

The Many Roles of MITF in Melanoma

Jiri Vachtenheim*

Department of Transcription and Cell Signaling, Institute of Medical Biochemistry and Laboratory Diagnostics, First Faculty of Medicine, Charles University and General University Hospital Prague, Czech Republic

Abstract

Microphthalmia-associated transcription factor (MITF) plays pivotal role in the maintenance of the melanocyte lineage, differentiation of normal and malignant melanocytes and the survival of melanoma cells. MITF regulates expression of many genes with critical functions in cell differentiation, proliferation, and pro-survival properties. Melanoma is an extremely resilient tumor for which no effective therapy exists when the tumor progresses into metastasis. Melanoma is a heterogeneous tumor in which the microheterogeneity arises already in the first stages of the tumor development. Because the dependence of the melanocyte lineage on MITF is critical, MITF is regarded as the paradigmatic lineage-addiction oncogene and its gene is amplified in a smaller subset of melanomas. The level of MITF protein greatly differs among the tumor cells. Intriguingly, low MITF level cells are slowly proliferating but constitute an invasive subpopulation of tumor cells. In this minireview, I briefly discuss the many roles and activities of MITF in melanoma cells and the future prospects for melanoma therapy.

Keywords: MITF; Melanoma; Phenotype switching; Melanoma proliferation; Differentiation; Invasion; Apoptosis

Introduction

Malignant melanoma is a highly aggressive skin cancer, the incidence of which is steadily on the rise. Melanoma is chemotherapy-resistant with high mortality. Most melanomas harbour either V600E mutation of the BRAF gene (about 60%) or mutations of the NRAS oncogene (about 20%). Therefore, BRAF or downstream MAPK pathway has been the focus of the targeted intervention in melanoma. Unfortunately, in the majority of cases, acquired resistance to BRAF or MAPK/ERK inhibitors occurs after months when monotherapy is applied [1-3], possibly through several mechanisms such as reactivation of MAPK/ERK route or deregulation of other signaling pathways, e.g. PI3K/AKT/mTOR [4], high ZEB1 levels [5] or a formation of therapy-induced prooncogenic secretome favouring tumor growth [6].

MITF gene encodes a transcription factor of the basic-helix-loop-helix-leucine zipper type. The MITF genomic locus has several promoters producing corresponding MITF isoforms which differ in the first exon and share exons 2-9 [7]. The MITF-M isoform (named MITF in this article) is melanocyte-specific and is expressed exclusively in melanocytes and melanoma cells. MITF determines the identity of the melanocyte lineage in the embryonic development, normal adult melanocytes and melanoma cells. MITF regulates a number of genes involved in melanocyte differentiation and pigment formation [8] and in the survival, migration, proliferation, invasion and progression of melanoma cells.

It has been known for a long time that the transcription of MITF gene is supported by four main transcription factors, each having the binding site in the MITF promoter: CREB, SOX10, LEF1 and PAX3 [9-14]. The α -MSH hormone increases cAMP level and thus substantially contributes to MITF transcription by CREB. The β -catenin pathway is an important activator of MITF expression in melanomas. More recently, receptor tyrosine protein kinase TYRO3 has been found to activate MITF expression through SOX10 [15]. p21 protein can also help activate MITF expression, constituting the positive loop (see below) [16]. On the other hand, BRN2 (POU3F2) directly represses MITF expression [17]. Similarly, SOX5 has been demonstrated to inhibit MITF expression [18]. Several other transcription factors, such as SOX2 [19], and several microRNAs can modulate MITF expression (reviewed in Vachtenheim and Ondrušová [20]). The chromatin remodeling complex SWI/SNF

was shown to be the necessary epigenetic transcriptional coactivator of MITF [21] and some of MITF targets [22].

Importance of MITF for Melanoma Differentiation and Proliferation

A large number of genes constitute the MITF targets. One group of genes comprises the melanogenic enzymes (TYR, TRP1 and DCT) involved in the formation of the pigment melanin. MITF also regulates many other genes which are responsible for melanin deposition, melanosome migration and transfer of melanosomes to keratinocytes [8,23,24]. MITF is therefore absolutely essential for pigment cell differentiation.

