

Tropomyosin expression in vertebrate hearts in relation to cardiogenesis and cardiomyopathies

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The assembly of a myofibril, contractile apparatus of striated muscles, involves the precise ordering of several proteins into a linear array of sarcomeres. Tropomyosin is one of the six proteins comprising the thin filament and is encoded by four different genes (TPM1, TPM2, TPM3, & TPM4) in vertebrates. The TPM1 generates at least 10 isoforms via alternative splicing and/or by using an alternate promoter. Several missense mutations in the TPM1 gene have been implicated in familial hypertrophic cardiomyopathy (FHC) and dilated cardiomyopathy (DCM). Heretofore, it was believed that TPM1 α was the key TM isoform produced in striated muscles. We have discovered a new alternately spliced isoform TPM1 κ of the TPM1 gene that contains exons 1a, 2a (2b in TPM1 α), 3, 4, 5, 6b, 7, 8, and 9a/b. TPM1 κ is expressed in the cardiomyocytes of a variety of vertebrates including humans. It is also expressed in skeletal muscles in axolotl and zebrafish. We have quantified mRNA and protein expression of TPM1 α & TPM1 κ in striated muscles in axolotl and humans. Although the transcript level of TPM1 α and TPM1 κ is comparable, the expression of TPM1 κ protein is significantly lower in hearts. Although over-expression of TPM1 κ in transgenic mice heart leads to DCM, transgenic animals live well and breed normally. We have evaluated the effect of cardiogenic small molecule, Shz-1 on tropomyosin isoform expression in vertebrate hearts in situ and in vivo. Small molecule mediated manipulation of isoform composition of sarcomeric protein has potential for future treatment of sarcomere diseases like FHC and DCM.

Biography

Currently, Dipak K. Dube is a Professor in the Department of Medicine and an Adjunct Professor in the Department of Cell & Developmental Biology, SUNY Upstate Medical University. He received his Ph.D. and D.Sc. degrees from University of Calcutta, India. He did his postdoctoral research at the Institute for Cancer Research, Philadelphia, USA. His major areas of research interests are Molecular Biology of Vertebrate Heart Development and Human Retrovirology. He has published about 150 full-length papers and is a member of the Editorial Board of Cardiovascular Toxicology, Journal of Cytology & Histology, and Clinical and Experimental Cardiology.

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