

POSTER SESSION 3

Session held on 6 July 2014

doi:10.1093/cvr/cvu098

Group 1 - Gene analysis, Transcription factors

P569

A novel role for NFATC1 in patients with both congenital heart disease and glaucoma

H. Hariri; T. Farhat; R. Khalaf; A. Fahed; C. Al-Haddad; M. Arabi; F. Bitar; G. Nemer
 American University of Beirut AUB, Biochemistry and Molecular Genetics, Beirut, Lebanon

Purpose: Congenital heart valve defects are the most frequent defects occurring in humans. We have recently shown two novel missense (P66L, I701L) mutations in one patient with tricuspid atresia. Functional analyses did show a defect in its cellular localization, transcriptional activities and DNA binding activity of the protein. The aim of this proposal is to unravel a role for NFATC1 in valve formation and glaucoma in humans.

Methods: We screened for mutations in the coding region of NFATC1 in a family with septal and valve defects in addition to glaucoma. PCR amplifications and DNA sequencing were carried out. Site directed

mutagenesis on the corresponding cDNA was undertaken, and subsequent transfections in cells were carried out to assess the localization and function of the protein.

Results: We found a previously documented polymorphism (rs62096875) leading to a missense mutation (V210M). The father and one of the children were heterozygous while the other sibling (patient) was homozygous for the mutation, and the rest of the family has a normal genotype. Genotype/phenotype correlation showed that the patient with the most severe phenotype is homozygous for the mutation prompting us to hypothesize that the polymorphism might be disease-causing. We constructed a V210M mutant plasmid and assessed the expression and function of the protein. Our results unravel a novel pathway implicating an interaction with Tbx5, probably responsible for the underlying phenotype.

Conclusion: Our results strongly suggest that NFATC1 plays a major role in congenital valvular diseases and eye defects. We hypothesize according to our result that the vascular endothelial growth factor (VEGF) is a downstream target for both NFATC1 and Tbx5 and is implicated both in heart and eye development.

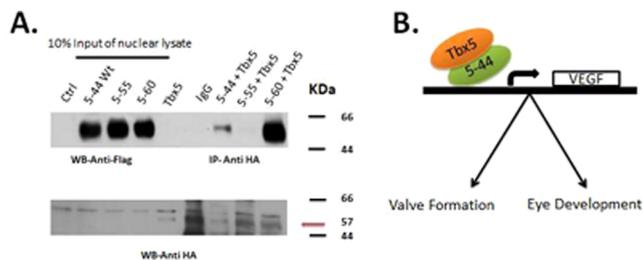


Figure 1: NFATC1 and TBX5 physically (A) and functionally (B) interact