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Editorial

Heart generation and regeneration☆

From ancient Greeks where liver regrowth was elegantly illustrated in the myths of Prometheus and Tityus [1], to the last 200 years with the discovery of organs capable of regrowing upon injury [2], "development and regeneration" has been a fascinating topic throughout history. In fact, studying organ regeneration provides a unique opportunity to learn how early progenitors give rise to terminally differentiated, mature cells at the cellular and organ levels, as nicely summarized by Thomas Hunt Morgan in his book "Regeneration" [3]. The field is getting more traction now, particularly for nonregenerative organs in mammals such as the heart, with the discoveries of induced pluripotent stem cells that are capable of becoming into any cell of the body and can be used to build organoids in a dish.

The heart is a vital, nonregenerative organ in humans. After heart injury such as myocardial infarction, patients can lose millions of cardiomyocytes. Given the lack of regenerative capacity after birth, the loss often leads to heart failure. Similarly, the majority of newborns and infants with congenital heart disease—the most common birth defect [4]—develop heart failure during adulthood [5,6]. While recent advancements in medical and surgical treatments have reduced the associated morbidity and mortality, heart failure is still the leading cause of death worldwide. For this reason, tremendous efforts are underway in the field of cardiac development and regeneration with a goal to restore sufficient new and viable myocardium.

Over the last decade, scientists have been able to generate heart tissues, as well as subtypes of cardiac cells from pluripotent stem cells by mimicking early cardiogenesis in vitro. Although cells derived from pluripotent stem cells lack most functional and morphologic properties of adult cells, they enable production of a large quantity of cardiac cells and thus, hold great promise in heart therapeutics and disease modeling. Moreover, sophisticated lineage tracing as well as single cell technologies have enabled more comprehensive analyses of cardiac progenitor cells that contribute to all major heart cells. Moreover, we have begun to uncover several key signaling pathways, transcription factors, and metabolic and functional cues that are critical for the generation of both embryonic and more mature cardiomyocytes. In this edition of the journal, we present a series of reviews on "Heart generation and regeneration". We review the critical stages of pre and postnatal cardiac development, examine novel concepts on heart regeneration, describe emerging research tools, and deliver an overview of where the field is currently moving.

First, Rowton et al. report on the cues and transcription factors that are activated from the early stages of cardiac differentiation to postnatal cardiomyocyte maturation. They also expand on the different strategies for heart regeneration after injury [7]. Shewale and Dubois review cardiac morphogenesis in various species and extend on recent developments in *ex vivo* embryo culture and imaging, in vitro pluripotent stem cell-based systems to study cardiogenesis, and the bioengineering and genetic manipulations that allow a more holistic study of cardiac development and congenial heart disease [8]. Emerging studies of stem cell based-cardiac organoids are reviewed by Miyamoto et al. [9]. The authors highlight recent discoveries and limitations of developmental and chamber cardiac organoids as well as microtissues and engineered heart tissues by focusing on the specific interventions and morphogens utilized in various organoid models. They conclude that harmonizing bioengineering interventions with developmental cues will further advance this exciting field. Samad and Wu offer an overview of the different single cell transcriptomic and chromatin accessibility protocols to build developmental trajectories, and report on recent studies that examine the application of these assays to heart development and pluripotent stem cell-derived cardiomyocytes [10].

The second half of the series centers around late embryonic and postnatal cardiogenesis and regeneration. Tampakakis et al. focus on the various roles of neurons and hormones during postnatal heart development and attempt to clarify some of the ambiguity in this field [11]. They enlist the specific effects of thyroid, glucocorticoids, insulin-like growth factor as well as sympathetic and parasympathetic neurons and neuronal factors on critical parameters of cardiomyocyte maturation and proliferation. Dong et al. provide ample evidence on the mechanistic contribution of cardiac trabeculae during cardiac chamber maturation [12]. Moreover, the authors link disruptions in the formation of trabeculae with cardiac disease including congenital heart defects, cardiomyopathies and arrhythmias diagnosed at postnatal stages. Wang and colleagues discuss the effects of non-coding RNAs in heart regeneration ("Non-coding RNAs in cardiac regeneration: Mechanism of action and therapeutic potential" by Dr Yi Wang, Jinghai Chen, Douglas B. Cowan, Da-Zhi Wang, https://doi.org/10.1016/j.semcdb.2021.07.007). They expand on the effects and mechanisms of several microRNAs and their translational applicability in treating heart failure and myocardial infarction. Additionally, they define and summarize various long non-coding RNAs and circular RNAs involved in heart regeneration. Finally, Gomez-Garcia et al. provide a comprehensive review on cardiomyocyte maturation and strategies to improve the maturation

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properties of human pluripotent stem cell derived-cardiomyocytes [13]. They also present evidence regarding the in vivo maturation of stem cell-derived myocytes used for cell-based therapies. Cardiac growth and maturation are depicted in the cover image (artwork by Cassie H. Kwon).

With emergence of new tools and high-throughput technologies, cardiac developmental and disease processes are unveiled at higher resolution in an unprecedented pace. Now is an exciting time to further explore the mechanisms underlying these processes, and we hope the current review series can serve as a valuable resource for scientists in the field. Ultimately, we look forward to future discoveries that can help treat the millions of patients with congenital and adult cardiac diseases.

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