From modification to malignancy: Bridging acetylation mechanisms and therapeutic innovations in melanoma (Review)

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Abstract. Melanoma, a highly malignant form of skin cancer, poses significant challenges in oncology due to its aggressive nature and resistance to conventional therapies. Epigenetic modifications, especially acetylation, have emerged as critical regulators of gene expression that influence the pathogenesis and progression of melanoma. Acetylation is a novel post-translational modification that involves the addition of an acetyl group to lysine residues both in histone and in non-histone proteins. In the context of melanoma, acetylation has been shown to occupy a pivotal role in regulating cellular proliferation, autophagy, apoptosis and metastasis, as well as drug resistance. The identification of acetylation-associated biomarkers and therapeutic targets in melanoma is currently an active area of research. The present review aims to elucidate the roles of acetylation modifications in melanoma, and to explore the potential of targeting these modifications for novel therapeutic interventions, with a unique perspective on the acetylation networks mediating therapy resistance.

Contents

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1. Introduction

Skin cancer remains a major global health burden, with melanoma representing the most aggressive subtype of cutaneous malignancy (1), which is responsible for approximately 80% of skin cancer-associated fatalities (2-5). Recent advances in post-translational modification research have identified that acetylation fulfills an indispensable role in regulating gene expression via dynamic modulation of chromatin structure (6,7). Emerging evidence indicates that aberrant acetylation homeostasis is pathologically associated with various dermatological disorders, particularly with the initiation, progression and therapeutic resistance of melanoma (8). Understanding both the underlying mechanisms and consequences of acetylation in melanoma is essential for guiding the development of novel therapeutic strategies targeting these epigenetic modifications. Notably, acetylation-associated biomarkers have been shown to have significant clinical relevance in melanoma diagnosis and prognosis, underscoring the translational importance of this field.

2. Melanoma and acetylation

Melanoma. Malignant melanoma originates from melanin-producing cells derived from the neural crest, and it can be induced by a range of factors, including physical factors, chemical and biological mediators, and genetic/molecular determinants (9,10). According to the World Health Organization classification, melanomas can be categorized into two major groups, namely those associated with sun exposure and those that are not, and these groups are reflected in distinct molecular pathways and different pathological histories (11). The sun-associated group is further subclassified based on the extent of chronic sun damage (CSD) into high-CSD and low-CSD melanomas (12). The latter group is

further subdivided based on the site of origin into mucosal, acral, uveal and spitzoid melanomas, melanomas arising in blue or congenital nevi, as well as rare variants originating in the central nervous system (13). Ultraviolet radiation (UVR) has a well-established etiological role in melanoma pathogenesis; however, its effects on skin physiology are complex, encompassing both detrimental impacts (for example, DNA damage and mutagenesis) and beneficial aspects, including vitamin D synthesis and immunomodulatory functions (14-16). The process of melanogenesis, regulated by neuroendocrine factors (for example, α-MSH and ACTH) and enzymatic pathways, not only determines skin pigmentation, but also modulates melanoma behavior and therapeutic responses (17). For example, eumelanin may confer photoprotective effects, whereas pheomelanin has been shown to promote oxidative stress and contribute to tumor progression (18,19). The skin operates as a neuro-immunoendocrine organ, producing a range of mediators (for example, CRH, β-endorphin and cannabinoids) that are able to locally modulate melanocyte function and contribute to melanoma pathogenesis. In advanced stages of the disease, melanoma-derived factors can disrupt systemic homeostasis, thereby altering energy balance and immune function beyond the local microenvironment, which has the effects of facilitating disease progression and metastatic spread (17).

Acetylation. Acetylation, a dynamic post-translational modification, serves as an epigenetic rheostat regulating chromatin accessibility, transcriptional activation and protein functional states. In cancers, dysregulation of this equilibrium, primarily mediated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), drives oncogenic transcription programs and post-translational rewiring of tumor suppressors (20). HATs, including the p300/CBP (CREB-binding protein) family and the GNAT/MYST subfamilies, catalyze the transfer of acetyl groups from acetyl-CoA to histone tails, thereby neutralizing their positive charges to relax chromatin structure and facilitate transcriptional activation (21,22). Beyond histone modification, key HATs, such as p300, function as transcriptional co-activators that are able to integrate signaling pathways through acetylating both histones and non-histone targets, including p53 and STAT3, thereby modulating apoptosis, cellular differentiation and immune responses. HDACs have the role of counterbalancing HAT activity, and they function through the removal of acetyl groups. These enzymes are divided into four classes of enzymes: Class I HDACs (HDAC1/2/3/8), which are ubiquitously expressed and predominantly localized to the nuclear compartment, where they exert their most prominent HDAC activity (23); Class II HDACs (HDAC4/5/6/7/9/10), which reside in the cytoplasm and translocate to the nucleus in response to specific cellular signaling cues; Class III HDACs, also termed sirtuins (SIRT1-7), which are NAD^+-dependent enzymes that remove acetyl groups to restore chromatin compaction and silence gene expression (24); and HDAC11, the sole member of Class IV HDACs, which exhibits higher defatty-acylase activity compared with its intrinsic deacetylase activity. Numerous studies have provided evidence in support of the crucial involvement of HDAC11 in different types of cancer, immune responses and metabolic processes (25,26).

The dynamics of acetylation critically influence melanoma pathogenesis through modulating chromatin accessibility, transcriptional programs and protein functional states (27). Aberrant histone and non-histone acetylation, driven by dysregulated HAT/HDAC activity, has been shown to contribute to melanoma initiation through the silencing of tumor-suppressive genes and hyperactivation of oncogenic pathways. During metastatic progression, imbalances in acetylation have the effect of promoting invasive phenotypes through 'rewiring' enhancer landscapes to favor pro-migratory gene networks, and suppressing differentiation signals. Clinical studies have shown that therapeutic strategies targeting acetylation, such as the use of HDAC inhibitors (HDACi) and sirtuin modulators, demonstrate dual efficacy in terms of restoring tumor-suppressive transcription and circumventing immune evasion, thereby underscoring the central role of this type of epigenetic modification across the melanoma continuum.

