eagle group

OPEN ACCESS

Journal of New Science Biotechnology

Mini Article

Emerging Approaches in Regenerative Biology

Galip S. Aslan[1], Gonca Misir[1], Fatih Kocabas[1, *]

[1]Department of Genetics and Bioengineering, Regenerative Biology Research Group, Yeditepe University, Istanbul 34755, Turkey

*Corresponding Author: Fatih Kocabas

Abstract

Regenerative biology is a rapidly growing field with an excitement around novel approaches in regenerative medicine. We employ various emerging approaches to address some of the major health issues such as lack of cardiac regeneration following myocardial infarction, limited availability of appropriately HLA-matched hematopoietic stem cells for bone marrow transplantations, inadequate availability of therapeutics for activation of regenerative responses, and difficulty in identification of resident adult stem cells. Approaches that we pursue include the use of neonatal mouse cardiac regeneration model, identification of cardiogenic or hematopoietic small molecules, ex vivo expansion of stem cells and metabolic identification of adult stem cells. Here we discuss how these technologies provide new angles towards discoveries in regenerative biology.

Keywords: Regenerative Biology, Stem Cell Biology, Cardiac Regeneration, Regenerative Small Molecules

ABBREVIATIONS

HSC: Hematopoietic Stem Cell; **HIF:** Hypoxia Inducible Factor; **CM:** Cardiomyocyte; **CDKI:** Cyclin-Dependent Kinase Inhibitor

Regenerative Biology Research Group

Regenerative Biology Research Group has been recently established in Yeditepe University, Istanbul. We have previously developed a novel method to isolate stem cells from bone marrow and heart which led to us discover of unique metabolic profile of mouse hematopoietic stem cells (HSCs) [1], human HSCs, glycolytic cardiac progenitors (GCPs) and their respective cardiac hypoxic niche [2]. Furthermore, we have utilized neonatal cardiac regeneration model in mice, which led us to identify an important regulator of postnatal cardiomyocyte cell cycle arrest gene known as Meis1 [3]. We are currently interested in 1) elucidating the molecular mechanism of mammalian cardiac regeneration 2) reactivation of cardiomyocyte cell cycle by using of regenerative small molecules, 3) metabolic identification of distinct tissue and cancer specific stem cells, and 4) expansion of stem cell both *in vivo* and *ex vivo* (Figure 1).

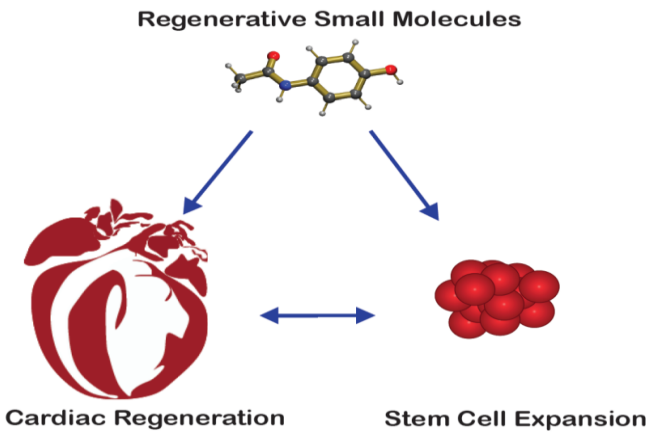

Figure 1: Schematic of research areas. We aspire to identify regenerative small molecules that could be utilized in cardiomyocyte cell cycle entry and hematopoietic stem cell expansion. In addition, we aim to determine cardiogenic and hematopoietic factors involved in cell cycle arrest.

Introduction

Regenerative biology and medicine is a translational area of research, where molecular biology and applications of tissue engineering interact to replace or repair damaged organs or tissues through induction of regeneration mechanisms in the body. Various approaches and organism are utilized to understand mechanisms of regeneration with the hope to apply in regenerative medicine. Here we discuss our research interests along with previous studies.

