MITF (microphthalmia-associated transcription factor)

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Identity

Other names: CMM8, MI, WS2, WS2A, bHLHe32
Location: 3p14.1
Local order: The MITF gene is located between the genes PDHB (telomeric) and PROK2 (centromeric).
Note: Total size: 228903 bps.
MITF has 18 transcripts and encodes a transcription factor that contains both a helix-loop-helix structure as well as a leucine zipper.
Target genes: MITF has been shown to recognize the E-box (CAYRTG) and M-box (TCAYRTG or CAYRTGA) sequences in the promoter regions of multiple target genes, including ACP5, BCL2, BEST1, BIRC7, CDK2, CLCN7, DCT, EDNRB, GPNMB, GPR143, MC1R, MLANA, OSTM1, RAB27A, SILV, SLC45A2, TBX2, TRPM1, TYR and TYRP1 (Hoek et al., 2008b).

DNA/RNA

Description
The gene encompasses 229 kb, and has 9 exons.

Transcription
Nine different isoforms have been described for MITF, each with different 5' specificity (MITF -A, -J, -C, -MC, -E, -H, -D, -B, -M).
All isoforms have exons 2-9 in common, encoding the functional domains of the transcription factors.

Protein

Description
526 aa, 58795 Da.
Regulates the differentiation and development of melanocytes, neural crest-derived cells, retinal epithelium (optic cup-derived retinal pigment epithelium), mast cells, and osteoclasts (Lin and Fisher, 2007; Adijanto et al., 2012).

Post translational modifications:
- Phosphorylation at Ser-405 significantly enhances the ability to bind the tyrosinase promoter.
- Phosphorylation at Ser-180 and Ser-516 by MAPK and RPS6KA1 activate the transcription factor activity and promote ubiquitination and subsequent degradation.
- Can be deubiquitinated by USP13, preventing its degradation.

Expression
Found in most human tissues.
Particularly high quantities in retina, uterus, pineal gland, and adipocytes (biogps.org).

Localisation
Nucleus.
**Function**

A transcription factor that activates the transcription of tyrosinase and tyrosinase-related protein 1 (TYRP1), and dopachrome tautomerase (DCT). These are enzymes that are specifically expressed in melanocytes (Yasumoto et al., 1995). For tyrosinase, MITF binds to a symmetrical DNA sequence found in the promoter region: a restricted subset of E-box motives containing canonical CATGTG sequence flanked by a 5’ thymidine (Aksan and Goding, 1998).

The regulation of the DCT promoter is even more complex and involves other proteins like CREB and SOX10; and PAX3 has an inhibitory effect on DCT activation by MITF (Bertolotto et al., 1998; Ludwig et al., 2004; Lang et al., 2005).

Not only does MITF activate genes involved in melanin synthesis, it also activates the transcription of genes involved in melanosome structure (PMEL17, MART-1), biogenesis (ocular albinism type 1 gene), and transport (RAB27A) (Du et al., 2003; Vetrini et al., 2004; Chiaverini et al., 2008). Also, MITF activates the transcription of the melanocortin 1 receptor gene which encodes a melanocyte-stimulating hormone receptor normally present on the plasma membrane of melanocytes: this binding is the first step in the hormonal regulation of pigmentation (Vachtenheim and Borovansky, 2010).

In addition, MITF plays a role in apoptosis through several target genes, showing importance of MITF in melanocyte development and survival.

MITF controls the transcription of BCL-2, and known inhibitor of apoptosis (McGill et al., 2002). Therefore, MITF mutation may explain the reduced number of melanocytes in certain disorders (Samija et al., 2010).

MITF also induces transcription of melanoma-inhibitor-of-apoptosis (BIRC7, ML-IAP) (Dynek et al., 2008). Furthermore, it regulates a receptor for hepatocyte growth factor (MET), whose activation inhibits melanocyte apoptosis (Beuret et al., 2007).

