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PATHOBIOLOGY IN FOCUS

The master role of microphthalmia-associated transcription factor in melanocyte and melanoma biology

Akinori Kawakami and David E Fisher

Certain transcription factors have vital roles in lineage development, including specification of cell types and control of differentiation. Microphthalmia-associated transcription factor (MITF) is a key transcription factor for melanocyte development and differentiation. MITF regulates expression of numerous pigmentation genes to promote melanocyte differentiation, as well as fundamental genes for maintaining cell homeostasis, including genes encoding proteins involved in apoptosis (eg, *BCL2*) and the cell cycle (eg, *CDK2*). Loss-of-function mutations of MITF cause Waardenburg syndrome type IIA, whose phenotypes include depigmentation due to melanocyte loss, whereas amplification or specific mutation of *MITF* can be an oncogenic event that is seen in a subset of familial or sporadic melanomas. In this article, we review basic features of MITF biological function and highlight key unresolved questions regarding this remarkable transcription factor.

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INTRODUCTION

As cellular differentiation and organ system development are largely regulated through distinct mRNA expression programs, it is not surprising that transcription factors have central roles in governing these complex and vital cellular events. Unique combinations of transcription factors specify discrete cell types. In melanocytes, MITF (microphthalmia-associated transcription factor) has a dominant role that has been termed 'master transcriptional regulator' of the melanocyte lineage.[1] MITF contains the basic helix-loop-helix leucine zipper (bHLH-Zip) DNA binding and dimerization motif, which also defines it as a distinct transcription factor class. It regulates key genes for melanocyte development and differentiation. MITF and other related family members, TFE3 and TFEB, together comprise the 'MiT' transcription factor family, which regulate gene transcription through homo- or hetero-dimerization and binding to E-box motifs consisting of the core hexanucleotide sequence CA[C/T]GTG.[1] MITF target genes include pigmentation enzymes and lineage survival factors, as well as many others.[2–4] In melanoma, MITF may function as an oncogene. In this review, we summarize prior discoveries regarding MITF function and highlight unanswered questions regarding MITF in melanocytes and melanoma.

DISCOVERY OF MITF

In 1942, Hertwig observed the offsprings of an X-ray irradiated mouse with abnormally small eyes (microphthalmia) and loss of pigmentation and named the mutant locus *m* (later expanded to *mi* and eventually to *Mitf*).[5] Various *Mitf* mutant mice show hearing loss due to loss of melanocytes in the inner ear (cochlea), as well as defective mast cells and osteoclasts, suggesting that MITF has important roles in these cell types.[6,7] Later, transgenic insertional mutagenesis identified *Mitf* as the gene responsible for the *Mi* phenotypes[8] and molecular studies revealed that MITF functions as a DNA-binding transcription factor capable of recognizing and regulating a sequence element vital for control of pigmentation enzyme gene expression.[1] Soon after that, Tassabehji *et al*[9] identified MITF loss-of-function mutations as the cause of Waardenburg syndrome type IIA in humans, which is characterized by small eyes, hypopigmentation, and hearing loss.

Several isoforms of MITF with distinct 5′ exons exist, owing to differential use of alternative promoters (Figure 1).[10] Expression patterns of the different isoforms range from widely expressed to tissue specific.[10] The M-isoform of MITF is expressed almost exclusively in melanocytes and

Cutaneous Biology Research Center, Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
Correspondence: Dr DE Fisher, MD, PhD, Cutaneous Biology Research Center, Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Bartlett Hall 622, Boston, MA 02114, USA.
E-mail: dfisher3@partners.org

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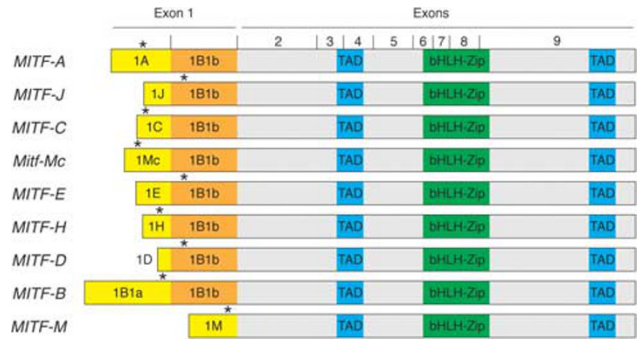

