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MITF: A Critical Transcription Factor in Melanoma Transcriptional Regulatory Network

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1. Introduction

Melanocytes are specialized cells found predominantly in the skin and eyes that form the pigment melanin, a polymer composed of several types of subunits formed from L-3,4-dihydroxyphenylalanine. Melanin is deposited in subcellular particles called melanosomes. Cutaneous melanocytes originate from neural-crest progenitors that migrate to the skin during embryonic development. In the skin, melanocytes reside in the basal layer of the epidermis and are present also in hair follicles. Skin melanocytes form an epidermal unit composed of one melanocyte having long cellular processes and about 30 keratinocytes.

Melanocytes are found also in a benign nevus, a common lesion observed in the skin which is a precursor of malignant melanoma. In the nevus, the melanocytes (called nevocytes) are morphologically different and although nevi are benign and the melanocytes in them are senescent, they may develop, though rarely, into melanoma, a highly malignant tumor whose incidence is rising steadily in western countries. Smaller part of melanoma tumors (approximately 10-15%) occurs in families with hereditary predisposition (Hansson, 2010). Most familial melanomas harbour germline mutations in the CDKN2A gene encoding the p16INK4 protein, a cdk inhibitor. Much smaller number of hereditary cases has germline mutations resulting in amino acid substitutions in the p14ARF or CDK4 proteins. Sporadic cases of melanoma predominate and can be grouped into four clinical subtypes: acral lentiginous melanoma, nodular melanoma, lentigo maligna and superficial spreading melanoma (SSM), which is by far the most common form of melanoma and develop into vertical-growth phase (VGP) melanoma. Lentigo maligna and SSM are most frequently associated with intermittent UV exposure (Gray-Schopfer et al., 2007).

About 60-70% of melanomas harbour mutations of the B-RAF gene (Davies et al., 2002) (in the vast majority the mutation is V600E), while mutations of N-RAS are present in about 10–25%

of all tumors. Activating N-RAS and B-RAF mutations demonstrate mutual exclusivity in melanomas. B-RAF mutations are present already in nevus cells, conferring senescence to these cells by a mechanism known as oncogene-induced senescence, possibly explaining the low rate of malignant transformation of nevi. Activation of these two oncogenes triggers the MEK-ERK kinase cascade that is almost invariably activated in melanomas; however, other signaling pathways can probably activate the cascade. Therefore, small molecule inhibitors of kinases in the pathway are considered as a promising tool for melanoma treatment (Solit et al., 2006; Bogenrieder and Herlyn, 2011). Although B-RAF inhibitors seem to be rational antimelanoma drugs, resistance occurs in a large proportion of patients, because other stimuli may also activate MAPKs (Alcala and Flaherty, 2012). Many other genes are deregulated during melanoma progression, mainly antiapoptotic genes and genes which are involved in the invasiveness, migration, and metastasis of melanoma, many of which are regulated by MITF-M (microphthalmia-associated transcription factor), a pivotal transcription factor of the melanocyte lineage (Figure 1).