MITF also plays a role in melanocyte proliferation by regulating several genes involved in the cell-cycle: cyclin-dependant kinase 2 (CDK2), transcription factor TBX2, and Dial protein (Diah1). These promote cell-cycle progression, prevent senescence and cell-cycle arrest, and increase cellular proliferation, respectively (Du et al., 2004; Carreira et al., 2005; Carreira et al., 2006).

However, MITF also has anti-proliferative properties by way of inducing cell-cycle arrest by activating cyclin-dependent kinase inhibitor 1A and 2A (CDKN1A/p21, CDKN2A/p16) (Carreira et al., 2005; Loercher et al., 2005).

It has been believed that both depletion and over-expression inhibit proliferation whereas normal levels promote proliferation (Kido et al., 2009).

MITF also has important roles in osteoclast and mast cell development and function.

In osteoclasts it activates transcription of functional proteins tartrate-resistant alkaline phosphatase (TRAP), cathepsin K, OSCAR, e-cadherin, OSTM1 and CLCN7 (Meadows et al., 2007).

In mast cells MITF activates the transcription of mast cell proteases 2,4,5,6, and 9, granzyme B, tryptophan hydroxylase, and kit, all important for differentiation and function (Kitamura et al., 2006).

**Up-stream regulation:** LysRS-Ap4A-MITF signaling pathway (Lee et al., 2004); Wnt signaling pathway (Takeda et al., 2000); alpha melanocyte-stimulating hormone signaling pathway (Bertolotto et al., 1998).

**Homology**

High homology to TFE genes (TFE3, TFEB, TFEC, etc.) and the myc family of bHLH transcription factors (Dickson et al., 2011).

**Mutations**

**Note**

The MITF promoter is partially regulated by certain transcription factors such as PAX3, SOX10, LEF-1/TCF and CREB during development.

Mutations affecting the MITF and the MITF pathway lead to pigmentary and auditory defects (Cimadamore et al., 2012; Pierrat et al., 2012).

**Germinal**

Mutations in the MITF at germline will lead to syndromes with pigmentary and/or auditory defects. Mutations in MITF are also known to give a predisposition to certain cancers, including melanoma and renal cell carcinoma (Bertolotto et al., 2011).

Heterozygous mutations lead to auditory/pigmentary syndromes such as Waardenburg type 2 and Tietz syndrome (Lin and Fisher, 2007).
Implicated in

Melanoma

Note
A malignant neoplasm of melanocytes, arising either from pre-existing benign nevi or de novo and occurring most commonly on the skin, but may occur in other locations.

There have been linkage and genome-wide association studies (GWAS) studies that have shown no evidence to implicate MITF in melanoma (Gillanders et al., 2003; Bishop et al., 2009). However, MITF has been shown to be mutated in a subset of melanomas and overexpressed in others (Garraway et al., 2005; Cronin et al., 2009). This raises the possibility of MITF’s involvement despite the lack of prior evidence for germline risk. Indeed, individuals with a specific MITF mutation (E318K) have a 5-fold increase risk of developing melanoma (Yokoyama et al., 2011). MITF amplification has also been associated with decreased survival and chemoresistance (Gallaway et al., 2005).

It is postulated the MITF may be a lineage specific oncogene in melanoma, particularly in the subset with CDKN2A mutations (Garraway and Sellers, 2006; Bennett, 2008). This hypothesis is supported by research that has shown that all melanoma cell lines that had MITF gene amplifications also had CDKN2A pathway inactivation (Gallaway et al., 2005). MITF’s role as a lineage specific oncogene is also supported by its important part in cell growth, survival, growth, and proliferation through BCL2, CDK2, TBX2, ML-IAP etc, as described above.

In addition, BRAF mutations (found in ~60% of melanomas) have a two-fold regulation of MITF transcription and is believed to keep MITF at appropriate levels promoting melanoma cell proliferation and survival.