Figure 1 Spliced mRNAs (messenger RNA) of human MITF (microphthalmia-associated transcription factor) isoforms. Each isoform has a unique promoter and a first exon that is at least partially unique. Exons 2 through 9 are common to all isoforms and encode the transactivation domain (TAD) and the basic helix-loop-helix leucine zipper domain (bHLH-Zip). For all isoforms except the B- and M- isoforms, exon 1 is formed from a unique exon spliced to exon 1B1b. The B-isoform contains the entire exon 1B and the M-isoform does not include any part of exon 1B. The M-isoform is specifically expressed in melanocyte lineages. Expression patterns of the other isoforms range from widely expressed to tissue specific. Expression of Mitf-Mc has not been confirmed in human cells. Asterisks indicate translation start sites.

melanoma.[10] Loss-of-function mutations in the shared bHLH-Zip regions affect not only melanocytes, but also other cell types including osteoclasts, mast cells, and retinal pigment epithelial cells.[6,7] Recent studies have suggested roles of MITF in cardiomyocytes and β cells, as well.[11,12]

TRANSCRIPTIONAL REGULATION OF MITF

PAX3 and *SOX10* mutations cause Waardenburg syndrome types I, III, or IV (in contrast to type IIa, which is caused by *MITF* mutations).[13,14] The finding that neural crest cells express PAX3 and SOX10 earlier than MITF led researchers to hypothesize that the products of those genes regulate *MITF-M* transcription.[15] Watanabe *et al* and Verastegui *et al* found that PAX3 and SOX10 activate *MITF-M* transcription in a *cis*-acting fashion in melanocytes and melanoma.[14,16] Meanwhile, PAX3 seems to repress *MITF* expression through POU3F2 (see below) in some melanomas.[17,18]

α-Melanocyte-stimulating hormone (α-MSH) increases pigmentation through increasing tyrosinase (*Tyr*) expression in mouse B16-F1 melanoma cells,[19] as well as numerous additional pigmentation related genes (see below). Based on the results that α-MSH activates the cAMP-CREB signaling pathway and MITF activates *TYR* transcription, Bertolotto *et al*[20] and Price *et al*[21] hypothesized and found that cAMP-CREB signaling activates *MITF-M* transcription in a *cis*-acting fashion. This pathway was later found to be critical for the UV-suntanning response. Here, UV radiation was seen to produce DNA damage in epidermal keratinocytes, followed by induction of p53, which transcriptionally activates expression of the pro-opiomelanocortin (*POMC*) gene that is post-translationally cleaved to produce α-MSH.[22] Secreted α-MSH binds to its receptor on epidermal melanocytes, the melanocortin 1 receptor (MC1R), triggering cAMP production and CREB-mediated *MITF-M* transcription.[20,21] Takeda *et al* found that the *MITF-M* promoter contains a LEF-1 consensus DNA-binding site, through which WNT3A activates *MITF-M* transcription.[23] Jacquemin *et al.* found that ONECUT2 activates *MITF-M* transcription in a *cis*-acting fashion.[24] In addition, the Hippo signaling effector proteins TAZ and YAP65 work as PAX3 co-activators to activate *MITF-M* transcription.[25]