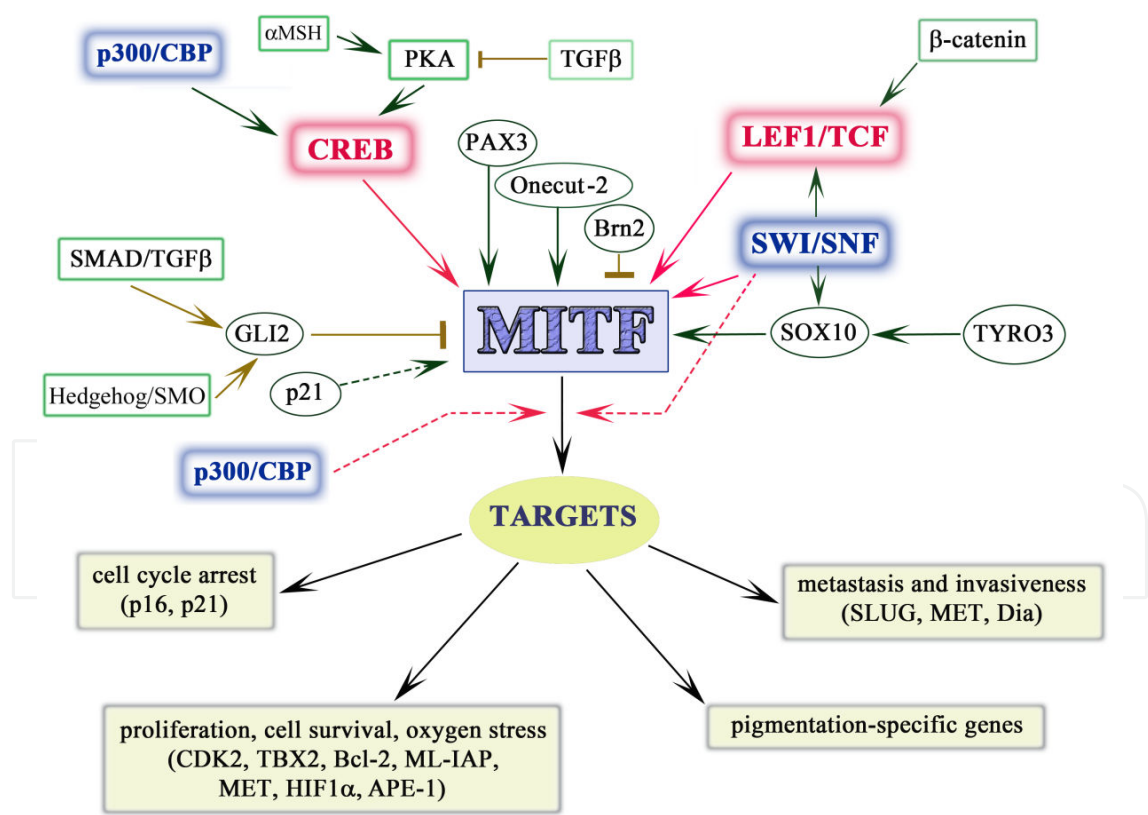


Figure 1. Transcriptional network of MITF-M in melanoma. The picture shows upstream MITF-M activators and main downstream transcription targets. The blue boxes indicate transcriptional coactivators and red boxes denote two transcription factors probably having more important role for the MITF-M expression in melanoma. Broken lines indicate that not all MITF-M targets may be coactivated by indicated epigenetic coactivators.

2. Regulation of MITF expression

MITF gene locus encodes a transcription factor of the basic-helix-loop-helix-leucine zipper (bHLH-LZ) type, belonging to a large family of bHLH factors comprising also for example the myc oncogenes. Together with TFE3, TFEB, and TFEC, MITF-M constitutes a small bHLH subfamily sharing high sequence similarity. MITF gene was identified twenty years ago and cloned from a microphthalmic and hypopigmented mutant mouse having transgene-insertion at the MITF locus (Hodgkinson et al., 1993). The MITF locus has at least nine promoters producing corresponding MITF isoforms which differ in the first exon and share exons 2-9 (reviewed by Steingrimsson et al., 2004; Levy et al., 2006). Only the MITF-M isoform is melanocyte-specific and expressed exclusively in melanocytes and melanoma cells, whereas some other tissues (osteoclasts, mast cells, heart muscle) express other isoforms of MITF. MITF-M determines the specification of the melanocyte lineage during the embryonic development and stands centrally in the transcriptional network of pigment cells, regulating a number of genes involved not only in melanocyte differentiation and pigment formation (Vachtenheim and Borovansky, 2010; Yajima et al., 2011), but also in the survival, migration, proliferation, invasion and metastasis of melanoma cells (Figure 1).

