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Perspective
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Development of Pharmacological Agents for the Activation and Directional Differentiation of Resident Stem Cells in Organs and Tissues

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Abstract

One of the most promising resources of the body for restoring the myocardium after ischemic damage and optimizing the functions of the cardiac muscle during aging are resident Cardiac Stem Cells and Bone Marrow Mesenchymal Stem Cells (CSC, BM MSC). The mechanisms of their interaction in the whole organism remain unclear. It seems that apoptosis has a key role in myocardial regeneration and conjugation of the functions of CSC and MSC in tissues after infarction and in the aging process. Apoptosis (in contrast to necrosis), simultaneously with the destruction of irreversibly damaged cells, initiates processes that stimulate the proliferation of cells that are in the early stages of differentiation. It was suggested that in the final products of apoptosis, Apoptotic Bodies (ApB), the activation factors and the code for tissue-specific differentiation of stem cells are contained.

Keywords: Apoptosis; Stem cells; Myocardial regeneration

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Perspective

It seems that ApB is prototypes of drugs that can selectively activate tissue-specific regeneration of resident cells of damaged organs, and also involve growth factors of mesenchymal stem cells of the bone marrow. To create pharmacological agents, it is necessary to identify the nature of signaling molecules located on the surface of ApB responsible for the homing of mesenchymal stem cells from blood to tissues, as well as to determine miRNA profiles in ApB, which are the code of tissue-specificity of cells. Measurement of the concentration of ApB in the circulating plasma and the determination of their transcriptome will allow to give an integral assessment of the intensity of programmed cell death as a whole, and on the miRNA profiles determine the severity of apoptosis in individual organs and tissues.

Materials and Methods

Apoptotic Bodies (ApB) of cardiomyocytes and fibroblasts were prepared according to the method of Hristov et al. [2004]. Influence of ApB on cardiomyogenesis was studied in the model of neonatal cardiomyocytes colonies from KSC c-kit$^+$, Sca$^+$, Isl1$^+$ -type by Belostotskaya, Golovanova [1]. Concentrations of RNA and mRNA were determined by UV-abs and fluorescence methods. In situ hybridization was used with sampling of the Y chromosome (ID Labs Biotechnology). Migration of BM MSC was studied in C57BL/6 mice. BM MSC was isolated from the tubular bones of C57BL/6 mice expressing the GFP protein. Sections of tissues were examined on a confocal microscope LSM5 PASCAL. The contractile function of the myocardium after the administration of ApB was assessed by Langendorf method.

Results and Discussion

CSC and apoptosis

The introduction of Cardiomyocytes (CM) Apoptotic Bodies (ApB) into the culture of myocardial cells strengthened the proliferation and differentiation of CSC in the colony. In the presence of CM ApB, the contraction frequency of CM colonies during 3 weeks of cultivation increased in

comparison with the control by more than 1,5 times. Fibroblasts ApB did not have such effect on the CM colony. After repeated intravenous administration of ApT to rats with post infarction heart failure, the ventricular contractility increased by 30% in 3 weeks after Myocardial Infarction (MI) compared to the control [2]. Injections of CM ApB to "old" Wistar rats caused an increase in myocardial contractility to values characteristic of the cardiac muscle of "young" animals. Fibroblasts ApB caused suppression of myocardial contractility. It is shown that the cardiomyocyte ApB activates the processes of cardiomyocyte pool renewal, and the fibroblasts ApB stimulate the development of clones, from which non-contractile structures of the myocardium, in particular the endothelium of the vessels, are formed.

BM MSC and apoptosis

BM MSC of animals (XY), introduced into the blood stream of rats (XX) after MI, went beyond the vessels to the perifocal zone of the infarction. For studying of the possible migration mechanism of BM MSC, laser dose rates were established on a fibroblast culture, this doses which *ex vivo* caused mainly apoptosis or necrosis of cells. In mice (C57BL/6), one of the auricles was irradiated with apoptotic or necrotic dose. The contralateral ear served as a control. After irradiation with an apoptotic dose and administration of BM MSC with GFP through the day on a cross-sectional preparation of the ear, the whole field of vision was covered by cells with a GFP-tag. On the preparation of the cut of the control ear, only single cells with GFP were detected. With the use of a necrotic dose of the laser, the transition of BM MSC from blood to tissue was not observed [3].

Conclusion

It seems that the functions of CSC and BM MSC in the areas of myocardial regeneration are match by ApB cells. Signal molecules are located on the outer surface of the ApB, which mediate the homing and directional movement of BM MSC into the zone of myocardial regeneration. BM MSC chemotaxis provides targeted delivery of growth factors and cytokines that are necessary to maintain proliferation and directional differentiation of CSC. Inside ApT have biologically active compounds that store memory of the tissue-specificity of the dead cell. It can be assumed that simultaneously with the launch of the effector cascade of apoptosis, which ends with the formation of ApB, microRNA expression takes place, the profile of which is a "code" of the tissue belonging to the cell. With endocytosis of ApB by resident stem cells, a specific set of trigger microRNAs expresses genes that determine the direction of CSC differentiation. It can be assumed that this hypothesis is valid not only for the heart but also for other organs and tissues.

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