This Review is the first in a thematic series on Regulation of Cardiovascular Lineage Commitment during Development and Regeneration, which includes the following articles:

- Making Muscle: Overview to “Cardiovascular Lineage Commitment during Development and Regeneration” Series
- Multipotent Cardiovascular Progenitor Cells
- Regulation of Smooth Muscle Cell Commitment
- Mesp1 as a Master Regulator of Cardiac Lineage Commitment
- Cardiopoietic Factors: Extracellular Signals for Cardiac Lineage Commitment

Michael Schneider, Guest Editor

Making Muscle
Overview to “Cardiovascular Lineage Commitment During Development and Regeneration” Series

Michael D. Schneider

Those unnerved by the evolutionary relatedness between humans and chimpanzees might do well to consider the humble brewer’s yeast, Saccharomyces cerevisiae, and fission yeast, S. pombe. At the biochemical level, we three are so similar that human orthologs can correct lethal defects of the corresponding yeast genes. Apart from merely single genes, this conservation extends to entire networks (eg, signal transduction by a web of protein kinases), modules (eg, cell cycle regulators), and multimolecular machines (eg, the telosome). For these reasons, although a stretch at first glance, yeast provide extraordinary insights into many underpinnings of cardiovascular medicine, shaping the course of research on cardiac muscle cell growth, proliferation, and aging.

However, for multicellular life, assembling the organism gives rise to a further job description: creating the right cell type, in precisely the right place, at the right time. Understanding this set of decisions and the responsible molecular circuits is a prerequisite if one is to appreciate the multiple ways in which developmental biology permeates cardiovascular disease, shaping the course of research on cardiac muscle cell growth, proliferation, and aging.

The present series of review articles for Circulation Research will address the problem of cardiac repair from a fundamental perspective, highlighting leading-edge studies of the cardiovascular cells’ origins, lineage decisions, and fates as an engine of discovery and an enabler of auspicous clinical opportunities. Many readers will already know that the 2 signature characteristics of stem cells (of their “stemness,” as it were) are the capacity for unusually long-term proliferative growth without senescence (ie, self-renewal), alongside the capacity to generate a variety of specialized differentiated daughter cell types (multi-, pluri-, or totipotency, depending on the scope of plasticity).

Embryonic stem (ES) cells, for example, are derived from the inner cell mass of the blastocyst, when the embryo is a hollow ball of roughly 100 cells, just a few days after fertilization. ES cells are pluripotent, lacking only the ability to create extraembry...
onic tissue like the placenta, and can generate the derivatives of all three germ layers of the embryo—endoderm (future gut and lung), ectoderm (future nervous system and skin), and mesoderm (future skeleton, skeletal muscle, blood, and cardiovascular system, including beating cardiomyocytes). Much the same is true for induced pluripotent stem (iPS) cells, which are largely equivalent to ES cells in function but can be derived from a patient’s own somatic cells using a cocktail of stemness transcription factors, overcoming the immunologic barriers that might confound the use of ES cell products as workable therapies.

Sean Wu, from Massachusetts General Hospital and Harvard Medical School, will review the ability for cardiac regeneration in the model organisms such as zebrafish, in which self-repair is most robust, along with emerging evidence for cardiomyocyte turnover in mammals, albeit at low levels. From this framework, Dr Wu will then review what is known about the cardiac progenitors in mouse embryos, including essential concepts such as the multiple origins of cardiomyocytes (left ventricle from the primary heart field; right ventricle, atria, and outflow tract from the second heart field; further right ventricle from the primary heart field; right ventricle, atria, and outflow tract from the second heart field); further contributions from the epicardium and, conversely, the bipotential fates of cardiovascular progenitors, whose offspring encompass cardiac, smooth muscle, and endothelium. This discovery of “multipotent cardiovascular progenitor cells” in ES cell cultures and in embryos is an especially apt and dramatic landmark in cardiovascular stem cell biology. Seemingly related cells persist in postnatal rodent and human hearts yet clearly are insufficient, at their normal numbers and state of activation, to rebuild dead ventricular muscle effectively. This tautology leads to the supposition that the resident cardiac progenitor cells evolved to cope with cardiac muscle cell turnover in the course of normal aging, not the acute and widespread death of cardiomyocytes from endemic coronary artery disease, the latter a feature chiefly of industrial and postindustrial societies. Notwithstanding many logistical and technical obstacles, the isolation and expansion of cardiomyocytes or their precursors from ES cells, iPS cells, and adult hearts arguably provides the strongest present opportunities for bona fide cardiomyocyte creation, toward cell transplantation strategies, and other translational applications. Concomitant possibilities exist, even if more speculative for the moment, to stimulate the resident cardiac progenitors and thereby promote endogenous self-repair.