The proliferation of melanoma is believed to occur predominantly through the activation of the MAPK pathway, fueled by mutated BRAF and NRAS. MITF also transcriptionally activates expression of CDK2, which can contribute to high proliferation rate incurred by MITF [25]. Intriguingly, some melanoma cell lines contain low MITF levels but proliferate rapidly (e.g. widely used A375 cells). In these cell lines, many deregulated signaling pathways presumably keep the high proliferation of melanoma cells. For example, the Hedgehog/GLI signaling [26], PI3K/AKT/mTOR [4] and Wnt/ β -catenin [11] signaling are active in melanomas and are crucial for tumor progression. Surprisingly, MITF activates also genes with adverse functions in proliferation such as the negative cell cycle regulators p21(WAF1) [27] and INK4A (coding the p16 tumor suppressor) [28]. Activation of these genes probably function only in normal melanocytes and benign nevi. The p16/CDKN2A gene has been earlier regarded as a "melanoma gene" and

*Corresponding author: Dr. Jiri Vachtenheim, Department of Transcription and Cell Signaling, Institute of Medical Biochemistry and Laboratory Diagnostics, Katerinska 32, Prague 2, 12108, Charles University Prague, First Faculty of Medicine, Czech Republic, Tel: 420224964110; Fax: 420224964152; E-mail: jiri.vachtenheim@1f1.cuni.cz

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is inactivated in 20% of melanoma families [29]. Noteworthy, frequent gene amplification and overexpression of cyclin D can contribute to melanoma proliferation [30,31].

Antiapoptotic Role of MITF

Besides these differentiation genes stand MITF targets with predominantly pro-survival function, having important implications for melanoma maintenance. MITF upregulates the expression of the general antiapoptotic protein BCL2 [32], which is important for the survival of both melanoma and other cells of the melanocyte lineage. A related gene, BCL2A1, is amplified in a subset of melanomas and is crucial for their survival. BCL2A1 is also a direct transcriptional target of MITF. Thus, MITF-BCL2A1 is a lineage-specific oncogenic pathway in melanoma targetable by obatoclax, an inhibitor of all BCL2 family members, which is effective in melanoma treatment and improves the response to BRAF-directed therapy [33]. The antiapoptotic signals have been reported to be mediated by the MITF target BPTF protein that transduces key pro-survival role driven by MITF [34]. Another proapoptotic MITF target is ML-IAP/livin [35]. Together, several strong antiapoptotic proteins are MITF targets acting downstream of MITF and mediating its antiapoptotic role. SLUG protein has been reported to be a crucial determinant of melanoma metastasis in the mouse model, and SLUG gene is also upregulated by MITF [36]. In humans, however, SLUG expression was low in melanoma metastases and high in benign nevi [37].

MITF as an Oncogene

MITF is a lineage identity-maintaining melanoma transcription factor. It has been discovered that MITF is amplified in a smaller subset of melanoma cell lines and tumors (the region of chromosome 3p containing MITF) [38-39]. So, not only the melanocyte lineage constituting normal melanocytes, but also melanomas are entirely dependent on MITF which provides pro-survival antiapoptotic signals. Due to this function, MITF is also regarded as an example of the "lineage addiction" oncogenes. Other cancers, such as prostate (where lineage-addiction oncogene is an androgen receptor, AR), intestine, lung or mammary contain, sometimes only predicted, lineage-addiction oncogenes [40]. In some melanomas or cell lines, the MITF level is low, raising the question whether the level is sufficient to sustain survival. At least two explanations might explain this situation. First, the requirement of MITF level may be highly variable, depending on the genetic context. Secondly, other antiapoptotic proteins may provide a surrogate survival function when MITF level is very low. MITF and other lineage-survival genes present in other tumors therefore implicate lineage dependency as a mechanism that is essential for tumor survival. The lineage addiction oncogenes are therefore potential targets for tumor treatment.

The Phenotype Switching and Decreased Levels of MITF in Invasive Cells

The phenotype switching normally occurs during tumor progression. Epithelial-to-mesenchymal transition (EMT) is a tumorigenic program through which epithelial cancer cells acquire mesenchymal, more prooncogenic phenotype. Melanoma cells, although they are not typically epithelial, also undergo EMT. The reversible phenotype switching is an event still not completely understood in melanoma. A "rheostat model" has been suggested, in which highly proliferating cells are differentiated and contain high MITF, while slowly proliferating cells contain low MITF and are more invasive [41]. This situation was observed in 501 mel cells, but

areas with low MITF and increased oncogenic protein BRN2 were indeed observed in tumors [17,42]. Furthermore, slowly-proliferating populations were observed expressing high AXL [43] or a proinvasive transcription factor GLI2 (a Hedgehog pathway signaling effector) [44], which was recently identified as an activator of survivin transcription across a number of tumor cell types including melanomas [45].