Notably, the acetylation landscape and its functional consequences may vary significantly across melanoma subtypes, including cutaneous, acral lentiginous and mucosal melanoma. Acral melanoma exhibits a distinct molecular profile compared with other cutaneous melanoma subtypes, characterized by a lower frequency of canonical driver mutations in the B-Raf proto-oncogene (BRAF) and NRAS proto-oncogene (NRAS) genes, but a higher prevalence of alterations, such as KIT mutations and copy number gains involving cyclin-dependent kinase 4 (CDK4) and cyclin D1 (CCND1) (28-31). This genomic instability, often manifested through structural variations and amplifications, is a hallmark of acral lentiginous melanoma, and may be influenced by mechanical stress rather than UVR, suggesting that the acetylome regulating these genomic regions is likely to differ substantially across the subtypes. Consequently, the differential acetylation landscape gives rise to varied therapeutic responses; for example, the reduced frequency of BRAF mutations in acral lentiginous melanoma has been shown to reduce the efficacy of BRAF/MEK inhibitors, whereas the activation of alternative pathways (for example, via KIT or CDK4) suggests a potential role for HDACi in targeting these non-canonical vulnerabilities either by modulating oncogene expression or reactivating silenced tumor suppressors. However, although acetylation dynamics are being increasingly mapped in cutaneous melanoma, subtype-specific patterns in acral lentiginous melanoma and mucosal melanoma remain incompletely defined. Preliminary acetylome profiling, however, has suggested unique enhancer acetylation landscapes in acral lentiginous melanoma/mucosal melanoma, potentially reflecting their distinct mutational spectra and microenvironmental contexts, which may influence tumor biology and responses to epigenetic therapies, including HDACi or CBP/p300 inhibitors. Dedicated studies using patient-derived models and subtype-stratified cohorts are warranted to elucidate the underlying mechanisms of the acetylation landscape and to optimize targeted strategies.

3. Acetylation modifications in melanoma pathogenesis and progression

Although the key roles of HATs and HDACs in melanoma are well-established, the specific functions of individual family members (such as different sirtuins or specific Class I HDACs)

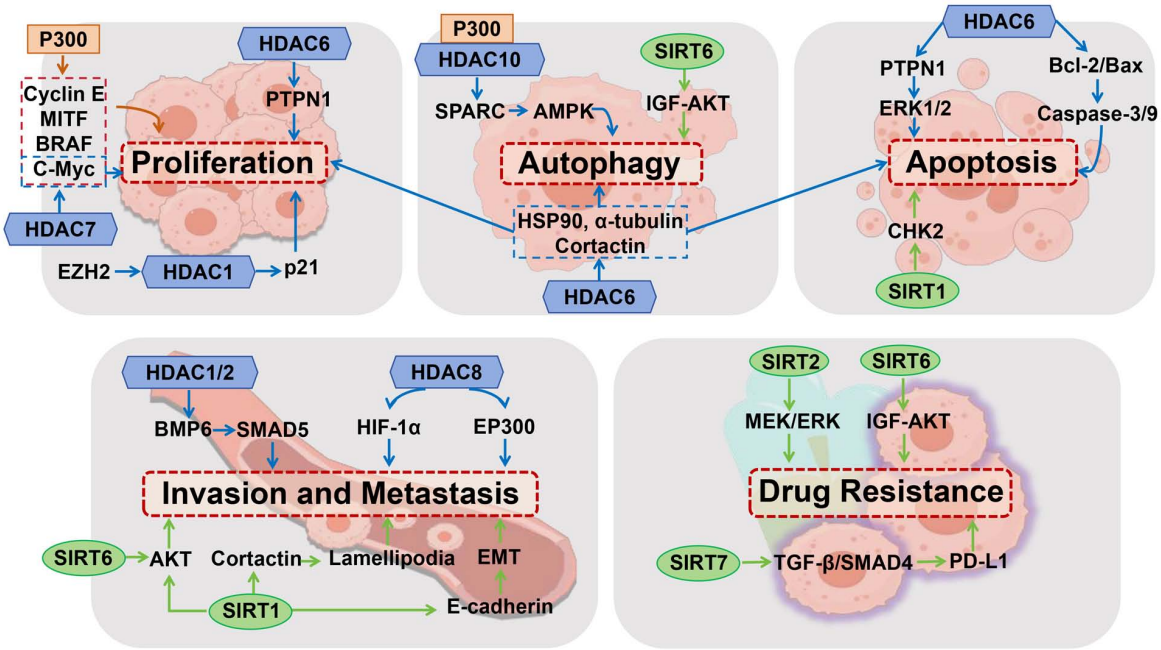

Figure 1. Acetylation-mediated regulation of melanoma progression. P300 enhances melanoma cell proliferation via acetylation of cyclin E, MITF, BRAF and c-Myc. EZH2 represses p21 through HDAC1, disrupting the cell cycle. HDAC6 modulates proliferation, autophagy, and apoptosis via α-tubulin, HSP90, cortactin, and the PTPN1-ERK1/2 pathway; its inhibition induces apoptosis via Bcl-2/Bax regulation. HDAC7 promotes growth via c-Myc, while P300 and HDAC10 coordinate SPARC-mediated autophagy. SIRT1 and SIRT6 regulate apoptosis and autophagy through CHK2 and IGF-AKT signaling, respectively. HDAC1/2 activate BMP6-SMAD5 to inhibit metastasis, while HDAC8 enhances invasion via deacetylation of HIF-1α and EP300. SIRT1 promotes migration through EMT, lamellipodia formation, and AKT deacetylation; SIRT6 antagonizes this effect. SIRT2 and SIRT6 drive resistance via MEK-ERK and IGF-AKT signaling. SIRT7 promotes PD-L1-mediated immune evasion by suppressing TGF-β-SMAD4 signaling. HDAC, histone deacetylase; EMT, epithelial-mesenchymal transition.

and their heterogeneity across melanoma subtypes require more detailed characterization. For example, the 'paradoxical' role of SIRT6 in promoting melanoma proliferation, and yet mediating drug resistance, highlights the complexity of acetylation network regulation and its potential context-dependence (32,33). Understanding the effects of nuanced alterations in the acetylation network is critical in terms of developing effective precision targeting strategies.

Acetylation-mediated control of cell fate in melanoma: Regulation of proliferation, autophagy and apoptosis. Acetylation has been shown to critically regulate key processes associated with melanoma, including proliferation, autophagy and apoptosis, through modulating both transcriptional activators and epigenetic repressors (Fig. 1). Subsequently, the following section will discuss various factors associated with acetylation and their underlying mechanisms of action (Table I).