Neural crest cells express FOXD3 before expressing MITF and differentiating into melanocytes.[15] FOXD3 represses melanocyte development in chicks.[26] Thomas *et al*[27] and Curran *et al*[28] independently found that FOXD3 represses *Mitf* gene expression in zebrafish and chicks. It remains unclear how FOXD3 represses *MITF-M* expression in humans. Goodall *et al*[29] examined the relationship between POU3F2 (also known as Brn-2) and MITF-M and found that POU3F2 represses *MITF-M* transcription in a *cis*-acting fashion in human melanoma cell lines. Transforming growth factor β (TGF-β) represses *MITF-M* and is thought to help maintain melanocyte stem cells in a quiescent state.[30] Yang *et al*[31] found that TGF-β represses *MITF-M* expression through PAX3. More recently, Pierrat *et al*[32] found that TGF-β represses *MITF-M* transcription through GLI2 and inhibiting CREB transcriptional activity. Landsberg *et al*[33] reported that tumor necrosis factor α (TNF-α) rendered melanoma cells tolerant to T cells targeting melanocytic differentiation antigens by repressing production of those antigens, suggesting that TNF-α represses *MITF* expression. Perotti *et al*[34] found that NFATc2 represses *MITF* expression through inducing membrane-bound TNF-α. Smith *et al*[35] found the opposite: TNF-α increased *MITF* expression. Under hypoxic conditions, HIF1α was observed to activate DEC1 (BHLHE40), and DEC1 was found to repress *MITF-M* transcription.[36] This mechanism might contribute to variability in MITF expression seen within melanomas, where hypoxic zones show distinct (lower) expression levels.[36] Mallarino *et al* used *Rhabdomys pumilio* (African striped mouse) as a model to study striped pigmentation patterns and found that ALX3 directly repressed *Mitf-m* transcription.[37]

MITF TARGET GENES

Melanocytes produce and transfer melanin pigments to keratinocytes, where the pigments help to protect the skin from UV damage. Tyrosinase initiates the melanin biosynthetic pathway, melanogenesis, by oxidizing tyrosine to L-DOPA. MITF stimulates melanogenesis by activating transcription of *TYR* and other pigmentation genes including *TYRP1*, *DCT*, *PMEL*, and *MLANA*.[38–40] MITF also regulates certain ubiquitously expressed genes that are important for melanocyte survival (eg, *BCL2*) and proliferation (eg, *CDK2*).[41,42]

Technologies such as DNA microarrays, RNA sequencing (RNA-seq), and chromatin immunoprecipitation-sequencing

(ChIP-seq) have enabled comprehensive analyses of transcription factor-target genes. By leveraging gene ontology analysis, it is possible to categorize the genes regulated by transcription factors and thereby predict potential functions of transcription factors.

Genome-wide analyses of gene expression and MITF-binding regions in melanoma cell lines and human primary melanocytes revealed that MITF target genes are enriched in pigmentation, DNA replication and repair, and mitosis.[2,4,43,44] MITF affects metabolism by activating expression of a key transcriptional regulator of metabolism, PGC1α, and promotes lysosome biogenesis through activating lysosomal genes.[45,46]

Genome-wide analyses also identified genes that MITF binds and are induced by MITF knockdown, suggesting that MITF could work as a repressor.[4] MITF and PU.1 were seen to repress gene transcription by recruiting Eos and a co-repressor complex in osteoclasts.[47] MITF repressed C/EBPα, a key transcription factor for basophil differentiation, to promote mast cell differentiation[48] and was seen to associate with FHL2 to repress *Erbin* expression in cardiomyocytes.[49] MITF also repressed *ZEB1* transcription in the 501mel human melanoma cell line,[50] as well as inflammation genes through repressing *c-Jun* expression in mouse and human melanoma cell lines.[51] MITF recruits RBPJK as a cofactor in repressing transcription of microRNAs miR-221 and miR-222 in human melanoma cell lines.[52] It remains mechanistically unclear how MITF represses target genes and what functional roles MITF has through repressing gene expression.

Thus, MITF promotes melanocyte differentiation and regulates essential functions for cell homeostasis including survival, cell cycle, and metabolism, through regulating its numerous target genes (Figure 2). Researchers have found MITF target genes ranging from expected pigmentation genes to unexpected ubiquitously expressed fundamental genes—and more genes remain to be identified and characterized. It is curious to know how MITF regulates interactions between melanocytes and other cell types such as keratinocytes, fibroblasts, and immune cells. It is important to know whether MITF target genes are dysregulated in melanoma and, if so, what roles the dysregulated genes have in melanoma development and responses to therapies.

