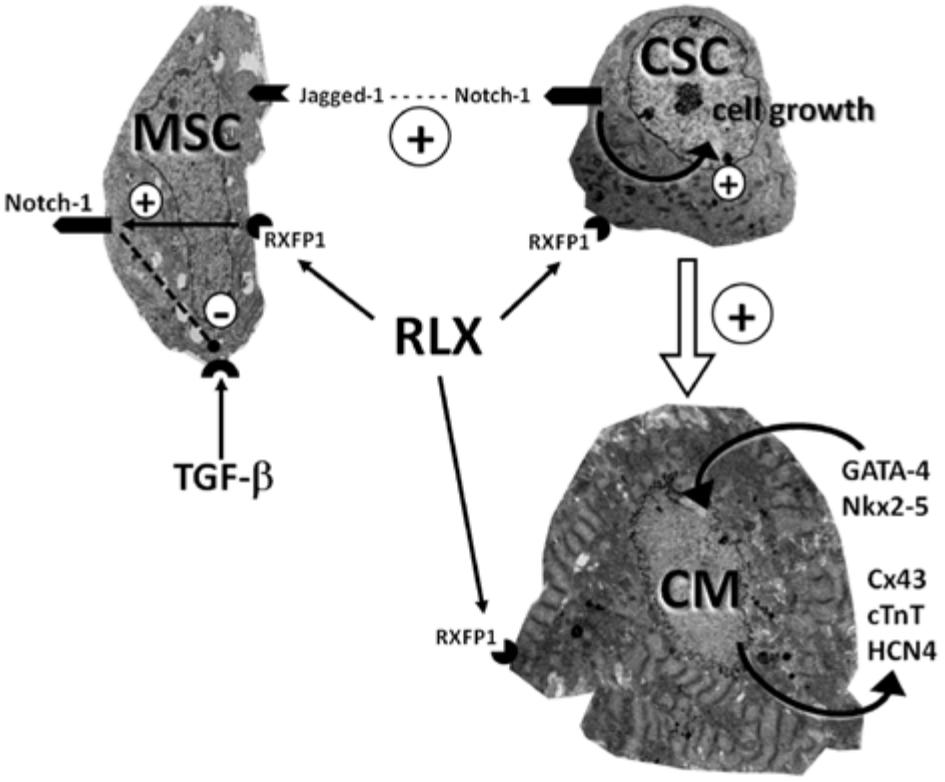

Figure 1. Schematic diagram of the effects of relaxin (RLX) on the stem cell populations in the heart. CSC, cardiac stem cell; MSC, mesenchymal stromal cell; CM, cardiomyocyte; RXFP1, relaxin family receptor 1; Cx43, connexin 43; cTnT, cardiac-specific troponin T. The cross-banded cytoplasmic structures in the developing cardiomyocyte are leptomeres, required for correct myofibril assembly.

Moreover, RLX knock-out mice are prone to develop cardiac fibrosis, a phenotype that can be reversed by exogenous RLX (Du et al. 2003). More recently, using primary cultures of mouse myocardial precursors, RLX was shown to up-regulate the co-ordinate expression of cardiogenic transcription factors (GATA-4 and Nkx2-5) and related structural myocardial genes (connexin 43, troponin T and HCN4 ion channel), thereby promoting the development of morphological and electrophysiological features of mature cardiomyocytes (Nistri et al. 2012).

It is well known that the three-dimensional arrangement of the developing heart – like any other organ - depends on the interaction between myocardial precursor and stromal cells of mesenchymal origin. In particular, mesenchymal stromal cells (MSCs) have the unique ability to create a network which moulds the shape of the organ, in which myocardial precursors can settle, proliferate and differentiate (Bani et al. 2010). Recent *in vitro* evidence has been provided that such cardiomyocyte-MSC interactions are dependent on juxtacrine signals operated by the interaction between the plasma

membrane receptor Notch-1 and its ligand Jagged-1, which are crucial to promote cardiomyocyte growth (Sassoli et al. 2012). Based on this background, we have then demonstrated that RLX can enhance Notch-1 in cultured MSCs, thereby interfering with TGF-b signalling, the major pro-fibrotic cytokine, and inhibiting the transformation of MSCs into collagen-producing myofibroblasts (unpublished data). These findings fit well with the known anti-fibrotic effects of RLX (Samuel et al. 2007) and suggest that, by similar mechanisms, RLX could improve the whole process of post-infarction cardiac remodelling, shifting it from spontaneous reparative scarring towards a myocardial regenerative pattern reminiscent of the embryonic heart development.

Taken together, the above notions suggest that RLX can be an endogenous regulator of cardiac morphogenesis during pre-natal life, acting on both myocardial and stromal precursor cells (Figure 1). Going a step further, RLX may be regarded as a novel cardiotropic drug useful to enhance the repair and – hopefully – promote regeneration of the diseased heart during adult life.

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