

HEMODYNAMIC REGULATION OF CARDIAC VALVE DEVELOPMENT

by

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It is well established that valvulogenesis is a result of a complex interplay between genetic and environmental factors. Hemodynamics is one such environmental stimulus that is well documented to influence the development of heart valves. Using advanced imaging modalities, such as optical coherence tomography, investigators have better understood the effects of altering hemodynamic loads in the embryonic (avian) heart. However, the field of valvulogenesis is currently stagnant with a paucity of studies aiming to understand the molecular mechanisms influenced/affected by hemodynamic stimuli. Deciphering these pathways is critical from a valve development perspective, but also becomes vital as potential therapeutic targets, given the fact that several adult valve diseases have a congenital origin. Towards this end, we have developed a novel *ex ovo* method to alter hemodynamic stimuli through the chick embryonic heart by partially constricting the outflow tract (OFT). We acknowledge that the concept of banding a part of the developing heart has been exploited by several researchers; however, performing the banding intervention outside the eggshell not only highlights the novelty of our avian system, but also permits us to obtain sufficient tissue (from a statistical analysis standpoint) to carryout molecular biology experiments which was, until this point, impossible to achieve. Using this system, we have shown for the first time, that perturbation of intracardiac hemodynamics has consequences at the cellular and molecular level. Altered hemodynamics not only affected OFT cushion volume and expression of key players involved in valve development, but also led to a decrease in epithelial-mesenchymal-transition, a pivotal process in valvulogenesis. The migratory capacity and secretory profile of atrioventricular cushions were also altered by

changing intracardiac hemodynamics. Furthermore, when the constriction around the OFT was removed, anomalous cardiac phenotypes, resulting due to OFT banding, could not be rescued, while the expression of some genes returned to that observed in control tissue. Lastly, OFT banding seemed to have an influence on gene expression only if hemodynamics were altered at a certain developmental period. However, expression of collagen appeared sensitive to altered blood flow through the embryonic heart even at very early periods of embryonic development.