CO-ACTIVATORS AND CHROMATIN REMODELING COMPLEXES

Transcription factors, co-factors, and chromatin remodeling complexes work together to regulate gene transcription by changing chromatin states. MITF recruits histone acetyltransferases p300 and CBP to activate gene transcription.[53,54] MITF requires BRG1, a core component of SWI/SNF complexes BAF and PBAF, to regulate pigmentation genes, but not other MITF target genes such as CDK2, BCL2, and TBX2, in the SK-MEL-5 melanoma cell line.[55,56] BRM, another core component of BAF, but not PBAF, also associates with MITF to regulate pigmentation genes, but

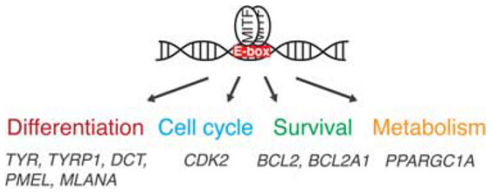

Figure 2 MITF (microphthalmia-associated transcription factor) functions and target genes. MITF regulates gene transcription through binding as a homodimer to the E-box motifs. MITF promotes differentiation through regulating pigmentation genes including *TYR*, *TYRP1*, *DCT*, *PMEL*, and *MLANA*; has pro-survival roles through regulating anti-apoptotic genes such as *BCL2* and *BCL2A1*; and regulates cell cycle and metabolism through regulating *CDK2* and *PPARGC1A*, respectively, in melanocytes and melanoma.

cannot completely substitute for BRG1.[56] Mass spectrometry revealed that MITF forms complexes with various proteins, including the PBAF chromatin remodeling complex.[57] Moreover, bioinformatic analyses of ChIP-seq and RNA-seq data showed that combinations of MITF, SOX10, TFAP2A, and YY1 recruit BRG1 and regulate genes involved in pigmentation and melanocyte development.[57] These studies suggest that MITF forms protein complexes with co-factors and chromatin remodeling complexes to regulate gene transcription. It remains unclear if MITF makes different complexes and, if so, what regulates the formation of different MITF-containing complexes.

THE MITOGEN-ACTIVATED PROTEIN KINASE SIGNALING PATHWAY AND MITF

The receptor tyrosine kinase c-Kit has important roles in melanocyte development, as does MITF.[58,59] Hemesath *et al* and Wu *et al* endeavored to decipher possible interactions between c-Kit and MITF and found that c-Kit activates mitogen-activated protein kinase (MAPK) and ribosomal S kinase 1 (RSK1), which in turn phosphorylate MITF at serine 73 and serine 409, respectively.[60,61] These phosphorylations promote ubiquitination and proteasomal degradation of MITF.[61] In addition, serine 73 phosphorylation is required for the interaction of MITF with p300/CBP *in vitro*.[54] Mutations of either one or both of serines 73 and 409 did not obviously affect pigmentation in mice.[62] However the role of MAPK signaling in modulating MITF levels has been clearly demonstrated in melanoma (see below) and seen to affect MITF protein and RNA levels, as well as target gene expression. Therefore, it remains to be determined whether these signal-dependent serine phosphorylations of MITF might modulate melanocyte function *in vivo*, but in ways that require environment-responsive contexts that remain to be determined.

The MAPK signaling pathway is activated by oncogenic mutation of *BRAF*, *NRAS*, *NF1*, or *KIT* and has key roles in melanoma.[63,64] In human primary melanocytes, activation of the MAPK pathway by exogenous $BRAF^{V600E}$ repressed *MITF-M* gene expression.[65] BRAF and MEK inhibitors increased expression of *MITF* and MITF targets in human

melanoma cell lines and increased MITF targets in human melanomas.[45,66–68] Among the targets found to be regulated by MITF in a BRAF/MAPK-dependent fashion was PGC1α, a master regulator of mitochondrial metabolism,[45] demonstrating the impact of MAPK-mediated MITF regulation on metabolic state in melanoma, as well as responsiveness to targeted therapies. These studies have suggested that the MAPK signaling pathway may repress *MITF-M* at the protein-stability level (via ubiquitin-dependent degradation), as well as the transcriptional level (via various mechanisms). In some melanoma cell lines, however, the MAPK signaling pathway was alternatively seen to activate *MITF-M* transcription; it remains unclear in exactly which cellular contexts these alternative modes of regulation occur.[69]

