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Which cells are involved in cardiomyogenesis in mammalian and zebrafish heart?

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There is no clear evidence on which cells are able to renew the adult mammalian myocardium. Studying cardiomyogenesis in the heart of newborn mammals and adult zebrafish, many researchers have concluded that new cardiomyocytes (CMs) are formed by dedifferentiation and division of pre-existing mature CMs. In addition, it is supposed that mature CMs of zebrafish are divided throughout life, not only renewing the myocardium, but also regenerating it after injury. In turn, it has been shown that mature CMs of mammals are divided only in the first 5-7 days after birth, and then permanently lose this ability. Investigating the phenomenon of intracellular development of resident cardiac stem cells (CSCs) with the formation of "cell-in-cell structures" (CICSS), we've found that transitory amplifying cells (TACs), being released after CICSS opening, are 2 times larger than the original CSCs (12-13 μm vs. 5-6 μm) and are able to divide and differentiate. We observed the presence of CICSS not only in the myocardium of adult mammals, but also in 18-day-old embryos and the neonatal rats. We found that CICSSs, formed in the embryonic phase, not only provide TACs for embryonic cardiomyogenesis, but, opening immediately after birth, release large numbers of proliferating TACs to support neonatal cardiomyogenesis. Counting the number of mitotic cells and measuring their size showed that only small cells

with $D < 13 \mu\text{m}$ are able to divide in the neonatal period. After that, their proliferation stops, and they transit from hyperplasia to hypertrophy. We demonstrated that adult myocardium of *Danio rerio* also contains CICSS. Upon opening, they release a large number of TACs, the dimensions of which are comparable to the dimensions of cells that divide inside the myocardium of newborn mammals. We assume that specifically TACs, but not mature CMs, form new CMs in mammals and zebrafish throughout life.

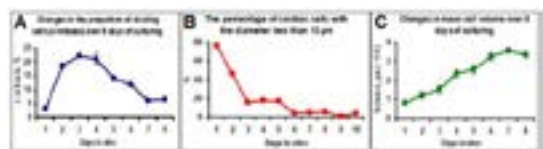


Figure 1: Growth of myocardial cells obtained from newborn rat heart in vitro. Proportion of dividing cells (A), proportion of cells with $D < 13 \mu\text{m}$ (B) and mean cell volume (C).

Recent Publications

1. Belostotskaya G B and Golovanova T A (2014) Characterization of contracting cardiomyocyte colonies in the primary culture of neonatal rat myocardial cells: A model of in vitro cardiomyogenesis. *Cell Cycle* 13(6):910-

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2. Belostotskaya G, Nevorotin A and Galagudza M (2015) Identification of cardiac stem cells within mature cardiac myocytes. *Cell Cycle* 14(19):3155-3162.
 3. Filippov S K, Sergeeva O Yu, Vlasov P S, Zavyalova M S, Belostotskaya G B, Garamus V M, Khrustaleva R S, Stepanek P and Domnina N S (2015) Modified hydroxyethyl starch protects cells from oxidative damage. *Carbohydrate Polymers* 134:314–323.
 4. Belostotskaya G B, Golovanova T A, Nerubatskaya I V and Galagudza M M (2018) Discovery of the phenomenon of intracellular development of cardiac stem cell – a new step in understanding of biology and behavior of tissue-specific stem cells. In the book “Evolutionary Physiology and Biochemistry: Advances and Perspectives”, Chapter 5:45-60.
 5. Belostotskaya G B, I V Nerubatskaya and M M Galagudza (2018) Two mechanisms of cardiac stem cell-mediated cardiomyogenesis in the adult mammalian heart include formation of colonies and cell-in-cell structures. *Oncotarget* 9:34159-34175.

Biography

Galina B Belostotskaya graduated from Leningrad State University and defended her thesis on a specialty “Radiobiology”. During late 15 years she has been studying the physiology of skeletal muscle cells and the behavior and cardiomyogenic potential of resident cardiac stem cells. Being the head of investigations she released 7 specialists and 2 graduate students. The works have been supported by the 11 Russian grants.

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