Editorial

Getting to the Heart of the Matter: A Perspective on Cardiomyocyte Biology

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Cardiovascular dysfunction has been documented as early as the 1760s when William Heberden remarked on a “…disorder of the breast marked with strong and peculiar symptoms” whose prognosis was “…the patients all suddenly fall down, and perish almost immediately” [1]. While our understanding of the underlying metabolic and cardiovascular processes that lead to myocardial infarction has greatly increased, treatment to limit the deterioration of cardiac function after an infarct event has been stymied by the nature of adult mammalian cardiomyocytes: they do not functionally contribute to the regenerative process. Recent studies in the last decade have revealed that although adult human cardiomyocytes possess the capacity to proliferate over the course of a lifetime, they do not proliferate in sufficient numbers after injury to regenerate functional cardiac tissue [2]. By contrast, neonatal mammalian cardiomyocytes retain their ability to proliferate in significant quantities [3]. Experiments using an injury model in mouse neonatal hearts have demonstrated a robust and almost total regeneration of heart tissue [3-5]. More importantly, human cases of neonatal myocardial infarction have shown complete functional resolution after injury [6]. While the field within cardiovascular regeneration has moved to identify a variety of questions ranging from the extrinsic controls that influence the final fate of neonatal cardiomyocytes to determining robust and reliable markers to identify cardiomyocyte stem cell populations, this editorial aims to shine light on another key player in the heart niche, the immune landscape.

It has been thought for many years that neonates are immunodeficient due to their weak responses to both bacterial infection and poor vaccine outcomes [7]. However, increasing evidence suggest that the neonates prioritize their immunosuppressive programs. These include developmental preference of regulatory T cells (Tregs) in order to maintain feto-maternal tolerance required during neonatal development and to reduce overzealous immune responses following the formation of the micro biome within the gut after birth [8,9]. The bias of the neonatal immune landscape to prefer a Th2 immune profile as opposed to a Th1 overall comports a milieu whose effect on neonatal heart development or regeneration has not been fully examined. Although several groups have determined the requirement of macrophages to resolve ischemic injury in the neonate, effects of general Th2 populations and/or Th2-driving cytokines on the heart niche is still inconclusive [10]. Experiments examining the transcriptional activity of cardiomyocytes during regeneration have demonstrated that anti-inflammatory associated cytokines such as interleukin-13 are modulated in the regenerating mouse heart, thereby hinting the requirement for Th2 associated effectors [11].

Studies examining extrinsic factors such as substrate stiffness or metabolic environment including the effects of hypoxia, coupled with intrinsic microRNA mechanisms to control cardiomyocyte fate has revealed a population that is dependent on a variety of external modulators to influence its eventual non-proliferative profile in the adult heart [12-14]. Are immune control mechanisms heavily favored in neonates also influencing the eventual loss of proliferative function seen in cardiomyocytes during adulthood? Are these external modulators working synergistically to drive neonatal cardiomyocyte fate? Concurrently, do neonatal cardiomyocytes inherently proliferate and external effectors silence this function or do neonatal cardiomyocytes modulate their own niche resulting in the eventual loss of their proliferative phenotype through changing environmental factors? Questions such as these coupled with growing evidence of the heterogeneity of cardiac stem cell population reveal a constantly shifting model of whether extrinsic controls influence intrinsic mechanisms or vice versa, and whether this relationship is more prevalent in specific subsets of cardiac stem cell populations [15,16].

More importantly, what are the evolutionary pressures on mammals specifically as opposed to other species with regenerative hearts such as zebra fish that led to the eventual selection of hearts that could no longer regenerate? [17,18]. What are the tradeoffs for adult mammals to restart in vivo cardiomyocyte

proliferative programs? Will these cardiomyocytes fail to mature or will they have reduced functionality/lifespan compared to the original population seeded at birth? Needless to say, the field of cardiomyocyte biology (Figure 1) is just beginning to reveal the complex interplay between cardiomyocyte and environment in both neonate and adult, and that makes it an exciting time to do research in cardiovascular sciences.

REFERENCES