MITF AS AN ONCOGENE

The EWS-ATF1 fusion protein in human clear cell sarcoma mimics the 'cAMP activated' state of melanocytes due to the homology between ATF1 and CREB coupled to the constitutive activation function of this fusion protein, which replaces cAMP-dependency with potent transactivation potential from the EWS fusion partner.[70] In this tumor, EWS-ATF1 was seen to activate *MITF-M* transcription, and MITF expression was seen to be required for survival and growth of the sarcoma,[70] supporting MITF's oncogenic role in human malignancy. Furthermore, the *MITF* locus is amplified in 5–20% of human melanomas.[64,65] Although Harbst *et al.* did not detect amplification of the *MITF* locus in 49 tumors from 22 patients,[71] amplifications were described in the Melanoma TCGA analyses from multiple institutions.[64] Technical differences such as in computational algorithms could contribute to these differences. Immortalized primary melanocytes infected with viral constructs expressing $BRAF^{V600E}$ cannot form colonies in soft agar, but with additional infection by virus expressing MITF, these cells form colonies in soft agar, suggesting that MITF is required for anchorage-independent growth.[65] Most melanomas express MITF, including BRAF mutant melanomas, suggesting MITF expression is rescued by mechanisms such as MITF gene amplification and activated Wnt signaling.[64,65,72] Although BRAF-MEK-MAPK signaling targets MITF for ubiquitination and proteolysis,[54,60,61] oncogenic dysregulation of MITF may help to maintain MITF levels.[65] Anchorage-independent growth can be enabled by MITF target genes such as PGC1α and c-Met.[45,73–76] During anchorage-independent growth, mitochondrial reactive oxygen species induced by detachment of cancer cells from extracellular matrix[77] can be reduced by proteins upregulated by PGC1α.[45,75,76] c-Met has a key role in KRAS-dependent anchorage-independent growth in KRAS mutant cancers.[74] The germline $MITF^{E318K}$ mutation was subsequently discovered by multiple groups to encode a familial melanoma gene and to increase the risk of both melanoma and renal cell carcinoma.[78,79] The $MITF^{E318K}$ protein has increased transcriptional regulatory activity compared with wild-type MITF, because the mutation occurs at a consensus sequence important for SUMOylation that normally suppresses MITF transcriptional function.[80] That this variant encodes gain-of-function activity was supported by the phenotypic finding of increased non-blue eye color among patients containing this germline allele.[79] All of these studies suggest that MITF functions as an oncogene in at least a subset of human melanomas. It is unclear whether MITF may be dysregulated by additional mechanisms within melanomas containing neither amplification nor a coding region mutation.

Fusion proteins of the other MiT family members, TFE3 and TFEB, were also seen to function as oncogenes in renal cell carcinoma or alveolar soft part sarcoma.[81–84] In pancreatic adenocarcinomas, MiT family members regulate autophagy and lysosomal genes required for cancer growth.[85] These results suggest that MiT family members can function as oncogenes in various cancers. Thus far, the functional effects of MITF and its family members within the oncogenic context have been seen to include alterations in survival (targeting BCL2 and BCL2A1, metabolism, autophagy, and multiple additional potential mechanisms).[41,45,85–87]

LOW-MITF MELANOMA

Bioinformatic analyses of melanoma gene expression datasets revealed that a subset of melanomas expresses a low level of MITF. MITF-low melanomas were described to be more invasive (metastatic) and MITF-high melanomas more proliferative (less invasive).[88] Shuttling between high and low MITF levels has been suggested to produce rheostat-like modulation of melanoma cells between those two states, likely in response to a variety of environmental triggers.[89] High MITF activates subsets of cell cycle and differentiation genes that make melanomas proliferative and more differentiated. Meanwhile, clear mechanisms to explain why MITF-low melanomas are invasive remain to be determined.