Central to the regulatory function mediated via protein acetylation is the HAT p300, which promotes melanoma-genesis through multiple interconnected mechanisms. One key mechanism which involves p300 is the direct activation of the cyclin E promoter, which thereby facilitates the G_1/S phase transition. Accordingly, inhibition of p300, either by expressing a dominant negative p300 mutant (DN p300) or using the pharmacological inhibitor Lys-CoA, was found to markedly reduce cyclin E transcription, thereby inducing cell cycle arrest (21). These findings aligned with its established role in facilitating G_1/S progression through the acetylation of key factors such as E2F1 (34). Furthermore, p300 has been shown to sustain the pro-proliferative activity of the lineage-survival oncogene MITF via catalyzing histone acetylation at its proximal regulatory regions. The inhibitory effect of p300 blockade on the proliferation of $MITF^{high}$ melanoma cells (cells that are characterized by high levels of the MITF transcription factor) underscores the significance of this regulatory axis (35). Beyond cell cycle and oncogene support, p300 also activates the BRAF kinase by promoting BRAF K601 acetylation, thereby enhancing its kinase activity and promoting melanoma cell proliferation. Significantly, this K601 acetylation contributes to resistance against $BRAF^{V600E}$ inhibitors in melanomas harboring the common $BRAF^{V600E}$ mutation, an effect that is counteracted by the opposing deacetylase activity of SIRT1 (36). These findings collectively illustrate the multifaceted roles of p300-mediated acetylation in melanoma (Table I).

Building on its multifaceted roles in melanoma, p300/CBP also acts as a critical positive cofactor for the Myc family of transcription factors (c-Myc, N-Myc and L-Myc). These potent regulators drive cell proliferation and suppress differentiation across diverse cell types. Specifically in the case of c-Myc, CBP has been shown to acetylate c-Myc *in vitro*. Crucially, co-expressing CBP with c-Myc *in vivo* was shown to enhance c-Myc acetylation, leading to reduced ubiquitination and consequently stabilizing the c-Myc protein (37).

Beyond the multifaceted roles of HATs such as p300, HDACs also have a crucial role in regulating tumor cell proliferation and apoptosis through epigenetic reprogramming. A key example is HDAC1, which cooperates with the polycomb group protein, enhancer of zeste homolog 2 (EZH2), to drive

Table I. Summary of HDAC-related function.

First author/s, year	Role of acetylation	Factor	Target	Mechanism	(Refs.)
Weinert *et al*, 2018	Proliferation, autophagy and apoptosis	p300	Cell cycle	Directly activates the cyclin E promoter	(21)
Kim *et al*, 2019			MITF	The MITF is regulated by p300-mediated histone acetylation.	(35)
Dai *et al*, 2022			BRAF	p300 promotes B-Raf proto-oncogene kinase activity.	(36)
Vervoorts *et al*, 2003			c-Myc	Co-expression of CBP with c-Myc stimulates acetylation.	(37)
Kim *et al*, 2019; Fan *et al*, 2011		HDAC1	Cell cycle	HDAC1 is a key component of EZH2 regulatory axis.	(35,38)
Kovacs *et al*, 2005; Pulya *et al*, 2021		HDAC6	Various cellular functions	Targeting substrates such as α-tubulin, HSP90, and cortactin.	(39,40)
Liu *et al*, 2018			ERK1/2	Interacting with the PTPN1; Activating ERK1/2 signaling.	(41)
Pulya *et al*, 2021; Bai *et al*, 2015			Bcl-2, Bax, caspase	Inhibiting HDAC6 resulted in a decrease in Bcl-2 and an increase in Bax/Caspase-3/9.	(40,42)
Ling *et al*, 2023		HDAC10	SPARC	Depletion of HDAC10 upregulates SPARC and inhibits melanoma growth.	(43)
Zhang *et al*, 2020		SIRT1	CHK2	SIRT1 deficiency induces CHK2 hyperacetylation and results in cell death via mitotic catastrophe.	(47)
Wang *et al*, 2018		SIRT6	IGF-AKT	IGF-AKT pathway mediates the effect of SIRT6 on autophagy in melanoma.	(32)
Min *et al*, 2022	Invasion and metastasis	HDAC1/2	BMP6	HDAC1/2 inhibits melanoma metastasis through regulating BMP6/SMAD5 signaling.	(50)
Kim *et al*, 2023		HDAC8	HIF-1α	HDAC8 deacetylates HIF-1α, enhancing its protein stability and transcriptional activity.	(52)
Emmons *et al*, 2023			EP300	By deacetylating EP300, HDAC8 inactivates its catalytic function.	(53)
Kong *et al*, 2022	Drug resistance	SIRT1	E-cadherin	SIRT1 suppresses E-cadherin expression.	(55)
Kunimoto *et al*, 2014; Porta *et al*, 2014; Yang *et al*, 2022			AKT	SIRT1 deacetylates AKT.	(57-59)
Bajpe *et al*, 2015; Zhao *et al*, 2022		SIRT2	MEK/ERK	Inhibition of SIRT2 leads to resistance by modulating the MEK/ERK pathway.	(60,61)
Strub *et al*, 2018; Wang *et al*, 2015		SIRT6	IGFBP2	SIRT6 haploinsufficiency upregulates IGFBP2 expression and confers resistance to MAPK inhibitors.	(33,62)

Table I. Continued.

First author/s, year	Role of acetylation	Factor	Target	Mechanism	(Refs.)
Yi *et al*, 2023		SIRT7	SMAD4	SIRT7 deacetylates SMAD4, thereby antagonizing the TGF-β-SMAD4 pathway.	(63)
Yu *et al*, 2023		HDAC2	PD-L1	HDAC2-mediated deacetylation promotes the nuclear translocation of PD-L1.	(64)
Gao *et al*, 2020		p300	PD-L1	p300-mediated acetylation of PD-L1 prevents its nuclear translocation.	(65)

BRAF, B-Raf proto-oncogene; HDAC, histone deacetylase; EZH2, enhancer of zeste homolog 2; ERK1/2, extracellular signal-regulated kinase 1/2; PTPN1, tyrosine-protein phosphatase non-receptor type 1; SPARC, secreted protein acidic and rich in cysteine; CHK2, cell cycle checkpoint kinase 2; SIRT, sirtuins; BMP6, bone morphogenetic protein 6; SMAD, small mothers against decapentaplegics; HIF-1α, hypoxia-inducible factor-1α; EMT, epithelial-mesenchymal transition.

cell cycle dysregulation in melanoma. EZH2 is highly expressed in metastatic melanoma cells, where it suppresses the expression of p21 (encoded by CDKN1A), a cyclin-dependent kinase inhibitor regulated by histone acetylation. Mechanistically, EZH2 facilitates the recruitment and retention of HDAC1 at the CDKN1A promoter, thereby repressing p21 transcription through histone deacetylation. Consequently, HDAC1 downregulation reactivates p21 expression, triggering G_1/S phase arrest and halting tumor progression (35,38).