EMT and increased invasivity is believed to be associated with lower levels of MITF, whereas increased proliferation is linked to higher MITF levels. However, the precise role of MITF in the phenotype switching is still incompletely characterized. The main hallmarks of EMT is the loss of E-cadherin (resulting in decreased adhesion to human keratinocytes) and increase of N-cadherin expression. SNAIL is also frequently increased [46]. Although ZEB1 is elevated during EMT in melanoma as in other tumors, ZEB2 has been described decreased in melanomas [46,47]. The role of SLUG in melanoma EMT is controversial. The prevailing opinion is that SLUG does not participate in EMT and melanoma invasion and progression. ZEB1, a known inducer of EMT and invasiveness, is typically elevated protein in EMT, whereas ZEB2 supports differentiation rather than EMT [46-50]. In conformity with this, melanomas display ZEB1 expression during EMT, but ZEB2 and SLUG stand on the differentiation, anti-EMT side. For instance, high levels of ZEB1 expression were found to be associated with acquired or inherent resistance to MAPK inhibitors in BRAF-mutated melanoma cell lines and tumors [5]. Wels et al. [51] reported that SLUG and ZEB1 cooperated to repress E-cadherin and promoted migration of melanoma cells.

An interesting finding linking directly the lower MITF levels with higher invasion involves the cell GTP levels [52]. It has been shown that MITF is an upstream regulator of guanosine monophosphate reductase (GMPR), an enzyme of guanylate metabolism. GMPR depletion can increase cellular GTP levels in cultured cells, an event eliciting greater melanoma invasivity. The lower GTP levels in cells overexpressing MITF or GMPR cause decreased invasion. Furthermore, when siRNA-mediated decrease of MITF was induced with consequent lowered levels of GMPR, even small increase of GTP (several per cents) generated high increase of invasion. The morphology of MITF-depleted invasive cells is accompanied with a larger number of invadopodia [53]. Suppression of RAC1 activity was required to reduce invasiveness caused by MITF depletion. Interestingly, this mechanism which increases invasion is not dependent on other upstream MITF-regulating factors and might explain the higher invasivity induced by low MITF. Downregulated MITF favoring invasive phenotype can be achieved also through the hypoxic conditions. Under hypoxia, HIF1 α activates protein DEC1 (BHLHE40) and DEC1 represses MITF transcription. Inhibitors of prolyl hydroxylase stabilizing HIF1 α suppressed melanoma growth in mouse xenografts [54]. The melanoma main driver mutation BRAF(V600E) has been shown to activate the MAPK pathway that reduces the MITF levels [55]. Intriguingly, BRAF(V600E) has thus also a second function: regulation of MITF levels. It can activate MITF expression through the activation of BRN2 which activates MITF expression, a result contrasting the previous function of BRN2 being a MITF repressor [17]. Because BRN2 expression is activated by mutated BRAF, this reversible regulation mechanism requires further investigation.

Conclusions and Perspectives for Melanoma Therapy

The understanding of MITF transcription factor functions have revealed basic insights into the melanocyte development and biology of melanoma. The phenotype switching can be reversible in melanoma. Further, melanoma cells display extreme microheterogeneity, which can

be extended even to a single cell level [56]. This opens the way toward extreme plasticity, migration and early metastasis to the tumors. In low MITF tumors the high expression of the receptor kinase AXL seems to be a frequent event constituting MITF-low/AXL-high phenotype, which predicts the resistance to drug treatment [57]. High AXL expression has been observed earlier in more than one third of melanomas [43], which were designated as MITF-negative. This opens the question whether melanomas completely lacking MITF are still melanomas. The high AXL tumors might have expressed low amounts of MITF, at least in some cells. The melanomas completely lacking MITF must have also lost all differentiation markers and such tumors are probably non-melanotic undifferentiated tumors where the antiapoptosis function has been changed from MITF to other antiapoptotic gene(s), e.g. AXL.

The many compounds available for the targeted therapy including phytochemical agents [58] and their combination make promise for future studies that should be conducted to carefully elucidate the synthetic lethal effect of agents on melanoma invasion, migration, and metastasis. Although melanomas possess some suitable molecular targets (mutated BRAF, MAPK pathway) for therapy, the resistance evolving in this kind of treatment requires finding other approaches of targeted therapy which would be beneficial for all patients irrespective of specific mutations or alterations harbored in specific tumor subsets.

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