IQRO JURNALI / 2023
GUVOHNOMA № 060680
E-ISSN : 2181-4341

VOL–2, ISSUE–1
https://wordlyknowledge.uz/

HEART DEVELOPMENT IN NEWBORNS

[1] **Ulug'bekov M.U.**
[2] **Xankeldiyeva X.K.**
[3] **Mirzayeva Z.U.**
Andija State Medical Institute , Uzbekistan

Annotation: The neonatal capacity for cardiac regeneration in mice is well-studied and has been used to develop many potential strategies for adult cardiac regenerative repair following injury. However, translating these findings from rodents to designing regenerative therapeutics for adult human heart disease remains elusive. Large mammals including pigs, dogs, and sheep are widely used as animal models of humans in preclinical trials of new cardiac drugs and devices. However, very little is known about the fundamental cardiac cell biology and the timing of postnatal cardiac events that influence cardiomyocyte proliferation in these animals. There is emerging evidence that external physiological and environmental cues could be the key to understanding cardiomyocyte proliferative behavior. In this review, we survey available literature on postnatal development in various large-mammal animal models to offer a perspective on the physiological and cellular characteristics that could be regulating cardiomyocyte proliferation.

Keywords: Postnatal heart development, Cardiomyocyte proliferation, Large mammals, Cardiac regeneration, Human heart disease

Congenital heart defects are the most lethal of anomalies in the first year of life and cardiovascular disease is the leading cause of death worldwide [1,2]. These lethal conditions are aggravated by the limited ability of cardiac muscle to repair or regenerate in adult mammals. Studies in mice reported several years ago provide evidence that the heart can regenerate after injury in the first few days after birth [3,4]. This finding has led to intensive research efforts directed towards understanding how regeneration in mammalian hearts occurs and what causes loss of regenerative ability. Moreover, there is increasing evidence that inducing developmental or regenerative pathways in adult mouse cardiomyocytes can promote cardiac repair after myocardial infarction [5,6]. However, relatively little is known of cardiac regeneration or repair mechanisms in larger mammals, including humans. Current efforts are directed towards examining postnatal heart development in large animal models as a means to understand human heart development, particularly since the US Food and Drug Administration (FDA) requires large mammal models to translate devices and potential therapies based on studies in mice and zebrafish.Cardiac maturation events, such as the timing of cell cycle arrest, multinucleation, polyploidy, expression of mature sarcomeric proteins, and induction of cardiomyocyte hypertrophic growth, are likely variable across mammalian species. Available studies support differences in postnatal maturation and regenerative potential in rodents and large animals used for laboratory studies, when compared to the human heart [7]. Further, the impact of physiological differences between the various model animal species, such as gestation time, age at weaning, age at sexual maturity, and growth rate, on postnatal

cardiac maturation has also not been taken into account in their use as models of human heart development and regenerative capacity [8]. The conservation of such characteristics across different species has important implications for translating findings from these mammalian model systems to human congenital heart repair or treatment of heart failure.

Before birth, the mammalian heart grows primarily through proliferation of differentiated, mononucleated cardiomyocytes that undergo complete cytokinesis to form new cardiomyocytes [9]. After birth, the ability of differentiated cardiomyocytes to proliferate and generate new muscle is lost, which is a major disadvantage for correction of congenital malformations or cardiac repair after injury [3]. The timing of cardiomyocyte cell cycle arrest and loss of regenerative ability after birth has been extensively studied in rodents, but information for large mammals is lacking [8]. In humans, there is no consensus on cardiomyocyte proliferative capacity after birth [10–12]. One study estimating mitotic and cytokinetic indices in neonates and children suggests that total cardiomyocyte number continues to increase after birth, with about 3-fold increase in cardiomyocyte number measured by 20 years of age [10]. Alternatively, human cardiomyocyte generation rates based on radiolabeling led to lower estimates of newly-formed cardiomyocytes in children and young adults [11,12]. Therefore, the exact proliferative capacity and timing of cardiomyocyte cell cycle arrest in postnatal humans is still not known. A case report published in 2016 described surprising recovery of heart function after neonatal heart injury in a human infant [13]. This has led to much speculation in the field regarding the ability of the postnatal human heart to repair after injury, with implications for the timing of surgical repair of congenital heart defects in infants. However, definitive findings on the proliferative or regenerative abilities of large mammals including pigs, dogs, sheep, and nonhuman primates have not been reported. Here we review published information on postnatal heart maturation and cardiomyocyte cell cycling as a means to assess the potential of the postnatal heart to repair or regenerate in various mammals.