Complementing the multifaceted roles of HATs such as p300, HDAC6 has emerged as a structurally unique epigenetic regulator. HDAC6, distinguished by its dual deacetylase domains and a C-terminal ubiquitin-binding zinc finger domain, targets substrates such as α-tubulin, heat shock protein 90 and cortactin (39). These substrates are involved in various cellular functions, including cell proliferation, apoptosis, autophagy and DNA repair (40). Functionally, HDAC6 has been shown to orchestrate a pro-survival signaling network in melanoma. It directly binds and stabilizes protein tyrosine phosphatase non-receptor type 1, thereby activating ERK1/2 signaling to drive cell proliferation, colony formation and metastasis, while suppressing apoptosis (41). This axis is further amplified by the regulation of mitochondrial apoptosis pathways mediated by HDAC6: HDAC6 inhibition has been shown to trigger reactive oxygen species (ROS)-dependent mitochondrial depolarization, leading to reduced levels of Bcl-2, increased levels of Bax, the release of cytochrome c and activation of caspases-9 and -3, ultimately inducing apoptosis (40,42).

Looking beyond HDAC6's regulation of pro-survival signaling networks, the secreted glycoprotein known as secreted protein acidic and rich in cysteine (SPARC) exemplifies how acetylation-dependent epigenetic mechanisms converge to control the cell fate of melanoma. Of crucial importance to this axis is HDAC10, which acts in concert with HAT p300 to dynamically modulate H3K27ac, a key epigenetic marker on histone H3, at SPARC regulatory elements. This epigenetic remodeling facilitates the recruitment of bromodomain-containing protein 4 (BRD4), a critical transcriptional co-activator, to SPARC enhancers, thereby repressing SPARC transcription. Notably, either HDAC10 depletion or its pharmacological inhibition was shown to reverse this repression, leading to the robust upregulation of SPARC. The resultant SPARC overexpression triggers AMPK-dependent autophagy (43), which, in turn, inhibits the activity of mechanistic target of rapamycin complex 1 (mTORC1), induces autophagosome formation and activates Unc-51-like kinase 1 (ULK1) to drive the lysosomal degradation of oncogenic cargo (44). This autophagic flux ultimately suppresses melanoma proliferation and metastasis. Crucially, SPARC-mediated autophagy also resensitizes BRAF inhibitor-resistant melanoma, rendering it susceptible to targeted therapy, thereby revealing a dual antitumor mechanism (45). Collectively, HDAC10 and SPARC form an epigenetic-metabolic checkpoint that regulates melanoma progression, thereby providing a molecular rationale for targeting this axis in combination therapies.

Beyond the SPARC/HDAC10 axis that couples epigenetic remodeling with autophagic flux, checkpoint kinase 2 (CHK2) has emerged as a critical guardian of genomic integrity, orchestrating DNA damage responses and cell fate

decisions in melanoma. Upon sensing DNA double-strand breaks, CHK2 undergoes ATM-dependent phosphorylation at Thr-68, triggering dimerization and activation to enforce either G_1/S or G_2/M cell cycle arrest, thereby either enabling DNA repair, or initiating apoptosis should the damage be irreparable (46). Intriguingly, the NAD^+-dependent deacetylase SIRT1 has been shown to directly interact with CHK2, deacetylating it at the Lys-520 site (47). This deacetylation subsequently antagonizes CHK2 phosphorylation and dimerization, effectively suppressing its activation. Consequently, SIRT1 deficiency induces CHK2 hyperacetylation, leading to aberrant kinase activation, mitotic catastrophe and ROS-dependent cell death, a mechanism exploited by oxidative stress in melanoma therapy (48). Simultaneously, the SIRT family member SIRT6 is positively associated with the levels of autophagy in melanoma. Mechanistically, SIRT6 has been shown to induce abnormal autophagy in melanoma through inhibiting the insulin-like growth factor 1 (IGF-1)-AKT signaling pathway (32). Collectively, the SIRT1-CHK2 and SIRT6-autophagy axes form an integrated network that balances cell survival and death in response to genomic and metabolic stresses.

This section of the review has systematically delineated how multiple acetyl-regulatory factors, including p300, HDAC1/6/7/10 and SIRT1/6, have been demonstrated to influence the fate of melanoma cells through modulating key molecules (Cyclin E, MITF, BRAF, c-Myc, p21, SPARC, CHK2 and IGF-AKT). However, existing studies have predominantly focused on individual factors, and thus both a holistic understanding of the dynamic equilibrium within the acetylation network and knowledge regarding its crosstalk with other signaling pathways (for example, MAPK and PI3K/AKT) are currently lacking. Notably, the divergent roles of SIRT1 and SIRT6 in regulating cellular apoptosis/autophagy vs. migration, coupled with HDAC6's established function as a multi-pathway hub, suggest that targeting these molecules may yield pleiotropic effects, although this would potentially be counterbalanced by a concurrent increase in off-target risks.

Acetylation-mediated control of cell fate in melanoma: Influence on invasion and metastasis. The invasion of melanoma cells, which represents a critical step in metastatic dissemination, relies on the epigenetic reprogramming of chromatin states that determines phenotypic plasticity. The epigenetic landscape of acetylation serves as a critical determinant of melanoma cell invasion and phenotypic plasticity (Fig. 1). Key evidence has come from a study by Mendelson *et al* (49), who stratified primary melanomas into low-risk (Epgn1, proliferative) and high-risk (Epgn3, invasive) subtypes based on enhancer landscapes driven by H3K27ac. This contradiction highlights how acetylated-driven enhancer remodeling dynamically balances pro- and anti-invasive gene networks, thereby determining their metastatic potential.

Complementing the epigenetic axis, the bone morphogenetic protein (BMP)/SMAD signaling pathway, representing a branch of the TGF-β superfamily, has been shown to orchestrate melanoma metastasis through dual regulatory modes. Min *et al* (50) demonstrated that HDAC1/2 deacetylases suppress metastasis through activating BMP6-dependent SMAD5 signaling, which leads to an upregulation of adhesion molecules (for example, E-cadherin) and inhibits matrix metalloproteinases (MMPs). On the other hand, HDAC1/2 loss triggers BMP6-SMAD5 axis suppression, which has the effect of enhancing invasion via epithelial-mesenchymal transition (EMT) transcription factors (for example, Twist and Slug) and extracellular matrix (ECM) degradation, a mechanism consistent with earlier findings reported in a study by Hornig *et al* (51). Therefore, the HDAC-BMP-SMAD cascade converges with the dynamics of H3K27ac enhancers to regulate melanoma invasion.

