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Coronary Arteries Shake Up Developmental Dogma

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Abstract

The leading cause of death worldwide is disease of the coronary arteries, the vessels that nourish the heart muscle. However, mechanisms that control their development and possible regeneration remain unknown. Recent work is challenging current dogma of coronary artery origins and illuminating key programs that govern coronary artery formation.

There has been remarkable progress over the past several decades toward defining the fundamental principles of blood vessel development, particularly during tumor angiogenesis. However, comparatively little is known about the cellular origins and developmental programs of organ-specific vascular beds. For example, while the coronary arteries supply oxygen and nutrients to the human heart, the mechanisms governing their formation remain incompletely understood. Failure of coronary arterial circulation leads to ischemic cardiac infarction and cardiac arrest, which is by far the leading cause of death worldwide. Thus, an understanding of the embryonic development of coronary arteries and their maintenance in adult life will inform the development of strategies to prevent or treat cardiovascular disease. In a recent paper published in *Nature* (Su et al., 2018), Dr. Kristy Red-Horse of Stanford University provides detailed insights into coronary artery formation at single-cell resolution, illuminating key mechanisms that may be of interest in the development of novel therapeutic strategies in coronary artery disease.

The Red-Horse lab studies coronary arteries as a model to understand how cell fate decisions are made in the mammalian embryo. For over a century, coronary vessels were viewed simply as branches of the aorta. Still other studies have suggested that coronary arteries arise from the proepicardium, a transient group of progenitor cells in the embryonic heart that in turn gives rise to the epicardium. Dr. Red-Horse challenged these early data by performing detailed cell lineage analyses, demonstrating that the cells comprising mouse coronary arteries in fact sprout from the sinus venosus, the venous inflow tract of the primitive heart. Such sprouting venous endothelial cells migrate and invade the muscle layer of the heart, forming a vascular plexus that is subsequently remodeled into arteries, veins, and capillaries (Red-Horse et al., 2010). Thus, Red-Horse demonstrated that differentiated venous endothelial cells re-specify to make arterial vessels, suggesting that some venous cells retain developmental plasticity and implicating reprograming as the mechanism underlying coronary artery formation in mammals.

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But how is this vein-to-artery “switch” achieved? The importance in answering this question extends beyond the studies of embryology because identifying the transcriptional landscape of endothelial cells during their critical transition to coronary arteries holds promising potentials to regenerative medicine. Red-Horse and colleagues combined single-cell RNA-sequencing (scRNA-seq) with classical lineage tracing and mouse genetics to study gene expression patterns during the transition of sinus venosus cells into coronary arteries. Specifically, mice that express Cre recombinase driven by the apelin receptor promoter (Apj) were used to fluorescently label cells of the sinus venosus. Red-Horse and colleagues isolated and analyzed hundreds of Apj-CreER-labeled cardiac endothelial cells just prior to coronary artery formation during embryonic heart development. Unexpectedly, this analysis revealed transcriptional heterogeneity within the coronary plexus and a gradual loss of venous endothelial cell identity until a sharp transcriptional threshold was reached, precipitating full arterial differentiation. Interestingly, it has long been thought that *in vivo* arterial morphogenesis requires blood flow. However, the arterial differentiation seen by Red-Horse was observed in a subpopulation of non-patent coronary plexus cells at embryonic day 12.5, indicating that blood flow is not required in this context. Thus, Red-Horse demonstrated that vein cells of the developing heart undergo an earlier-than-expected cell fate switch, prior to blood flow, to create a distinct pre-artery subset.

It remained unclear whether this pre-artery subset is necessary for the formation of the mature coronary artery. To answer this question, Red-Horse blocked pre-artery specification using genetically engineered mice that overexpress the transcription factor COUP-TFII. COUP-TFII expression is known to antagonize the arterial program by inducing venous fate (Chen et al., 2012; Fish and Wythe, 2015). Importantly, Red-Horse demonstrated that forced COUP-TFII expression before pre-artery specification blocked these cells from contributing to coronary arteries, while induction of COUP-TFII after specification had no effect on subsequent arterial differentiation. Thus, pre-artery specification at a discrete developmental time point is required for subsequent arterial development. Interestingly, whereas COUP-TFII was previously thought to limit arterial growth by suppressing Notch signaling (You et al., 2005), Red-Horse showed that COUP-TFII may block pre-artery specification by inducing cell-cycle genes, in a Notch-independent manner.

An open question remains how individual cell fate decisions are made to generate veins versus arteries. Lineage tracing revealed that, although most pre-artery cells did go on to form coronary arteries, some became incorporated into capillaries that connect coronary arteries with veins. It seems that certain endothelial cells adopt arterial fate but maintain a degree of plasticity dependent on cues in the tissue environment. Among the obvious candidates for pre-arterial fate regulation is the Notch signaling pathway, which specifies artery formation by restricting angiogenesis. Therefore, how Notch signaling activity impacts gene-expression profiles that generate pre-artery cells would be of significant interest in follow-up studies.

Finally, whereas the sinus venosus is considered as the major origin of coronary endothelium, recent studies from the Red-Horse lab and others have shown that the endocardial cells can provide an alternative pool of coronary progenitors (Sharma et al., 2017; Wu et al., 2012). Whereas endothelial contribution to the coronary vasculature is

minor in healthy hearts, these additional progenitors can compensate to rebuild the coronary vasculature in mice with an abnormal sinus venosus. Interestingly, although the sinus venosus and endocardium both produce similar cell types, they appear to do so through different mechanisms. For example, while Vegf-A is involved in endocardial progenitor cell budding (Zhang and Zhou, 2013), vessel sprouting from the sinus venosus is highly dependent on Vegf-C (Chen et al., 2014). Much remains to be learned about the molecular signals that integrate these two coronary progenitor sources into the mature coronary vasculature. A complete understanding of this process using single-cell transcriptomics in combination with lineage tracing analysis will inform the development of potential therapeutic targets for the regeneration of coronary vessels following injury or disease of cardiac tissue.

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