The vascular side of this story is emphasized by Mark Majesky, from the University of Washington in Seattle. What, precisely, are the subtypes of smooth muscle cell progenitors in vertebrate embryos, their respective origins, and developmental histories? Understanding smooth muscle cells’ formation and maintenance mechanistically requires knowledge of not only the specific precursor–product relationships but also the necessary DNA-binding transcription factors and the partners they tether to DNA indirectly (corepressors, chromatin-silencing complexes, coactivators, and chromatin-remodeling complexes). Smooth muscle fate and plasticity also are governed by so-called microRNAs, including mir145 and 143. This class of noncoding RNAs typically governs cell phenotypes by controlling the translation of messenger RNAs into their cognate proteins and plays key roles in cardiovascular biology as well. In the adult vascular tree, the resident smooth muscle progenitors include those of the adventitia, media, pericytes, and microvessels. More controversial has been the origin of adult smooth muscle from circulating progenitor cells, raising the question which circulating cell is the “right” one for therapeutic angiogenesis in peripheral vascular diseases or in ischemic hearts. Other important clinical perspectives to be discussed include the role of smooth muscle progenitor cells in transplant atherosclerosis and in pathological wall remodelling.

What precedes the predecessors? Development entails a series of choices, by which cell fate (initially pluripotent) is progressively restricted to an ever-narrower range of possibilities. The ES cell gives rise to primitive endoderm, ectoderm, and mesoderm. The cells of the primitive mesoderm, in turn, become patterned to create the cardiovascular system more specifically. One indispensable gene at this latter stage is the intriguing yet underappreciated helix–loop–helix transcription factor, Mesp1, to be reviewed by Cedric Blanpain, from the Universite Libre de Bruxelles. Mesp1 is the earliest marker of mesoderm that migrates through the primitive streak and its essential role in mesoderm patterning was unmasked by a combined deletion of Mesp1 along with its close relative Mesp2, in which circumstance the cardiovascular system fails to arise. Conversely, forced expression of Mesp1 suffices in ES cells to increase the formation of cardiac and vascular smooth muscle, and its direct targets within the genome include previously reported enhancer regions for Nkx2.5 and Hand2. Such experiments vividly demonstrate the importance of understanding the mechanisms controlling the stepwise transitions from primitive mesoderm (expressing T/brachyury) to precardiac mesoderm (expressing Mesp1) and then to cardiac mesoderm (expressing cardiogenic transcription factors rather than, say, the ones for blood).

The ultimate question then becomes, “What induces the inducers?” Extracellular signals that can drive or, alternatively, suppress cardiac muscle creation during development, and regeneration will be the subject of my contribution to this series, together with my Oxford collaborator Roger Patient. Work on this subject has concentrated in particular on members of the transforming growth factor-β superfamily, especially activin A and bone morphogenetic proteins, along with Wnt proteins that, more variably, are essential or inhibitory, depending on their type and timing. Use of defined peptide growth factors to generate cardiac muscle more efficiently from ES cells than would occur spontaneously has been an active line of
inquiry for 15 years, often mimicking essential conditions that are known to be encountered early in the embryo. Directed differentiation of progenitor and stem cells continues as a highly fruitful strategy not only for fundamental studies but also for preclinical cell grafting and the creation of human stem cell–derived cardiomyocytes as novel platforms for drug discovery and toxicology. It is presently unknown whether such strategies might be applicable in patients themselves, to unleash the latent progenitor and stem cells that lurk in human hearts.

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None.

References


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