Beyond the epigenetic reprogramming of invasion-associated chromatin states, hypoxia-inducible factor 1 (HIF-1) has been found to be pathologically overexpressed, and its overexpression drives the malignant transformation of melanocytes through enhancing their proliferation, metastasis and immune evasion. Critically, acetylation dynamics have the effect of 'fine-tuning' the activity of HIF-1α and that of its downstream regulators. Among these regulators, the Class I HDAC, HDAC8, has emerged as a pivotal orchestrator. Mechanistically, HDAC8 deacetylates HIF-1α, which has the effect of enhancing its protein stability and transcriptional activity, thereby promoting the expression of its target genes and accelerating cellular migration (52). Moreover, through deacetylating the HAT EP300, HDAC8 inactivates its catalytic function, thereby redirecting chromatin accessibility towards pro-invasive transcription factors such as c-Jun. This modification has been shown to enhance melanoma cell invasion and resistance to stress, thereby promoting the development of brain metastasis (53). Considered altogether, HDAC8 integrates HIF-1α stabilization and EP300 suppression to establish a feed-forward loop that amplifies melanoma aggressiveness, and this dual mechanism underscores HDAC8 as a therapeutic node to disrupt metastatic adaptation in hypoxic and inflammatory microenvironments.

Building on the HIF-1α-HDAC8 axis that drives metastatic adaptation, the EMT emerges as a pivotal reprogramming event, enabling melanoma cells to dissociate from primary tumors and invade distant tissues. Central to this plasticity is dynamic lysine acetylation, which fine-tunes the activity of EMT-associated transcription factors (54,55). Among the multiple acetylation regulators, the NAD^+-dependent deacetylase SIRT1 is pathologically overexpressed in metastatic melanoma, providing a signature that correlates with poor prognosis (56). Interestingly, SIRT1 has been shown to promote cell migration and invasion by inducing EMT through the suppression of E-cadherin expression (55). Moreover, SIRT1 regulates the extension of lamellipodia, which are crucial structures for cell migration, by deacetylating cortactin (56,57). Previous studies have shown that SIRT1 inhibitors, including nicotinamide, are able to significantly impair melanoma cell migration through blocking lamellipodial extension, whereas SIRT1 activation enhances the migratory capability of the cells (56,57). In addition, phosphoinositide 3-kinase (PI3K) has been shown to facilitate the formation of membrane protrusions induced by platelet-derived growth factor (PDGF), a process that is regulated by SIRT1 through deacetylation of AKT (57-59). On the other hand, nuclear-localized SIRT6 was found to exert an antagonistic effect on cytoplasmic SIRT1-AKT signaling through suppressing AKT activity at the chromatin level, thereby contributing to the regulation

of melanoma cell migration. This SIRT1-SIRT6 antagonism creates a therapeutic vulnerability: SIRT1 inhibitors (for example, nicotinamide) lead to impairments of lamellipodial extension and EMT, whereas SIRT6 activation restricts metastatic dissemination. Targeting this axis may therefore prove to be an effective means of disrupting the acetylation-dependent 'migratory plasticity' of melanoma cells.

The role of acetylation in driving melanoma invasion and metastasis is highly context-dependent. For example, the distinct subgroups defined by H3K27ac patterns, the regulation of HIF-1α and p300 by HDAC8, and the promotion of EMT and cytoskeletal dynamics by SIRT1 collectively underscore the central importance of epigenetic reprogramming in determining metastatic potential. However, it is critical to understand how these processes dynamically respond to the tumor microenvironment (TME) *in vivo*, including hypoxia and immune cell infiltration. Although current studies have provided robust evidence for the pro-metastatic roles of HDAC8 and SIRT1, the validation of effective selective inhibitors through creating metastatic models has remained limited. Future studies are required that have the objective of integrating spatial omics technologies to map the evolution of acetylation modifications across primary tumors, circulating tumor cells and metastatic niches, which should lead to the identification of actionable targets. Notably, targeting metastasis-associated acetylation regulators (for example, HDAC8 and SIRT1) may face significant challenges due to the essential functions that they perform in normal physiology (for example, embryonic development and immune regulation), which will necessitate a rigorous evaluation of the therapeutic window.

Acetylation-mediated control of cell fate in melanoma: Influence on drug resistance. DNA-damaging agents, including alkylating drugs such as temozolomide, dacarbazine and fotemustine, are pivotal in the treatment of metastatic melanoma. However, melanoma cells often develop resistance to these agents, and this can be attributed, in part, to epigenetic alterations mediated by acetylation activity. Overall, the intricate interplay between acetylation modifications and the cellular response to various anticancer agents underscores the complexity of melanoma biology (Fig. 1).

Within the regulatory network of melanoma resistance and immune evasion, the sirtuin family exerts pivotal control through dynamic acetylation modifications, with individual members exhibiting both functional heterogeneity and paradoxical roles across tumor progression stages. For example, SIRT2, a member of the sirtuin family, drives resistance to BRAF inhibitors (for example, vemurafenib) through deacetylating and activating the MEK/ERK pathway (60,61). Interestingly, SIRT6 haploinsufficiency has been found to cause an upregulation of IGF binding protein 2 (IGFBP2) expression through mechanisms involving increased chromatin accessibility and H3K56 acetylation at the IGFBP2 locus, coupled with enhanced IGF-AKT signaling. This upregulation subsequently confers resistance to MAPK inhibitors in BRAF-mutant melanoma cells, thereby highlighting its context-dependent function (33,62).

Furthermore, SIRT7 critically promotes melanoma progression by enhancing tumor cell survival and facilitating immune evasion. Deficiency in SIRT7 leads to an increase in tumor cell death under stress conditions *in vitro* and a suppression of tumor growth *in vivo*. Mechanistically, SIRT7 directly deacetylates SMAD4 protein, which antagonizes the TGF-β-SMAD4 signaling pathway, ultimately leading to an upregulation of programmed death-ligand 1 (PD-L1) protein. This SIRT7-mediated increase in PD-L1 enables immune evasion and contributes to resistance against immune checkpoint blockade therapies (63). The regulation of PD-L1 itself is also subject to acetylation dynamics, as revealed by contrasting findings: HDAC2-mediated deacetylation was found to promote PD-L1 nuclear translocation, enabling it to form a complex with phosphorylated (p-)STAT3 and to activate early growth response 1-mediated tumor angiogenesis (64), whereas p300-mediated acetylation prevents PD-L1 nuclear translocation, thereby reprogramming immune-response-associated gene expression and consequently enhancing the antitumor response to PD-1 blockade (65). Collectively, these findings underscore the intricate and often context-specific interplay between sirtuin-mediated acetylation, immune regulation and therapeutic resistance pathways in melanoma.

