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

Catherine Roberts
Doctor of Philosophy
Institute of Child Health
University College London
2013

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.