Cardiac regeneration was first characterized in salamanders and zebrafish where new cardiac muscle is generated after resection of up to 20% of the adult heart [14,15]. Cell lineage tracing in zebrafish demonstrated that the newly-formed muscle arises from pre-existing cardiomyocytes which dedifferentiate, proliferate, and regenerate [16,17]. Notably, the new heart muscle forms in the absence of a collagen-rich scar, which is in contrast to mammalian adult cardiac injury [15]. Zebrafish heart regeneration is enabled by proliferation of mononucleated cardiomyocytes and signaling from the epicardium [18]. Ploidy of cardiomyocytes affects cardiac regenerative ability with diploid cardiomyocytes capable of proliferation and formation of new muscle after injury [19]. Thus, the innate cardiac regenerative capacity in zebrafish includes cardiomyocyte proliferation, induction of regenerative signals from the epicardium, and lack of fibrosis or scar formation.

Mammalian cardiac regeneration after ventricular resection was first observed in neonatal mice, where new heart muscle was formed by proliferation of existing cardiomyocytes [3]. The regenerative period in mice ends soon after birth, within 3–7 days. During this period, cardiomyocytes become binucleated, undergo cell cycle arrest, and initiate hypertrophic growth [20]. At the same time, circulatory demands increase, oxidative metabolism is induced, cardiac fibroblasts produce collagen-rich extracellular matrix (ECM), and circulating macrophages take up residence in the heart [21]. The ability of hearts to regenerate or repair after injury has been linked to ploidy

and mononucleation in a comparative study of mouse strains [22]. ECM stiffness and presence of cardiac fibroblasts also have been implicated in cardiomyocyte maturation and cell cycle arrest [23–25]. Macrophages are also necessary for postnatal heart regeneration, most likely through promoting angiogenesis needed for cardiac vascularization after birth [26]. The exposure of neonatal mice to atmospheric oxygen at birth has been proposed as the means of loss of regenerative capacity through induction of oxidative damage, and hypoxia can prolong the regenerative period after birth or promote repair after injury in adults [27,28]. Moreover, thyroid hormone signaling has been implicated in postnatal cardiomyocyte cell cycle arrest, loss of regenerative ability, and increased metabolic rates in mice [29]. It is currently not known if these mechanisms related to loss of regenerative ability of the postnatal mouse heart extend to larger mammals with much longer gestation times, increased size, and greater cardiac tissue complexity at birth.

While rodents undergo neonatal cardiomyocyte proliferative arrest and a switch to hypertrophic growth within a few days after birth, how this relates to neonatal proliferative capacity in larger mammals, including humans, is unknown. Further, in order for the regenerative repair induced by various approaches in the injured adult mouse heart to be developed into viable therapies for human heart disease, clinical trials are required in large animal models to show efficacy of the proposed therapeutic strategy. Pigs, sheep, dogs, and non-human primates are the most common animals utilized in cardiac preclinical trials, but cats, cows, and horses also are occasionally used [30]. However, the fundamental cell biology of the heart, particularly cardiomyocyte proliferation and growth mechanisms, is largely uncharacterized in these animals. It is thus important to first know the major events in postnatal heart maturation, as well as the characteristics of the cardiac cellular milieu, when considering which type of large animal to use for preclinical studies of cardiovascular devices and reparative therapies. Recently published initial reports suggest that pigs have a similar neonatal regenerative period as mice, with regenerative potential being lost by 3 days after birth [31,32]. However, it is not known how this neonatal maturation and limited regenerative capacity compares to human postnatal heart repair mechanisms. Ultimately, it is imperative to identify the ideal mammalian model that recapitulates postnatal human cardiac development for translation of therapeutic advances in cardiac repair from animal model systems to humans. Here, we discuss fundamental physiology of various model systems alongside features of postnatal cardiac development, to offer a perspective on the physiological and cellular similarities that could be used as a starting point for translatability from large animal models to human postnatal cardiac development.