The role of acetylation modifications in mediating melanoma resistance to targeted therapies (for example, BRAF/MEK inhibitors) and immunotherapies (for example, anti-PD-1) is increasingly being recognized, especially concerning the contributions of sirtuins (SIRT2/6/7) and specific HDACs (for example, HDAC2). The regulation of PD-L1 acetylation status by p300, and its impact on immune checkpoint inhibitor efficacy, represent a discovery that has significant clinical translational potential. Nevertheless, resistance mechanisms are highly complex and heterogeneous, where alterations in a single acetylation factor may constitute only one component of an intricate resistance network. Furthermore, when evaluating strategies targeting acetylation (for example, combining HDACi or sirtuin inhibitors) to reverse resistance, it is essential to consider their dual effects on both tumor cells and immune cells (for example, T-cell function), as exemplified by SIRT7's involvement in tumor cell survival and PD-L1 regulation. Therefore, optimizing the time, dosage and sequence of combination therapies is critical for overcoming resistance.

4. Acetylation modifications in melanoma diagnosis and prognosis

The prognostic significance of acetylation in melanoma has become evident, based on the multidimensional regulatory axis that includes epigenetic reprogramming, metastatic competence and remodeling of the TME. Numerous studies have shown that acetylation levels differ across different tumor types, and that these are correlated with various clinicopathological parameters and patient survival rates (66-69). For example, malignant melanoma cells have been shown to exhibit higher levels of HDAC1/2/3 expression compared with their non-cancerous counterparts. This positions acetylation status not only as a potential biomarker for staging, but also as a dynamic guide for therapeutic intervention.

The HAT Tip60 (Tat interactive protein, 60 kDa) exemplifies this prognostic value, as its expression is inversely correlated with primary tumor thickness, serving as an independent prognostic marker across disease stages; diminished Tip60 levels were also found to be associated with significantly

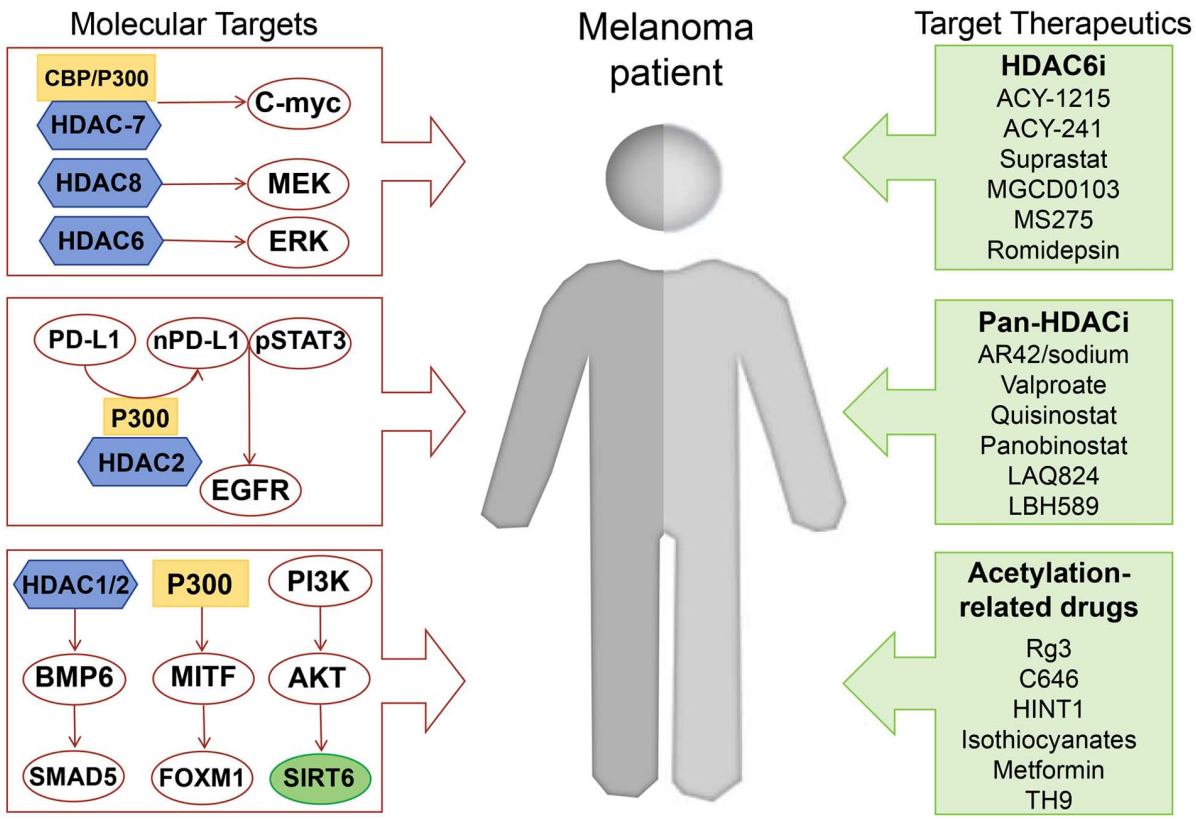

Figure 2. Integrated signaling pathways and targeted therapeutic agents in melanoma. Pathways are outlined in red boxes with directional arrows. Drug categories are color-coded in light green. Schematic depicts interconnected pathways driving melanoma pathogenesis: CBP/P300 and HDAC 7/8/6 regulate the expression of c-Myc, MEK and ERK. SIRT6 is the downstream product of the PI3K-AKT pathway and P300-MITF-FOXM1 transcriptional network controlling melanocyte differentiation and proliferation. HDAC1/2-BMP6-SMAD5 pathway modulating TGF-β signaling. HDAC6-selective inhibitors (HDAC6i): ACY-1215, ACY-241, Suprastat, MGCD0103, MS275, and romidepsin. Pan-HDAC inhibitors (Pan-HDACi): AR42/sodium valproate, quisinostat, panobinostat, LAQ824, and LBH589. Acetylation-targeting agents: Rg3, C646, HINT1, isothiocyanates, metformin, and TH9. HDAC, histone deacetylase; HDACi, HDAC inhibitor.

reduced 5-year disease-specific survival rates in patients with melanoma (70-72). Mechanistically, Tip60 promotes apoptosis through p53 acetylation at K120 (73,74), and its downregulation results in decreased levels of acetylated DNA methyltransferase 1 (ac-DNMT1). This Tip60/ac-DNMT1 axis is critically associated with melanoma progression, and low levels of ac-DNMT1 are correlated with poorer prognosis in stage IV disease; by contrast, elevated levels of ac-DNMT1 are a predictor of improved survival (75).