Supporting this theory is the fact that pure up-regulation of MITF inhibits melanoma cell proliferation and re-expression reduces tumorigenecity in vivo (Wellbrock and Marais, 2005).

And MITF expression by immunohistochemistry has been shown to decrease with disease progression, and be a predictor of overall and disease-free survival (Salti et al., 2000; Zhuang et al., 2007).

As mentioned above, MITF is not expressed in all melanomas. This indicates that there are different subsets of melanomas which differ in their need of MITF for their progression and survival (Salti et al., 2000; Miettinen et al., 2001; Granter et al., 2002). There is also evidences that the role of MITF may change within a melanoma during progression (Hoek et al., 2008a).

Renal cell carcinoma

Note
Malignant transformation of the renal parenchyma.

Associated with Von Hippel-Lindau syndrome: a rare, autosomal dominant disease predisposing to clear cell renal cell carcinoma, as well as hemangioblastomas, pheochromocytomas, pancreatic cysts and neuroendocrine tumors, endolymphatic sac tumors, and a general increase risk in cancer; results from mutation of the VHL tumor suppressor gene on chromosome 3p. A subset of renal cell carcinomas, more common in children, are associated with TFE3 mutations, a member of the microphthalmia (MIT) family, closely related to MITF.

Recent studies have shown that the same MITF mutation associated with increased risk of melanoma (E318K) also leads to increased risk of renal cell carcinoma (Bertolotto et al., 2011). However, it is unclear at this time the role that MITF in particular plays in renal tumors. It may be that this mutation leads to disrupted interaction with TFE3. Or it is possible that mechanisms are similar to that of melanoma, however, MITF is not associated with normal kidney function in the same way that it is in normal melanocyte function. Research is ongoing in this area.

Waardenburg syndrome

Note
A group of autosomal dominant inherited conditions that involve deafness and lack of pigment of the hair, skin, and/or eyes. There are 4 main types of WS, 1 and 2 being most common. MITF is the gene associated with Waardenburg syndrome 2a (WS2a), characterized by sensorineural hearing loss and patches of depigmentation, with or without ocular albinism. These features may show variable expression and penetrance.

Some of the mutations are single or multiple amino acid changes that alter the helix-loop-helix or leucine zipper motif. There are other mutations that create a shortened, non-functional version of MITF. It is believed that all of these mutations disrupt the formation of the dimers necessary for proper function and development; thereby there is an insufficient concentration of the MITF protein within the cytoplasm for normal function (haploinsufficiency). Also, as described above, MITF regulates BCL-2, ML-IAP, and MET. Without adequate amounts of MITF there is over-apoptosis of melanocytes. This leads to a decreased number of melanocytes in certain areas of the skin, hair, eyes, inner ear, etc (Tachibana, 1997; Samija et al., 2010).

Patients with WS1 will have the addition of craniofacial deformities and those with WS3 (Klein-Waardenburg syndrome) have limb deformities, both are due to mutations in PAX3, which is part of the MITF pathway, those with WS4 (Waardenburg-Shah Syndrome) will also have Hirchsprung’s syndrome, associated with mutations in 3 genes: SOX10, endothelin 3, and endothelin receptor B (Tassabehji et al., 1995; Widlund and Fisher, 2003).
Tietz syndrome

Note
An autosomal dominant disorder characterized by generalized hypopigmentation (fair skin and light-colored hair) and profound bilateral congenital hearing loss. Penetration is complete.

The mutation is a change or deletion of a single amino acid in the basic motif region. This resultant altered protein cannot bind to DNA, thereby affecting the development of melanocytes, and therefore, melanin production (Smith et al., 2000). The mechanism is similar to Waardenburg syndrome, but more severe. In a heterozygote the abnormal protein cannot dimerise effectively even with a normal allele product, i.e. even the normal allele does not function. This concept is referred to as a dominant negative. There is effectively no normal MITF available (Smith et al., 2000).

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