Literature :

1. Bui AL, Horwich TB, Fonarow GC (2011) Epidemiology and risk profile of heart failure. *Nat Rev Cardiol* 8: 30–41 [PMC free article] [PubMed] [Google Scholar]

2. Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A (2013) Temporal trends in survival among infants with critical congenital heart defects. *Pediatrics* 131: e1502–1508 [PMC free article] [PubMed] [Google Scholar]

3. Porrello ER, Mahmoud AI, Simpson E, Hill JA, Richardson JA, Olson EN, Sadek HA (2011) Transient regenerative potential of the neonatal mouse heart. *Science* 331: 1078–1080 [PMC free article] [PubMed] [Google Scholar]

4. Haubner BJ, Adamowicz-Brice M, Khadayate S, Tiefenthaler V, Metzler B, Aitman T, Penninger JM (2012) Complete

cardiac regeneration in a mouse model of myocardial infarction. *Aging (Albany NY)* 4: 966–977 [PMC free article] [PubMed] [Google Scholar]

5. Tzahor E, Poss KD (2017) Cardiac regeneration strategies: Staying young at heart. *Science* 356: 1035–1039 [PMC free article] [PubMed] [Google Scholar]

6. Wang J, Liu S, Heallen T, Martin JF (2018) The Hippo pathway in the heart: pivotal roles in development, disease, and regeneration. *Nat Rev Cardiol* 15: 672–684 [PubMed] [Google Scholar]

7. Rumyantsev P (1991) *Growth and Hyperplasia of Cardiac Muscle Cells*, Taylor & Francis, [Google Scholar]

8. Vivien CJ, Hudson JE, Porrello ER (2016) Evolution, comparative biology and ontogeny of vertebrate heart regeneration. *NPJ Regen Med* 1: 16012. [PMC free article] [PubMed] [Google Scholar]

9. Foglia MJ, Poss KD (2016) Building and re-building the heart by cardiomyocyte proliferation. *Development* 143: 729–740 [PMC free article] [PubMed] [Google Scholar]

10. Mollova M, Bersell K, Walsh S, Savla J, Das LT, Park SY, Silberstein LE, Dos Remedios CG, Graham D, Colan S, Kuhn B (2013) Cardiomyocyte proliferation contributes to heart growth in young humans. *Proc Natl Acad Sci U S A* 110: 1446–1451 [PMC free article] [PubMed] [Google Scholar]

11. Bergmann O, Bhardwaj RD, Bernard S, Zdunek S, Barnabe-Heider F, Walsh S, Zupicich J, Alkass K, Buchholz BA, Druid H, Jovinge S, Frisen J (2009) Evidence for cardiomyocyte renewal in humans. *Science* 324: 98–102 [PMC free article] [PubMed] [Google Scholar]

12. Bergmann O, Zdunek S, Felker A, Salehpour M, Alkass K, Bernard S, Sjostrom SL, Szewczykowska M, Jackowska T, Dos Remedios C, Malm T, Andra M, Jashari R, Nyengaard JR, Possnert G, Jovinge S, Druid H, Frisen J (2015) Dynamics of Cell Generation and Turnover in the Human Heart. *Cell* 161: 1566–1575 [PubMed] [Google Scholar]

13. Haubner BJ, Schneider J, Schweigmann U, Schuetz T, Dichtl W, Velik-Salchner C, Stein JI, Penninger JM (2016) Functional Recovery of a Human Neonatal Heart After Severe Myocardial Infarction. *Circ Res* 118: 216–221 [PubMed] [Google Scholar]

14. Oberpriller JO, Oberpriller JC (1974) Response of the adult newt ventricle to injury. *J Exp Zool* 187: 249–253 [PubMed] [Google Scholar]

15. Poss KD, Wilson LG, Keating MT (2002) Heart regeneration in zebrafish. *Science* 298: 2188–2190 [PubMed] [Google Scholar]

16. Kikuchi K, Holdway JE, Werdich AA, Anderson RM, Fang Y, Egnaczyk GF, Evans T, Macrae CA, Stainier DY, Poss KD (2010) Primary contribution to zebrafish heart regeneration by gata4(+) cardiomyocytes. *Nature* 464: 601–605 [PMC free article] [PubMed] [Google Scholar]

17. de Pater E, Clijsters L, Marques SR, Lin YF, Garavito-Aguilar ZV, Yelon D, Bakkers J (2009) Distinct phases of cardiomyocyte differentiation regulate growth of the zebrafish heart. *Development* 136: 1633–1641 [PMC free article] [PubMed] [Google Scholar]

18. Cao J, Poss KD (2018) The epicardium as a hub for heart regeneration. *Nat Rev Cardiol* 15: 631–647 [PMC free article] [PubMed] [Google Scholar]