Treatment of HGF-CDK4 (R24C) mouse melanomas with gp100-specific CD8+ cytotoxic T cells resulted in decreased expression of gp100 and other pigmentation genes, suggesting that MITF was repressed.[33] Also, inhibition of TNF-α increased pigmentation gene expression, suggesting that TNF-α repressed MITF expression.[33] MITF-low, NF-kB-high, AXL-high human melanoma cell lines, and human melanoma tumors are relatively resistant to $BRAF^{V600E}$ inhibition and AXL is a candidate for the resistance.[90,91] However, the response to AXL inhibition varies among melanomas, so the precise mechanism of the resistance remains incompletely understood.[90,91]

Single-cell quantitative RT-PCR revealed that the MITF expression level is heterogeneous in 501mel human melanoma cell monolayers, with high-, intermediate-, and low-MITF subpopulations of melanoma cells.[92] Single-cell RNA-seq of metastatic melanoma clinical samples identified a subset of melanoma cells expressing a low level of MITF and a high level of AXL.[93] These findings support the concept that cell populations within a melanoma may shuttle between high and low MITF expression levels.

It remains unclear how MITF is repressed *in vivo* and how melanoma cells survive with low MITF. As mentioned above, genomic amplification of MITF might help to maintain MITF expression in the setting of MAPK pathway activation, although the majority of BRAF/NRAS/NF1 mutant melanomas do not harbor MITF copy number gains. It is likely that distinct survival responses occur in MITF-low (or MITF-absent) melanomas. MITF could be repressed by several different mechanisms, and the repression mechanisms could determine how melanoma responds to therapies such as immune checkpoint inhibitors and MAPK inhibitors.

TARGETING MITF

MITF could be an attractive target for melanoma therapy, since it is essential for melanoma survival yet has limited requirements in non-melanocyte cellular lineages. In this way it parallels other lineage specific transcription factor oncogenes, such as the estrogen receptor and androgen receptor. However, unlike those nuclear hormone receptors, which are more straightforwardly targeted by small molecules (due to their ligand binding dependencies), drug targeting of MITF is significantly more challenging. HDAC inhibitors were seen to repress *MITF-M* transcription through potent repression of SOX10 expression.[94] Ubiquitination of proteins promotes and deubiquitination attenuates protein degradation. As MITF is degraded via the proteasome, inhibition of MITF deubiquitination promotes MITF degradation.[61] Zhao *et al* found that USP13 deubiquitinated MITF in melanoma cells and knockdown of USP13 decreased MITF protein and growth of those cells in soft agar and mouse xenografts.[95] Screening using a TRPM1 promoter-driven luciferase reporter revealed that a compound ML329 reduced MITF and MITF target gene expression.[96] Screening revealed that nelfinavir, a human immunodeficiency virus drug, repressed *MITF-M* transcription by repressing PAX3.[68] Nelfinavir also sensitized melanomas to MAPK inhibitors.[68]

As discussed above, melanomas can be tolerant of a low level of MITF, and low-MITF melanoma can be more invasive in specific contexts.[33,88–93] It is unclear whether a high-MITF melanoma would survive partial inhibition of MITF; nonetheless repression of MITF must be approached with caution, and the optimal MITF levels and physiological conditions for effective therapeutic repression remain to be determined.

CONCLUSIONS AND PERSPECTIVES

Researchers have discovered many predicted and unpredicted roles of MITF, and these findings have revealed new aspects of melanocyte and melanoma biology. However, many important and intriguing questions remain to be resolved.

