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Gene Section

Mini Review

TRPM1 (transient receptor potential cation channel, subfamily M, member 1)

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Identity

Other names: LTRPC1; MLSN; MLSN1; Melastatin-1

HGNC (Hugo): TRPM1

Location: 15q13.3

Note

TRPM1, the founding member of TRPM family was originally identified as melastatin 1 and accordingly all 8 family members are named TRPM (melastatin) (Montell et al., 2002). TRPM1 expres-sion is restricted to the pigment cells of skin and eye. The protein encoded by this gene is similar to that of transient receptor potential (TRP) calcium channel family members. The protein expression is inversely correlated with melanoma aggressiveness, suggesting a role in melanoma metastasis.

DNA/RNA

Description

The TRPM1 gene consists of 27 exons, spans at least 58 kb genomic DNA, on chromosome 7 in mouse. In humans, the chromosomal localization of TRPM1 is on chromosome 15q13.3 region from 29080845 to 29181216 on the reverse strand. The TRPM1 gene encodes a 5.4kb (5428bp) mRNA transcript (Hunter et al., 1998; Fang and Setaluri, 2000). The promoter region of this gene contains 4 consensus binding sites for the microphthalmia-associated transcription factor (MITF), one of those binding site includes an M box, a motif shared by pigmentation genes (Hunter et al., 1998; Miller et al., 2004; Zhiqi et al., 2004). A 1-kb PvuII fragment from this region is capable of driving reporter gene expression in mouse and human melanoma cells.

Transcription

5.4 kb mRNA (full length transcript) with open reading frame of 4.812 (NT 129 to NT 4940, GenBank Accession No. NM_002420). Northern hybridization studies showed the presence of multiple short transcripts (1.8kb, 4kb, and 5.4kb) in human melanocytes as well as pigmented metastatic melanoma cell lines. However the full length mRNA is detectable only in melanocytes. (Fang and Setaluri, 2000).

Pseudogene

No pseudogenes for TRPM1 have been identified.

Protein

Note

The open reading frame of TRPM1 (from NT 129-4940), encodes 1603 aa protein of predicted molecular mass ~182kDa. Cloning of full length human cDNA TRPM1 (GenBank Accession No. AF071787, with open reading frame from NT321- NT4922) resulted in 1533 aa protein product (Hunter et al., 1998; Fang and Setaluri, 2000). The shorter N-terminal isoform, TRPM1 (MLSN1-S), lacking the transmembrane domains, encodes for 500 aa protein (Fang and Setaluri, 2000). Rabbit polyclonal antibodies generated against the N-terminal part of TRPM1 detected proteins with molecular weights of 120 kDa and several minor bands ranging from 35 to 240kDa, including a doublet at 45kDa in primary neonatal melanocytes (Zhiqi et al., 2004).

Regulation of TRPM1: Short form of TRPM1 interacts directly and suppress the activity of full length form of TRPM1 (MLSN1-L), preventing its translocation to the plasma membrane (Xu et al., 2001), representing a mode of regulation of the channel activities. Presence of multiple isoforms of TRPM1 in normal melanocytes as well as pigment cell melanoma treated with a pharmacological agent suggests that TRPM1 can be regulated at the level of both transcription and mRNA processing (Fang and Setaluri, 2000). MITF is shown to be a major transcriptional regulator of TRPM1 expression through its interaction within the proximal promoter region (Miller et al., 2004; Zhiqi et al., 2004). Transfection of p53 or induction of endogenous p53 in melanocytes by ultraviolet (UV) radiation represses TRPM1 accompanied by decreased mobilization of intracellular Ca^{2+} and decreased extracellular Ca^{2+} uptake, indicating the role of p53 in TRPM1 regulation (Devi et al., 2007).

Description

TRPM1 is alternatively spliced and the splice variants are strongly depending on the cell type. Northern blot and RT-PCR analysis showed that the alternative splicing of TRPM1 mRNA produces short TRPM1 mRNAs derived from the 5' or 3' ends of the full length TRPM1. One of the major isoforms is predicted to encode a short protein (MLSN1-S) that includes only the N-terminal segment but not any transmembrane domain and is incapable of functioning independently as an ion channel.

Expression

TRPM1 is expressed exclusively in pigmented cells of the skin and the eyes.

Localisation

Isoforms of TRPM1 is mostly likely located on plasma membrane. Of the two major isoforms of TRPM1, L form (MLSN1-L) is localized on the cell membrane and the S form (MLSN1-S) is localized in the cytoplasm (Xu et al., 2001).

Function

TRPM1, transfected in heterologous HEK293T cells, acts as a calcium channel protein. The shorter isoform of TRPM1 has a regulatory effect on longer isoform, potentially suppresses the transport of longer isoform to cell membrane (Xu et al., 2001). Role of TRPM1 in cellular differentiation and proliferation was reported in human pigmented melanoma cell lines treated with hexamethylene bisacetamide (HMBA), were the expression of TRPM1 is upregulated (Fang and Setaluri, 2000). Lentiviral shRNA mediated knockdown of TRPM1 resulted in reduced intracellular Ca^{2+} and decreased Ca^{2+} uptake suggesting a role of TRPM1 in Ca^{2+} uptake by melanocytes (Devi et al., 2007).

Homology

Sequence similarity analysis revealed a limited homology to TRP family of calcium channel proteins and ~45% identity within the first 1200 amino acids of C.elegans (Prawitt et al., 2000).

Mutations

Note

Several single nucleotide polymorphisms have been identified but none of them is shown to be associated with any disease.

Implicated in

Melanoma

Note

The exact role of TRPM1 in melanoma is not known.

Disease

Homogeneous TRPM1 mRNA expression in primary cutaneous melanoma correlates with prolonged disease free survival, and with the progression of the tumor, the TRPM1 is diminished or completely abolished in metastatic melanoma (Duncan et al., 1998; Duncan et al., 2001; Deeds et al., 2000; Miller et al., 2004). Reduced expression of TRPM1 gene in the retina of homozygous appaloosa horses with CSNB (congenital stationary night blindness) and coat spotting patterns compared to non appaloosa horses suggests a role for TRPM1 in normal night vision and melanogenesis (Bellone et al., 2008).

Prognosis

Down regulation/suppression of TRPM1 expression correlates with tumor progression. Decreased expression or absence of TRPM1 is a marker of poor prognosis and overall survival of melanoma patients.

Breakpoints

Note

No break points described so far.

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