19. Gonzalez-Rosa JM, Sharpe M, Field D, Soonpaa MH, Field LJ, Burns CE, Burns CG (2018) Myocardial Polyploidization Creates a Barrier to Heart Regeneration in Zebrafish. *Dev Cell* 44: 433–446

e437 [PMC free article] [PubMed] [Google Scholar]

20. Gunthel M, Barnett P, Christoffels VM (2018) Development, Proliferation, and Growth of the Mammalian Heart. *Mol Ther* 26: 1599–1609 [PMC free article] [PubMed] [Google Scholar]

21. Lavine KJ, Epelman S, Uchida K, Weber KJ, Nichols CG, Schilling JD, Ornitz DM, Randolph GJ, Mann DL (2014) Distinct macrophage lineages contribute to disparate patterns of cardiac recovery and remodeling in the neonatal and adult heart. *Proc Natl Acad Sci U S A* 111: 16029–16034 [PMC free article] [PubMed] [Google Scholar]

22. Patterson M, Barske L, Van Handel B, Rau CD, Gan P, Sharma A, Parikh S, Denholtz M, Huang Y, Yamaguchi Y, Shen H, Allayee H, Crump JG, Force TI, Lien CL, Makita T, Lusis AJ, Kumar SR, Sucov HM (2017) Frequency of mononuclear diploid cardiomyocytes underlies natural variation in heart regeneration. *Nat Genet* 49: 1346–1353 [PMC free article] [PubMed] [Google Scholar]

23. Qian L, Huang Y, Spencer CI, Foley A, Vedantham V, Liu L, Conway SJ, Fu JD, Srivastava D (2012) In vivo reprogramming of murine cardiac fibroblasts into induced cardiomyocytes. *Nature* 485: 593–598 [PMC free article] [PubMed] [Google Scholar]

24. Yahalom-Ronen Y, Rajchman D, Sarig R, Geiger B, Tzahor E (2015) Reduced matrix rigidity promotes neonatal cardiomyocyte dedifferentiation, proliferation and clonal expansion. *Elife* 4: [PMC free article] [PubMed] [Google Scholar]

25. Li Y, Asfour H, Bursac N (2017) Age-dependent functional crosstalk between cardiac fibroblasts and cardiomyocytes in a 3D engineered cardiac tissue. *Acta Biomater* 55: 120–130 [PMC free article] [PubMed] [Google Scholar]

26. Aurora AB, Porrello ER, Tan W, Mahmoud AI, Hill JA, Bassel-Duby R, Sadek HA, Olson EN (2014) Macrophages are required for neonatal heart regeneration. *J Clin Invest* 124: 1382–1392 [PMC free article] [PubMed] [Google Scholar]

27. Puente BN, Kimura W, Muralidhar SA, Moon J, Amatruda JF, Phelps KL, Grinsfelder D, Rothermel BA, Chen R, Garcia JA, Santos CX, Thet S, Mori E, Kinter MT, Rindler PM, Zacchigna S, Mukherjee S, Chen DJ, Mahmoud AI, Giacca M, Rabinovitch PS, Aroumougame A, Shah AM, Szweda LI, Sadek HA (2014) The oxygen-rich postnatal environment induces cardiomyocyte cell-cycle arrest through DNA damage response. *Cell* 157: 565–579 [PMC free article] [PubMed] [Google Scholar]

28. Nakada Y, Canseco DC, Thet S, Abdisalaam S, Asaithamby A, Santos CX, Shah AM, Zhang H, Faber JE, Kinter MT, Szweda LI, Xing C, Hu Z, Deberardinis RJ, Schiattarella G, Hill JA, Oz O, Lu Z, Zhang CC, Kimura W, Sadek HA (2017) Hypoxia induces heart regeneration in adult mice. *Nature* 541: 222–227 [PubMed] [Google Scholar]

29. Hirose K, Payumo AY, Cutie S, Hoang A, Zhang H, Guyot R, Lunn D, Bigley RB, Yu H, Wang J, Smith M, Gillett E, Muroy SE, Schmid T, Wilson E, Field KA, Reeder DM, Maden M, Yartsev MM, Wolfgang MJ, Grutzner F, Scanlan TS, Szweda LI, Buffenstein R, Hu G, Flamant F, Olgin JE, Huang GN (2019) Evidence for hormonal control of heart regenerative capacity during endothermy acquisition. *Science* 364: 184–188 [PMC free article] [PubMed] [Google Scholar]