The Role of Putative Tbx1 Target Genes in the Pathogenesis of the 22q11 Deletion Syndrome Phenotype

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Abstract

The 22q11 deletion syndrome (22q11DS/DiGeorge Syndrome [DGS]) is a congenital disorder with complex aetiology including cardiovascular, thymic/parathyroid, craniofacial and neuro-behavioural phenotypes. These arise via abnormal development of embryonic structures including the pharyngeal arch/artery apparatus and the secondary heart field. Large (3Mb) hemizygous deletions of 22q11 are found in most human cases. The *TBX1* transcription factor is found within the deleted region. Animal models and nondeleted patient data suggest haploinsufficiency of *TBX1* is the major underlying cause of 22q11DS.

To investigate the role of *Tbx1* in cardiovascular development, putative transcriptional targets were previously identified using microarray. This thesis examines the role of two such targets, the *Cyp26* gene family and *Hes1*. These genes are known to be involved, respectively, in the retinoic acid and Notch-signalling pathways. Both pathways are important in pharyngeal/cardiovascular development. Control of RA homeostasis/dosage is required for normal development and the Cyp26 enzymes metabolise RA to less active forms. Embryonic *Cyp26* genes have altered expression in *Tbx1*$^{-/-}$ mice. This project investigated the effect of chemically blocking Cyp26 function upon pharyngeal/cardiovascular development in the chick. Furthermore, a mutant mouse model was used to establish whether loss of *Cyp26b1* function could result in the 22q11DS phenocopy observed. Finally, epistasis experiments ascertained whether a genetic interaction exists between *Tbx1* and *Cyp26b1*. The transcriptional repressor *Hes1* is required for pharyngeal/cardiovascular development in the mouse. This thesis presents data showing a conserved role for *her6* (zebrafish homologue) in zebrafish pharyngeal development and verification of a *tbx1*/*her6* genetic interaction during pharyngeal development.

Overall, work presented in this thesis provides further evidence that *Tbx1* coordinates a number of signalling pathways in pharyngeal/cardiovascular development. This data refines the role of *Tbx1* and RA-regulatory genes in 22q11DS cardiovascular phenotypes and corroborates the importance of an interaction between *tbx1* and *her6* (*Hes1*) in pharyngeal development.