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From skeletal muscle to cancer: Insights learned elucidating the function of tropomyosin

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ABSTRACT

The tropomyosins (Tms) are a family of actin filament binding proteins that possess a simple dimeric α-helical coiled-coil structure along their entire length. Our knowledge of Tm structure and function has greatly expanded since they were first discovered in skeletal muscle almost 65 years ago. In multicellular organisms they exhibit extensive cell type specific isoform diversity. In this essay we discuss the genetic mechanisms by which this diversity is generated and its significance to actin-based cellular functions.

1. Introduction

Tropomyosins (Tms) are a family of actin filament-binding proteins that were first identified during studies of skeletal muscle contraction. They have since been identified in a diverse array of eukaryotic organisms including yeasts, worms, flies, crustaceans, frogs, birds, and mammals. At the structural level Tms are elongated proteins that possess a dimeric α-helical coiled-coil structure along their entire length. The coiled-coil structure is based on a repeated pattern of seven amino acids with hydrophobic residues at the first and fourth positions and is highly conserved in all Tm isoforms from yeast to human. Although they appear to exhibit a relatively simple protein structure, molecular and genetic studies revealed a level of complexity among metazoan Tms that is not fully understood. For example, vertebrates contain four genes that encode more than 40 distinct isoforms. An unresolved question is the functional significance of this diversity: Why so many isoforms? Answers to this question are providing insights into various aspects of protein structure, cytoskeletal architecture and cellular functions, as well as molecular aspects of human diseases such as cancer. Below we briefly discuss the genetic basis for Tm isoform diversity and highlight some examples where specific forms of Tm are implicated in cellular functions. For a more in-depth analysis of various aspects of Tm function readers are referred to the excellent monograph on Tms by Gunning (2008).

2. Tm gene families and protein diversity

Animals including nematodes, flies, frogs, birds, and mammals possess multiple Tm isoforms. This isoform diversity is generated by a combination of multiple genes, some of which contain alternative promoters and some of which exhibit alternative RNA splicing of primary RNA transcripts. In vertebrates four different genes have been characterized, termed TPM1, TPM2, TPM3 and TPM4 (Fig. 1). The Tm gene family appears to have arisen through gene duplication of an ancestral gene. It is worth noting that a comparison of the intron–exon organization of invertebrate and vertebrate Tm genes suggest that alternative splicing for the generation of Tm isoforms diversity arose relatively early in metazoan evolution. For example, the exon organization of the mammalian TPM1 gene (also referred to as the α-gene, because it encodes skeletal muscle α-Tm) is almost identical to that of one of the *Drosophila* and *Caenorhabditis elegans* Tm genes (reviewed in Lees-Miller and Helfman, 1991). The alternatively spliced exons among different isoforms within a gene correspond to different functional domains of the protein. The expression of a diverse group of isoforms in a cell-type specific manner strongly suggests that the various isoforms are required for specific cellular functions. Understanding the function of this isoforms diversity is providing a greater understanding the actin-based cytoskeleton in cellular processes.

3. Skeletal muscle contraction

Tms were first identified and characterized in studies to elucidate the mechanism of skeletal muscle contraction (Bailey, 1948). One classic physiological response is that of the excitation/contraction

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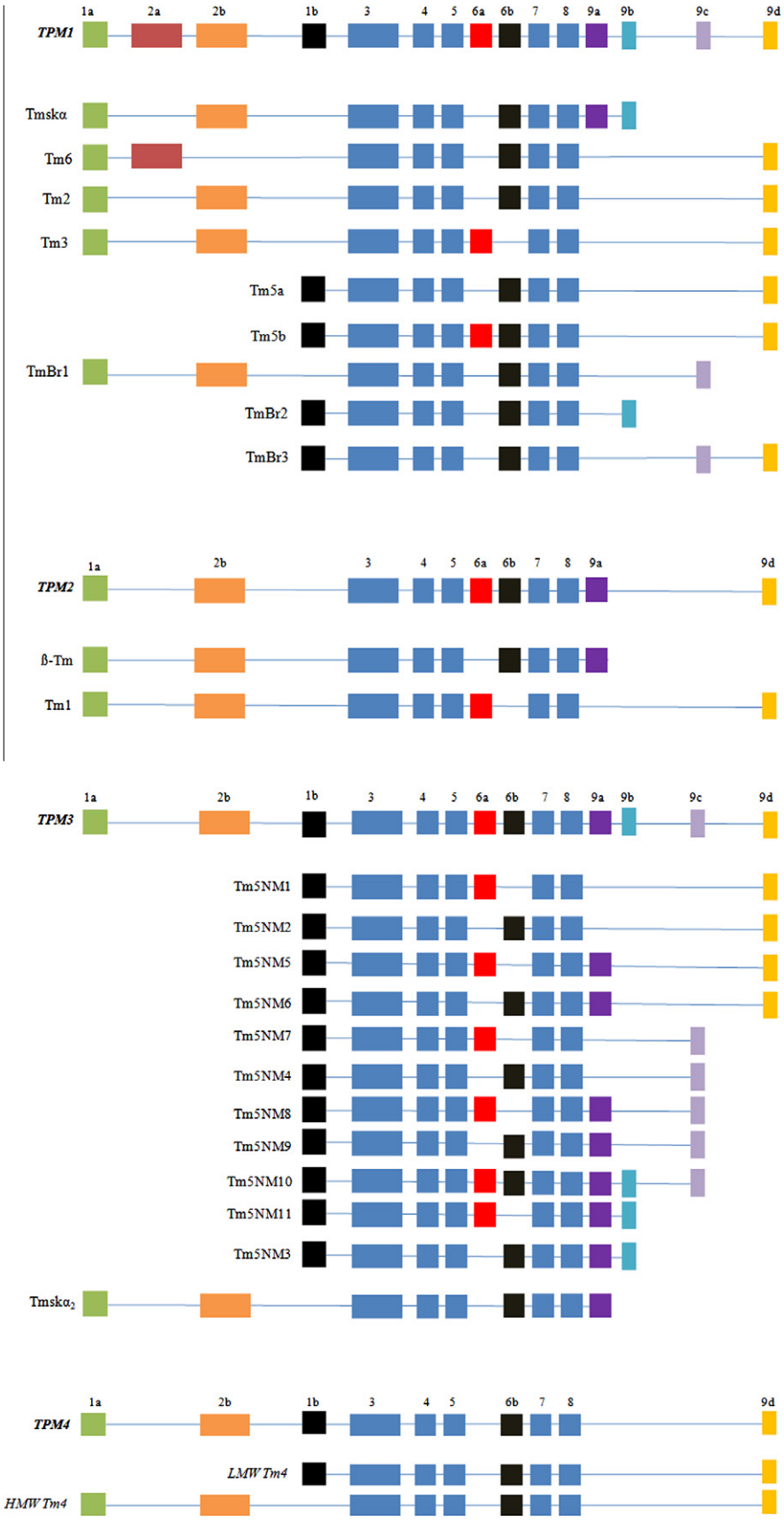

Fig.1. Schematic of the exon organization of the four mammalian Tm genes, referred to as TPM1, TPM2, TPM3 and TPM4. Exons are represented by boxes and introns by solid lines. In general isoforms expressed from the upstream promoter, corresponding to exon 1a, are characterized as high molecular weight (HMW) isoforms containing 284 amino acids, whereas isoforms expressed from the internal promoter, corresponding to exon 1b, are characterized as low molecular isoforms (LMW) isoforms containing 248 amino acids. Compiled from Gunning (2008) and Wang and Coluccio (2010).