Galina Belostotskaya, J Clin Exp Cardiology 2015, 6:4
http://dx.doi.org/10.4172/2155-9880.S1.023

OMICS International
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5th International Conference on
Clinical & Experimental Cardiology
April 27-29, 2015 Philadelphia, USA

Intracellular development of cardiac stem cells as a strategic avenue to secure self-renewal, regeneration and maintenance of the mammalian myocardium

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A large incoherence of databanks illustrating the rates self-renewal of cardiac cells and the inability to make a background for the low efficiency of post-infarction mammalian myocardial regeneration is associated with the absence of the understanding of biology and behavior of the resident cardiac stem cells (CSCs) in normal and pathological conditions.

In culturing of newborn, 20- and 40-day-old Wistar rat myocardial cells (*in vitro*) and in a cardiac cell suspension (*ex vivo*) of 1.5-year-old rat, one-year-old bull, adult 4-5-month-old mice C57bl/6N and 45-year-old woman an unknown mode of reproduction of new cardiac cells has been demonstrated. It has been shown that apart from clones resident Isl1+, c-kit+ and Sca1+ CSCs are capable to develop within a population of the mature myocardial cells via forming intracellular bodies. The latter termed and now known as "cell-in-cell structures" are described for immune cells (to be involved into cytophagocytosis and emperipolesis) and for tumors (entosis), but the data concerning a process of stepwise CSCs structures formation are absent. In contrast to known "cell-in-cell structures", CSC development occurs in cytoplasm of the cardiac cells inside the capsule with 3-5 small holes (micropyles) on its surface. For the first time both *in vitro* and in *ex vivo* the reproduction and the initial steps of CSCs differentiation inside the capsule located within the host cell with the formation of transit amplifying myocytes (TAMs) had been identified. It has been shown that the process of intracellular development is finished by the capsule rupture to release cardiac biomarker-positive CSCs-derived TAMs.

In vitro simulation of myocardial infarction (acidosis and hypoxia) would result in blocking the differentiation of CSCs inside clones, but 10-15 times increased the number of "cell-in-cell structures", formed *in vitro* by CSCs identified among neonatal rat myocardial cells. However, analysis of cardiac cells suspension (*ex vivo*) of C57bl/6N mice after returning from a 30-day space flight (Project BION-M1) showed that the flight and microgravity stimulated clone for-mation without changing the number of intracellular CSCs-structures as compared to the con-trol.

The results obtained allowed to hypothesize that the self-renewal of mammalian myocardium should be going both via proliferation and differentiation of CSCs with the formation of clones, and by their division and partial differentiation inside the mature myocardial cells. Moreover, in an intact (healthy) heart, modes of new cardiac cells formation mentioned occur with the similar frequency: approximately 1 event per 100000 of myocardial cells.

We assume that a process of the myocardial cell number maintenance studied is appearing to be a dynamic system to exploit two ways for forming of new functionally active cardiac cells. i.e., (i) the development of resident CSCs within the clones, which are localized between the cells of the heart muscle, and (ii) inside the mature cells of the heart with formation of TAMs which af-ter their release from intracellular capsules also finally differentiate between the cells of the myocardium. In case of prolonged microgravity (in the absence of inflammation) restoration of damaged myocardium occurs mainly through the formation of clones. However, aggressive conditions arising during ischemia and infarction, prevent the clone formation, but promote the transition of CSCs for more long intracellular mode of development. We assume that the latter can explain the "tolerance" of CSCs during cardiac disorders.

Biography

Galina Belostotskaya was born in 1947 in St. Petersburg (former Leningrad), graduated from Leningrad State University in 1970 and defended her thesis in 1984 on a specialty "Radiobiology". From 1986 to the present day she is working in the Sechenov Institute of Evolutionary Physiology and Biochemistry of the Russian academy of sciences as a Senior researcher and the Head of Cytoanalysis centre. In recent years, she has been studying the resident muscle stem cells and published more then 10 papers in Russian Journals and 2 articles in "Cell Cycle" (2014) and Bioelectromagnetics (2014). Being the head of investigations she released 7 specialists and 2 graduate students. The works have been supported by the 10 Russian grants.

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