Regulation of MITF-M transcription is complex and several positive regulators activate the expression (Figure 1), having the corresponding binding motifs in the melanocyte-specific MITF-M promoter. Transcription factor LEF-1/TCF, one of the effectors of the β -catenin pathway, activates MITF-M promoter (Yasumoto et al., 2002). This pathway has been demonstrated to be highly activated in melanoma cells with MITF-M being the necessary mediator of the final pro-survival cellular effects (Widlund et al., 2002; Sinnberg et al., 2011). Transcription factors Sox10 and Pax3 also upregulate MITF-M transcription (Watanabe et al., 1998; Potterf et al., 2000). Sox10 is also stimulated by protein kinase TYRO3, another positive MITF-M regulator in melanoma (Zhu et al., 2009).

CREB is another transcription factor activating MITF-M expression. The α MSH hormone increases cAMP level, therefore activates PKA (protein kinase A) and the consequence is an increased MITF-M expression and pigmentation. Recently, it has been described that TGF- β represses protein kinase A activity and therefore reduces the CREB-dependent transcription of the MITF-M promoter (Pierrat et al., 2012). CREB requires the coactivators p300/CBP. These proteins, which are histone acetyltransferases, interact with MITF-M and are believed to coactivate at least some MITF-M target genes (Sato et al., 1997; Price et al., 1998). Furthermore, the phosphorylation of serine 73 is required for MITF-M-p300 interaction, at least after the Kit signaling (Hemesath et al., 1998). Controversially, however, it has been observed that MITF-M with mutation of this serine and the N-terminus truncated (including the S73) MITF-M construct were fully capable of activating promoter-reporter and the endogenous target tyrosinase (Vachtenheim et al., 2007).

Whereas the role of p300/CBP in coactivating endogenous targets might be disputable, another prominent epigenetic mechanism has been found to be crucial for MITF-M expression. The chromatin remodeling complex SWI/SNF has been found to be essential for the MITF-M expression in melanoma cells (Vachtenheim et al., 2010). The chromatin remodeling complex

SWI/SNF is composed of about 10-12 proteins and exists in the cells as several subcomplexes capable of changing the local structure of chromatin at the promoter sites. It has important functions in expression of various lineage specific genes and plays an essential function in basic cell processes that include mainly regulation of transcription, DNA replication and repair, and homologous recombination. The SWI/SNF is strongly implicated in human cancer, as several SWI/SNF subunits has been reported missing or strongly downregulated in tumors, and numerous experimental findings suggest that this complex functions as a tumor suppressor (reviewed by Reisman et al., 2009; Wilson and Roberts, 2011). The complex requires at least one ATPase subunit (Brg1 or Brm) and the presence of ATPase Brg1 and Brm is mutually exclusive in the subcomplexes. The components of SWI/SNF are generally highly expressed in melanoma cell lines and at least one ATPase of the complex, Brg1 or Brm, is always present in melanoma cell lines (Vachtenheim et al., 2010; Keenen et al., 2010). The positive effect of SWI/SNF on MITF-M transcription is direct, since both Brg1 and Brm were recruited to the MITF-M promoter *in vivo*, as revealed by chromatin immunoprecipitation assays (Vachtenheim et al., 2010). In addition, it is possible that SWI/SNF augment the MITF-M expression through LEF-1/TCF because Brg1 interacted with β -catenin and the SWI/SNF complex enhanced transcription of LEF-1/TCF downstream genes (Barker et al., 2001). Recently, we have found (Ondrušová et al., submitted) that Brg1 knockdown in melanoma cells downregulates also Sox10, an upstream MITF-M regulator, so this mechanism might also contribute to the MITF-M regulation. It is intriguing that for most cancers, SWI/SNF complex is a clear tumor suppressor, whereas a small number of cancer types has been recognized (prostate cancer, gastric and colorectal cancer, and melanoma) for which the SWI/SNF seems to function as a tumor promoter, probably by upregulating genes required for proliferation, antiapoptotic activity, invasivity or other characteristics of cancer cells.