Similarly, the HAT p300 demonstrates significant stage-dependent prognostic relevance. Clinical analyses have revealed a redistribution pattern in advanced melanoma, characterized by nuclear depletion and cytoplasmic accumulation, and this is strongly correlated with the higher American Joint Committee on Cancer (AJCC) cancer stages. This redistribution is mechanistically driven by the BRAF-MAPK/ERK pathway, which targets nuclear p300 for ubiquitin-proteasomal degradation. Consequently, a high BRAF/low nuclear p300 profile predicts metastatic transition, whereas a low BRAF/high nuclear p300 signature aids in distinguishing nevi from melanoma (36,76). Critically, Kaplan-Meier survival analysis was employed to confirm that low nuclear p300 expression, but not low p300 cytoplasmic expression, is a strong predictor of significantly worse overall and disease-specific 5-year survival rates (77).

Collectively, these findings have underscored the complex interplay between specific HATs (Tip60, p300), histone deacetylases (HDACs), and associated modifiers (for example, ac-DNMT1) within the acetylation landscape, solidifying their crucial roles as prognostic indicators and potential therapeutic targets across the spectrum of melanoma progression. However, translating these findings into clinical practice faces challenges: Validating the value of independent prognostic indicators requires large-scale, multicenter prospective cohorts, and standardized protocols need to be established for detecting and scoring systems. Overcoming these challenges will enable acetylation-associated biomarkers to facilitate clinical risk stratification, thereby guiding therapeutic decision-making.

5. Acetylation modifications as therapeutic targets in melanoma

Recent studies have provided valuable insights into the mechanisms via which HDAC influences melanoma progression, which have highlighted the potential of HDACi as a therapeutic strategy (Fig. 2). The development of HDACi as therapeutic agents holds promise for the treatment of melanoma; however, the specific effects of these inhibitors may differ, according to the HDAC isoform and the cellular context (Table II).

Table II. Summary of HDAC-related therapeutic agents.

First author/s, year	Category	Medicine	Target	Mechanism	Model	(Refs.)
Booth *et al*, 2017	HDACi	AR42/sodium valproate	Pan-HDACi	Enhancing of anti-PD-1 and anti-CTLA4 antibodies	TPF-12-293 cells	(79)
Heijkants *et al*, 2018		quisinostat	Pan-HDACi	Combining the treatment with CDK inhibition using flavopiridol	Uveal melanoma cell lines	(93)
Gallagher *et al*, 2018		panobinostat	Pan-HDACi	Inducing caspase-dependent apoptotic cell death	Patient derived melanoma	(94)
Booth *et al*, 2017		Suprastat	HDAC6i	Increasing the infiltration of $CD8^+$ effector and memory T-cells	SM1 murine melanoma model	(80)
Vo *et al*, 2009; Lisiero *et al*, 2014		LAQ824; LBH589	Pan-HDACi	Enhancing the efficacy of ACT	B16 murine model	(90,92)
Noonepalle *et al*, 2020		MGCD0103; MS275	Class I-HDACi	Upregulating PD-L1 expression	B16 murine melanoma	(83)
Badamchi-Zadeh *et al*, 2018		Romidepsin	HDAC1/2-inhibitor	Increasing the frequency of vaccine-elicited $CD8^+$ T cells	C57BL/6 mice	(95)
Shan *et al*, 2014	Other acetylation-related treatments	Rg3	-	Inducing cell cycle arrest; decreasing HDAC3 and increasing p53 acetylation	A375; SK-MEL-28; Xenograft tumor	(96)
Yan *et al*, 2013		C646	-	Inducing cell cycle arrest	WM35 cells	(97)
Mitsiogianni *et al*, 2021		Isothiocyanates	-	Inducing cell cycle arrest and cellular senescence in melanoma cells by inhibiting p300/ CBP	A375, Hs294T, VMM1 and B16F-10 melanoma	(103)
Li *et al*, 2018		Metformin	-	Inhibiting KAT5-mediated SMAD3 acetylation, transcriptional activity and TRIB3 expression	C57BL/6 mice and KK-Ay mice	(104)

HDAC, histone deacetylase; CDK, cyclin-dependent kinase; ACT, Adoptive T-cell therapy; SMAD3, small mothers against decapentaplegics 3.

HDACi. HDACi hinder the effective repair of DNA damage. This persistent damage either disrupts or inhibits essential cellular processes, including transcription and DNA replication, which ultimately triggers a cell death mechanism in cancer cells (78).

HDACi and immune checkpoint therapy. The integration of HDACi with immune checkpoint therapy represents a paradigm-shifting approach in melanoma treatment, leveraging epigenetic priming to overcome tumor immune evasion. Notably, pan-HDACi agents such as AR42 or valproic acid, when combined with kinase inhibitors such as pazopanib, have demonstrated significant antitumor activity that extends beyond growth suppression to the downregulation of the immune checkpoint molecules, PD-L1/PD-L2. This epigenetic reprogramming leads to a critical enhancement of tumor responsiveness to subsequent immune checkpoint blockade, thereby amplifying antitumor immunity (51,79). The synergy arises through multifaceted mechanisms; For example, HDACi remodel the TME by promoting the infiltration of macrophages, natural killer (NK) cells, neutrophils and activated T cells (80), whereas Class I HDACi also modulate checkpoint ligand expression, causing an upregulation of PD-L1 and PD-L2 in melanoma (81,82). For example, the pan-HDACi LBH589 (targeting Class I/II/IV) in combination with PD-1 blockade was shown to reduce tumor burden and to extend survival in melanoma models. Similarly, selective HDAC6 inhibitors, such as Suprastat, exhibit combinatorial efficacy with PD-L1 blockade by reshaping immune populations, having the effect of reducing the numbers of pro-tumoral M2 macrophages while enhancing infiltration of antitumor $CD8^+$ T-cells and memory T-cells (83,84). This rational combinatorial approach, which is grounded in overcoming epigenetic-mediated immune resistance, underpins the clinical success that has already been observed in metastatic melanoma and other malignancies that target co-inhibitory pathways. However, the process of clinical translation warrants caution: Even though preclinical studies (for example, utilizing LBH589, Suprastat) have demonstrated efficacy, early clinical trial results have been mixed. Therefore, developing more selective HDACi (for example, HDAC6 inhibitors) or tumor-targeted HDACi, or optimizing currently existing dosing regimens (for example, intermittent administration), may help to improve the therapeutic window and efficacy of this combination therapy.

