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"Identification of novel buffering mechanisms in aortic arch artery development and congenital heart disease"

By

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Cell Biology, Neuroscience, and Physiology Program

B.A. 2014, Arcadia University, Pennsylvania

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Friday, March 24th, 2023
10:30 A.M.
In conference room MSB G-609B

ABSTRACT

The remarkable robustness of embryonic development to genetic and environmental perturbations has been long appreciated; however, little is known about buffering mechanisms underlying the constancy of development. Yet, aberrations in developmental programs can lead to lethal outcomes, exemplified by congenital heart disease (CHD). Defective morphogenesis of the aortic arch is a lethal CHD phenotype common in 22q11 deletion syndrome (22q11DS). Previously, we found that the second heart field (SHF) gives rise to the pharyngeal arch artery (PAA) endothelium. Here, we show that robust PAA development is dependent on both a threshold and an optimum number of SHF-derived endothelial cells (ECs) and that the optimum number is regulated by *VEGFR2* and *Tbx1* gene dosage. We discovered that PAA development is rescued by a compensatory endothelium when the number of SHF-derived ECs falls below the optimum but remains within the threshold. To determine the source of compensating endothelium and the mechanisms regulating its recruitment, we used *in toto* confocal imaging to investigate EC connectivity, fate, and gene expression at single-cell and single-molecule resolutions. Our studies demonstrate that the loss of SHF-derived ECs leads to alterations in the pharyngeal tissue microenvironment, resulting in increased synthesis of *VEGFA*, eliciting ectopic angiogenesis from the nearby veins but not arteries. We show that this rescuing mechanism is regulated by *Tbx1*, a major 22q11DS disease gene; the absence of a single allele of *Tbx1* prevents this angiogenic response leading to unpredictable arch artery morphogenesis and lethal CHD in $Tbx1^{+/-}$ animals. Together, our work uncovers a novel buffering mechanism underlying the fidelity of arch artery development and provides insights into the pathogenesis of CHD.