Neonatal Mouse as a Model for Mammalian Cardiac Regeneration

Limited rate of cardiomyocyte turnover exist in the adult heart [4,5]. This low rate of myocyte turnover in the heart is one of the hurdles to replace reservoir of cardiomyocytes following myocardial injuries. In addition, this limited the studies regarding the identification of factors involved in cardiomyocyte cell proliferation. However, we have recently developed a cardiac injury model on neonatal mice [3,6,7] We have successfully used this model to show that neonatal mice are capable to completely regenerate their heart after resection of entire ventricular apex and ischemic myocardial infraction [3,7]. As a proof of concept, we have used this mammalian cardiac regeneration model to identify Meis1 as one of the key regulators involving in postnatal CM cell cycle arest [3]. In this study, we have reported that increased expression of *Meis1* induces expression of CDKIs, which are responsible for CM cell cycle exit in postnatal period of mouse in where mouse cardiomyocytes lose proliferative capacity. Thus, we work on the molecular mechanisms of heart regeneration by using neonatal mouse cardiac regeneration model and development of therapeutical strategies to reactivate this regenerative phenomenon in adult heart.

Identification of Regenerative Small Molecules

Small molecules are low molecular weight compounds that may involve in biological process. This small size, which is usually smaller than 500 Daltons, provides flexibility to diffuse across cell membranes. Regenerative small molecule research aims to determine small molecules that facilitate repair or regeneration process via targeting key components of the molecular pathways effecting cell cycle and regenerative response. Availability of neonatal cardiac regeneration models [6,7] that could be utilized in identification of cardiogenic small molecules provided a new platform to discover regenerative small molecules targeting cardiomyocyte cell cycle. This allows us to test regenerative small molecules *in vivo*. In addition, we perform *in silico* screenings and *in vitro* assays for cardiogenic drug discovery, followed by validation of hits in ex vivo neonatal rat cardiomyocyte culture.

Development of Ex vivo Platforms for Stem Cell Expansion

Stem cells are one of the greatly investigated topics to be used for therapeutical purposes. HSCs are multipotent stem cells and common ancestors of all blood cells, deposited in cord blood and bone marrow. HSCs transplantation is used for leukemia, multiple myeloma patients and others [8]. Ex vivo stem cell expansion followed by cell therapy is dream of scientists in regenerative biology research. This requires understanding of molecular pathways involved in stem cell cycle. In the last decade, there has been an accumulating knowledge regarding factors regulating stem cell maintenance as well as proliferation *in vivo*. For instance, we found that at least 200 genes in hematopoietic stem cells (HSCs) have been characterized and described in the literature by loss-of-function or overexpression studies. This information could be translated into development of ex vivo platforms for stem cell expansion that could be used towards to HSC transplantation used in life-saving procedure including immune, hematologic and genetic diseases (reviewed in [9]). Furthermore, this could allow overcoming issues during allogeneic HSC transplantation, owing to the limited availability of appropriately human leukocyte antigen (HLA)-compatible HSCs. Thus, we aim to discover small molecules that induce HSCs both *in vivo* and *ex vivo* to be used in HSC transplantation.

A Metabolic Approach To Stem Cell Identification

Metabolism plays important role in maintenance and survival of stem cells in their relatively hypoxic microenvironments (reviewed in [15]). We recently showed that stem cells utilize cytoplasmic glycolysis rather than mitochondrial phosphorylation [10]. This phenomenon appears to be common among various adult stem cells such as HSCs and cardiac progenitors [2,10]. This provides a metabolic approach that could allow previously unidentified stem cell populations in different tissues and organs.

