CDB SEMINAR

Wataru Kimura

Life Science of Tsukuba Advanced Research Alliance,
University of Tsukuba

Tuesday, March 21, 2017
15:00~16:00 A7F Seminar Room

Oxygen Metabolism and Cardiac Regeneration

Summary

The adult mammalian heart is one of the least regenerative organs, and therefore injury to this organ system results in a significant health and economic burden globally. Although it has been shown that a low level of cardiomyocyte turnover does occur in adult mammals, it is not sufficient to induce functional recovery in the damaged heart. In contrast, some vertebrate species (including zebrafish and urodele amphibians) and immature mammals are capable of full cardiac regeneration through proliferation of pre-existing cardiomyocytes. Despite these findings, little is known about what distinguishes proliferative cardiomyocytes from terminally-differentiated non-proliferative cardiomyocytes.
Interestingly, across vertebrate species there is a strong correlation between oxidative metabolism and proliferative capacity of cardiomyocytes. For example, cardiomyocytes in zebrafish and mammalian fetuses are less oxygenated compared to postnatal mammals. Our prior work showed that there is a drastic metabolic transition from glycolysis to mitochondrial respiration immediately after birth in postnatal mammalian cardiomyocytes. Our further studies indicated that this steep rise in mitochondrial energy production in the postnatal cardiomyocytes induces an increased reactive oxygen species (ROS) levels and oxidative DNA damage, which in turn directly triggers cell cycle arrest.
These results raised an important question: how are cardiomyocytes that contribute to myocyte turnover in the adult heart protected from oxidative stress? We postulated that proliferative cardiomyocytes in the adult hearts are hypoxic and thus protected from oxidative DNA damage. To test our hypothesis, we traced the lineage of hypoxic cardiomyocytes in the adult heart with Cre-loxp based genetic lineage tracing system utilizing the protein stabilization of Hif-1α, a master regulator of cellular hypoxia response. With this system, we identified a rare cardiomyocyte population with preserved embryonic/neonatal features which contributed to cardiomyocyte renewal.
Based on these findings, we reasoned that systemic hypoxemia may decrease mitochondrial metabolism, and thereby activate cell cycle re-entry in terminally differentiated adult cardiomyocytes. We exposed adult mice to severe hypoxia (7% atmospheric oxygen) for 2 weeks. After exposure, mitochondrial metabolism and oxidative DNA damage were both markedly reduced in adult cardiomyocytes. Remarkably, we observed the activation of cardiomyocyte cell cycle re-entry in the adult heart. Furthermore, the exposure of mice to 7% oxygen for 2 weeks after myocardial injury by permanent ligation of the left anterior descending coronary artery was sufficient to induce a significant recovery of systolic cardiac function. Our data suggest that hypoxia and targeting hypoxia signaling can be novel therapeutic directions to treat cardiac injury and diseases.

Host:
Tomoya Kitajima
Chromosome Segregation, CDB
tkitajima@cdb.riken.jp
Tel:078-306-3346 (ext:4447)