It should be noted that the cut-homeodomain transcription factor Onecut-2 (OC-2) also stimulates MITF-M promoter activity. It binds to its promoter (although no OC-2 binding sites were found in the promoter region) and overexpression of ectopic OC-2 in transfected cells stimulates MITF-M promoter activity. Moreover, OC-2 is expressed in melanocytes (Jacquemin et al., 2001). We observed that even cdk inhibitor p21, which itself is a target of MITF-M, is its transcriptional activator (Sestakova et al., 2010). It probably stimulates the CREB pathway and is widely expressed in melanoma cell lines and tumors, and presumably protects malignant cells against apoptotic stimuli.

The POU domain containing transcription factor Brn-2 (N-Oct-3) has been recognized as a repressor of MITF-M expression in melanoma cells (Goodall et al., 2008). Brn-2 bound to MITF-M promoter both in gel-shift assays and in chromatin immunoprecipitation, indicating a direct repression. An inverse correlation between Brn-2 and MITF-M expression was found in melanomas and transfection assays showed that expression of exogenous Brn-2 substantially repressed the MITF-M promoter-reporter. Brn-2 also marked the subpopulation of low MITF-M cells in melanomas (which are heterogenous in MITF-M expression) and these cells displayed low proliferation but high invasiveness (also see below).

One of the effectors of the Hedgehog signaling, transcription factor GLI2, which also mediates the effect of the TGF- β /SMAD pathway, is another repressor of MITF-M expression (Javelaud

et al., 2011). GLI2 expression inversely correlates with MITF-M expression in melanoma cell lines, and GLI2 and M-MITF represses each other's expression (Javelaud et al., 2011). The GLI2 expressing cells with low MITF-M level resemble in biological properties the Brn-2 positive tumor cells (see above), having more invasive and migratory behavior. The Hedgehog pathway is derailed in melanoma (Stecca et al., 2007) acting mainly via GLI1 but does not have inhibitory activity on MITF-M expression. Obviously more investigation is required to elucidate the function of the Hedgehog and TGF- β /SMAD pathways and GLI effectors in melanoma.

3. Downstream targets of MITF

A large number of genes is transcriptionally regulated by MITF-M. Which genes are activated also depends on how high is the level of MITF-M and whether the regulation occurs in normal or malignant melanocytes (Goodall et al., 2008; Carreira et al., 2006; Javelaud et al., 2011). Intriguingly, besides many pro-proliferative and pro-survival genes that are regulated by MITF-M, cell cycle inhibitors p21 and p16 are also its targets (Carreira et al., 2005; Loercher et al., 2005), presumably mainly in normal melanocytes or at higher levels of MITF-M, which favor differentiation (Figure 1). MITF-M interacts with the Rb protein (Yavuzer et al., 1995) which cooperates with MITF-M to induce p21 (Carreira et al., 2005). Importantly, MITF-M regulates almost all genes the products of which are involved in specific melanocyte differentiation, i.e. the formation of the pigment melanin and its deposition into melanosomes. The enzymes involved in melanin formation are tyrosinase and tyrosinase-related proteins 1 and 2 (TRP-1 and TRP-2, also known as dopachrome tautomerase, Dct). Even many genes encoding structural melanosomal proteins and factors involved in the melanosome motility are regulated by MITF-M (reviewed in Vachtenheim and Borovansky, 2010). Interestingly, exceptional melanoma cell lines which are transcriptionally silent for MITF-M and do not express the downstream genes tyrosinase, TRP-1, and TRP-2, do not express these markers even after the exogenous transfer of MITF-M, so these cell lines are MITF-M nonresponsive (Vachtenheim et al., 2001). It is therefore likely that the loss of all melanoma markers did occur in these cell lines concomitantly with their absolute dedifferentiation during the loss of MITF-M expression, after which they in fact do not biochemically resemble melanomas.