Glycolytic metabolism of HSCs is considerably significant to maintain their quiescence and survival in hypoxic microenvironment. We have found that glycolytic metabolism as well as oxidant defence of HSCs are regulated by transcriptional regulation of *Hif-1α* and *Hif-2α*. Moreover, we have identified Meis1 and Profilin 1 (*pfn 1*), involved in the regulation of switching from anaerobic glycolytic metabolism to oxidative phosphorylation in HSC. In addition, we have showed that *pfn1* positively regulates HSC retention in bone marrow via interacting with Gα13, which transcriptionally increases EGR1 levels [11,12]. In the light of these studies, we believe that metabolic profiling of stem cells could be invaluable

to identify previously unknown stem cell populations in different tissues or tumors and their respective microenvironments.

Regenerative biology is rapidly developing field with many landmark studies leading to regenerative medicine applications [3,6,13,14]. We focus on to identify responsible mechanism involving in cell cycle regulation and reactivation of regeneration process. In short, we seek for regenerative small molecules to activate regenerative capacity of cardiomyocytes and expansion of HSCs. In addition, we aspire to identify tissue and cancer specific stem cells by utilizing metabolic profiling based on our recently developed method [1].

Acknowledgments

This study was funded by Yeditepe University, Istanbul.

Conflict of Interest Statement

All authors declare that they have no conflicts of interest concerning this work

Reference:

1. Kocabas F, Zheng J, Zhang C, Sadek HA. Metabolic Characterization of Hematopoietic Stem Cells. Hematopoietic Stem Cell … 2014.
2. Kocabas F, Mahmoud A, Sosic D, Porrello E, Chen R, Garcia J, et al. Erratum to: The Hypoxic Epicardial and Subepicardial Microenvironment. Journal of Cardiovascular Translational Research 2012;5:666–666.
3. Mahmoud AI, Kocabas F, Muralidhar SA, Kimura W, Koura AS, Thet S, et al. Meis1 regulates postnatal cardiomyocyte cell cycle arrest. Nature 2013;497:249–53.
4. Bergmann O, Bhardwaj RD, Bernard S, Zdunek S, Barnabé-Heider F, Walsh S, et al. Evidence for cardiomyocyte renewal in humans. Science 2009;324:98–102.
5. Bergmann O, Zdunek S, Frisén J, Bernard S, Druid H, Jovinge S. Cardiomyocyte Renewal in Humans. Circulation Research 2012.
6. Porrello E, Mahmoud A, Simpson E, Hill J, Richardson J, Olson E, et al. Transient Regenerative Potential of the Neonatal Mouse Heart. Science 2011;331:1078–1080.
7. Mahmoud A, Porrello E, Kimura W, Olson E, Sadek H. Surgical models for cardiac regeneration in neonatal mice. Nat Protoc 2014;9:305–311.
8. Kondo M, Wagers AJ, Manz MG, Prohaska SS, Scherer DC, Beilhack GF, et al. Biology of hematopoietic stem cells and progenitors: implications for clinical application. Annu Rev Immunol 2003;21:759–806.
9. Walasek MA, Os R van, Haan G de. Hematopoietic stem cell expansion: challenges and opportunities. Ann N Y Acad Sci 2012;1266:138–50.
10. Simsek T, Kocabas F, Zheng J, Deberardinis RJ, Mahmoud AI, Olson EN, et al. The distinct metabolic profile of hematopoietic stem cells reflects their location in a hypoxic niche. Cell Stem Cell 2010;7:380–90.
11. Zheng J, Lu Z, Kocabas F, Böttcher RT, Costell M, Kang X, et al. Profilin 1 is essential for retention and metabolism of mouse hematopoietic stem cells in bone marrow. Blood 2014;123:992–1001.
12. Kocabas F, Zheng J, Thet S, Copeland NG, Jenkins NA, DeBerardinis RJ, et al. Meis1 regulates the metabolic phenotype and oxidant defense of hematopoietic stem cells. Blood 2012;120:4963–72.
13. Poss KD, Wilson LG, Keating MT. Heart regeneration in zebrafish. Science 2002;298:2188–90.
14. Witman N, Murtuza B, Davis B, Arner A. Recapitulation of developmental cardiogenesis governs the morphological and functional regeneration of adult newt hearts following injury. Developmental 2011.