MITF-M transcription is activated by the cAMP-CREB signaling pathway, the canonical Wnt signaling pathway, PAX3, SOX10, and ONECUT2, and is repressed by ALX3, FOXD3, POU3F2, TGF-β, TNF-α, and hypoxia (Figure 3).[14,16,19–21,23,24,26–33,35–37] Other signaling pathways and transcription factors may also regulate *MITF-M* transcription. Indeed, it is plausible that dysregulation of certain signaling pathways may be found to cause dysregulation of MITF, representing alternative oncogenic mechanisms to the previously characterized genomic amplification and E318-mutation. The relative roles of those factors in the regulation of *MITF-M* transcription in different physiological conditions remain important areas of current investigation.

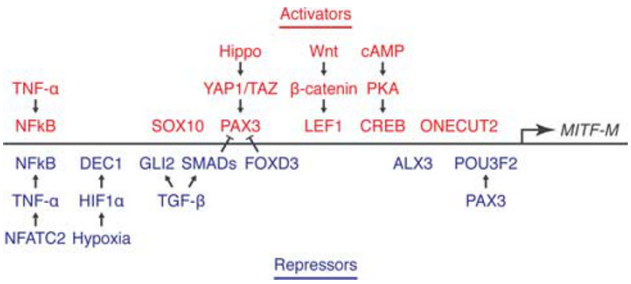

Figure 3 Transcriptional regulation of *MITF-M*. The cAMP-CREB signaling pathway, the canonical Wnt signaling pathway, PAX3, SOX10, and ONECUT2 activate *MITF-M* transcription in a *cis*-acting fashion. The Hippo signaling effector proteins TAZ and YAP1 work as PAX3 co-activators. POU3F2 and ALX3 repress *MITF-M* transcription in a *cis*-acting fashion. PAX3 could also repress *MITF-M* transcription by activating *POU3F2* transcription. In hypoxic conditions, DEC1, induced by HIF1*α*, represses *MITF-M* transcription in a *cis*-acting fashion. FOXD3 represses *MITF-M* transcription through inhibiting DNA binding of PAX3 or by another mechanism. Transforming growth factor β (TGF-β) represses *MITF-M* transcription through GLI2 and through repression of *PAX3* transcription by its downstream effectors SMADs. Tumor necrosis factor α (TNF-α) could activate and repress *MITF-M* transcription.

MITF regulates key genes in multiple vital processes, such as pigmentation, survival, invasiveness, and the cell cycle (Figure 2). Like the studies finding that MITF regulates sets of lysosomal and metabolic genes,[45,46] further analysis and categorization of MITF targets could uncover new roles of MITF, including ways in which its functions modulate responses to melanoma therapeutics. It remains incompletely understood which transcription factors and chromatin remodelers MITF cooperates with to regulate gene transcription in different functional contexts, and whether different combinations of MITF and transcription factors/chromatin remodelers determine which categories of genes MITF regulates. To what extent does MITF regulate the same genes in melanocytes and melanoma? How does the mutational or epigenetic landscape of a particular melanoma determine which functions of MITF will dominate within a specific melanoma? How might this information guide therapeutic strategies? Which melanomas are functionally independent of MITF's biological roles, and what mechanisms have supplanted MITF-dependency? Are those factors, in turn, targetable for therapeutic benefit? Immunotherapy is an extremely promising, yet still imperfect treatment for most patients with melanoma.[97] The regulation of pigmentation and other melanoma antigens by MITF raises the question of

whether MITF may affect an immune response against melanoma through regulating the expression of antigens and other melanoma genes related to tumor immunity.

Advances in our understanding of the biological functions of the MITF transcription factor have revealed fundamental insights into basic biology of pigmentation, melanocyte development, and melanoma. This remarkable 'Master Regulator' of the melanocyte lineage has key roles in both normal and pathologic states, and there is a strong indication that it continues to hold valuable clues of importance in benign and malignant diseases. Researchers' curiosity, serendipity, passion, and hard work may help to answer these questions, and thereby fundamentally expand our knowledge of melanocyte and melanoma biology and improve the lives of melanoma patients.

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DISCLOSURE/CONFLICT OF INTEREST

The authors declare no conflict of interest.

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