MITF-M transcriptionally activates a number of genes that act prosurvival in melanomas. The cyclin dependent kinase 2, which proved crucial in melanoma proliferation (Du et al., 2004) is an important target of MITF-M. MITF-M further regulates HIF1 α , a hypoxia response factor (Busca et al., 2005) and APE-1/Ref-1, through which MITF regulates cellular response to ROS (Liu et al., 2009). The c-Met, a receptor kinase for the hepatocyte growth factor, has proinvasive features and promotes metastatic process in several tumors including melanoma. c-Met has been shown to be a target of MITF-M. Gel shift assays with melanoma cell nuclear extracts demonstrated binding by endogenous MITF-M protein to the c-Met promoter at the consensus MITF-M binding site and exogenous MITF-M activated the c-Met expression (McGill et al., 2006). Additionally, MITF-M is a transcriptional activator of Tbx2 gene (Carreira et al., 2000). T-box family of transcription factors are crucial in embryonic development. Tbx2

has been implicated in morphogenesis of a wide range of organs including limbs, kidneys, lung, mammary gland, and heart. Tbx2 is expressed in melanoma cell lines in positive correlation with MITF-M. Tbx2 promoter contains a consensus MITF-M recognition element to which MITF-M is recruited and activates Tbx2 expression (Carreira et al., 2000). As Tbx2 is overexpressed in several cancers including melanoma and plays a role in suppressing senescence, MITF-M modulates the survival of melanoma cells also via this factor.

MITF-M also upregulates the expression of clearly antiapoptotic genes. First, it activates the general antiapoptotic protein Bcl-2 (McGill et al., 2002), which is important for the survival of both melanoma and melanocyte lineage. Second, melanoma inhibitor of apoptosis (ML-IAP, livin) is a potent inhibitor of apoptosis in melanoma and is directly regulated by MITF-M (Dynek et al., 2008). It was shown that MITF-M was recruited to the ML-IAP promoter by chromatin immunoprecipitation and gel shift assays, activated ML-IAP promoter-reporter, and downregulation of MITF-M abrogated ML-IAP expression. The SLUG protein was reported to be a crucial determinant of melanoma metastasis, and its gene is also upregulated by MITF-M (Gupta et al., 2005). Another important gene regulated by MITF-M is Dia (DIAPH1, encoding the diaphanous-related formin Dia1). Increased MITF-M level favors expression of Dia and higher proliferation of melanoma cells. On the contrary, lower MITF-M downregulates Dia but the cdk inhibitor p27 is stabilized resulting in slower proliferation but higher invasive potential. Thus, a “rheostat” model is proposed where MITF-M levels determine the proliferation, differentiation, and invasiveness of melanoma cells (Carreira et al., 2006). Noteworthy, many other genes were identified as potential MITF-M targets, by the microarray analysis (Hoek et al., 2008). The SWI/SNF complex has been shown to be an important coactivator for many target genes, especially those involved in pigment formation, in human melanoma cell lines (Keenen et al., 2010). Of the two ATPases of the complex, Brg1 seems to be more important than Brm since its knockdown downregulates the MITF-M target genes more efficiently than Brm knockdown (Vachtenheim et al., 2010).

MITF-M is considered to be a melanoma oncogene because mutations and amplifications were found in patients' samples (Garraway and Sellers, 2006; Levy et al., 2006; Cronin et al., 2009). Copy gains at the MITF locus were found in about 10% melanoma samples and mutations of the MITF-M pathway were also described, even in the Sox10 gene (Cronin et al., 2009). Recently, novel MITF-M mutation, E318K, has been identified. This mutation is a germline allele variant (Yokoyama et al., 2011). E318K MITF-M encodes a protein with impaired sumoylation of MITF-M and differential regulation of several MITF-M targets. For example, the mutant enhances MITF-M protein binding to the HIF1 α promoter, a MITF-M known target, and increases its transcriptional activity (Bertolotto et al., 2011; Yokoyama et al., 2011). The presence of this allele constitutes more than fivefold risk factor for melanoma and renal cell carcinoma. Further, the mutant protein enhanced melanocytic and renal cell carcinoma clonogenicity, migration and invasion, further implicating this MITF-M variant as a risk factor for these two cancers (Bertolotto et al., 2011). Together, as MITF-M is strictly required for the embryonic development of melanocytes, maintains the survival of melanoma, and gene amplifications and mutations in the protein coding region have been found, it is considered as a lineage addiction oncogene.

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