Though the combination therapy involving HDACi and the immune checkpoint cytotoxic T-lymphocyte associated protein 4 (CTLA-4) targeting agent nivolumab has demonstrated improved efficacy in patients with melanoma (80), there remains a notable scarcity of studies that have directly investigated the mechanistic links between acetylation and immune checkpoints such as CTLA-4, lymphocyte-activation gene 3 (LAG-3) and T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT). Limited evidence has suggested that HDACi is able to modulate the tumor immune microenvironment, potentially enhancing T cell function and antigen presentation. For example, Li *et al* (85) demonstrated that co-inhibitory receptors such as CTLA-4, LAG-3 and PD-1 provide essential balancing signals for T cell activation. Their study also revealed that the intrinsic HDAC activity within the Tcf1 transcription factor is crucial for preventing the excessive induction of CTLA-4 in T follicular helper (Tfh) cells, thereby protecting their B-cell helper function. Specifically, mutations in key amino acids within the HDAC domain of Tcf1 led to the de-repression of CTLA-4 in Tfh cells. In spite of these insights, however, the direct mechanistic interplay between HDACi and the regulation of CTLA-4, LAG-3 or TIGIT expression and function specifically within the context of melanoma remains poorly understood. The majority of published studies to date have focused on the phenotypic outcomes of combination therapies, rather than on the underlying epigenetic modifications. Therefore, elucidating how HDACi modulate the acetylation status of histones or non-histone proteins associated with genes encoding these immune checkpoints in melanoma represents a critical and promising direction for future research.

HDACi and adoptive cell therapy (ACT). ACT represents a transformative approach for metastatic melanoma, and its efficacy may be significantly enhanced through strategic epigenetic modulation with HDACi (86,87). HDACi reprogram the tumor-immune interface via dual mechanisms: i) through inducing chromatin relaxation to enhance tumor antigen presentation; and ii) through reversing T-cell exhaustion by restoring acetylation-dependent transcriptional programs in $CD8^+$ T cells (88,89). Crucially, preclinical studies have demonstrated how this mechanistic synergy is translated into therapeutic enhancement. For example, the pan-HDACi LAQ824, when combined with ACT using gp100-specific pmel-1 T cells, was shown to cause a significant amplification of the cytotoxic function of the transferred cells, which led to a heightened level of tumor eradication in a B16 melanoma model (90,91). In addition to enhanced tumor cell eradication, this combination also led to superior antitumor efficacy. Similarly, combining the pan-HDACi LBH589 with gp100-specific T-cell therapy led to substantially prolonged T-cell survival and reduced tumor burden in melanoma models (92). Furthermore, the activity of HDACi extend beyond modulating immediate effector functions. For example, previous studies have shown that exposure to HDACi and interleukin-21 (IL-21) caused a reprogramming of differentiated human $CD8^+$ T cells into central memory-like T cells. This dedifferentiation process is initiated through histone H3 acetylation at the CD28 promoter region, which facilitates IL-21-mediated p-STAT3 binding to the CD28 locus, thereby generating a highly persistent T cell population (91). These findings collectively served to position HDACi as essential adjuvants for overcoming the epigenetic barriers that limit ACT efficacy in immune-cold melanomas.

Utilizing HDACi to enhance ACT, especially through modifying memory T cell phenotypes and augmenting their persistence, represents an innovative therapeutic strategy. However, this approach is currently being validated primarily in murine models. When translating HDACi such as LAQ824 or LBH589 to human ACT, critical evaluations must focus on their potential toxicity towards both the infused T cells and the host immune system, as well as the impact they may have on T cell receptor diversity. Furthermore, substantial optimization work needs to be undertaken to precisely control the HDACi treatment conditions (concentration, duration) during *ex vivo* T cell expansion, which is required in order to maximize the therapeutic benefits while minimizing functional impairment.

HDACi and other treatments. The combination of HDACi with CDK blockade offers a paradigm-shifting strategy for overcoming therapeutic resistance in refractory melanomas.

The potential of this as combination therapy has been robustly demonstrated preclinically: Utilizing BRAF wild-type cutaneous melanoma tumors as a model, Heijkants *et al* (93) reported that the combination of pan-HDACi quisinostat and pan-CDK inhibitor flavopiridol significantly reduced tumor volume to a greater extent than was accomplished via flavopiridol monotherapy. Promising therapeutic effects were also observed in patient-derived xenograft models of cutaneous melanoma (93).

Looking beyond CDK inhibition, HDACi further enhance targeted therapy through distinct molecular mechanisms. Another study, conducted by Gallagher *et al* demonstrated the synergistic effects of combining the BRAF inhibitor encorafenib with the HDACi panobinostat in melanoma cells (94). This combination induced caspase-dependent apoptotic cell death, primarily via the downregulation of c-Myc expression and by decreasing PI3K pathway activity, suggesting that the combination of HDACi and MAPK inhibitors may have therapeutic potential in melanoma treatment.

The therapeutic scope of HDACi combinations extends significantly into the immunomodulatory landscape. The combinatorial targeting of epigenetic regulators, especially through HDACi and the bromodomain and extra-terminal domain (BET) family, has emerged as a transformative strategy to overcome therapeutic resistance in melanoma. The HDACi romidepsin (RMD) and the BET inhibitor IBET151, both individually and in combination, have been shown to enhance the frequency of vaccine-elicited $CD8^+$ T cells and to improve therapeutic and prophylactic protection against B16-OVA melanoma. Additionally, the increased IL-6 production and pro-apoptotic gene expression following RMD^+ IBET151 treatment are likely to be contributors towards the enhanced cancer vaccine responses (95). These findings have identified HDACi as versatile adjuvants whose synergistic interactions with CDK inhibitors, BRAF inhibitors and BET inhibitors extend beyond simple growth suppression to encompass targeted elimination and enhanced immune surveillance. Optimizing these potent combinations represents a critical frontier for advancing melanoma treatment, necessitating a focus on clinical translation studies to fully realize their potential.

Other acetylation-associated treatments. Emerging pharmacological strategies targeting acetylation dynamics extend beyond traditional HDACi, demonstrating multifaceted antitumor potential through epigenetic-metabolic crosstalk and combinatorial synergy. For example, Rg3, a bioactive compound extracted from ginseng roots, has demonstrated efficacy in inhibiting melanoma cell proliferation via downregulating HDAC3 expression and enhancing the level of p53 acetylation on lysine residues. This dual action not only serves to arrest cell cycle progression but also potentiates p53-dependent transcriptional activation; *in vivo* studies that were performed using A375 xenografts confirmed these significant antiproliferative effects (96). Complementing these natural agents, synthetic inhibitors such as C646 have been shown to target p300/CBP acetyltransferase activity to induce cell cycle arrest and to synergize with DNA-damaging agents. Notably, C646 enhances cisplatin-induced apoptosis in melanoma cells via sensitizing cells to genomic instability (97-100).

Further broadening the therapeutic landscape, isothiocyanates (ITCs), which are phytochemicals abundant in cruciferous vegetables, function as pan-HDACi to suppress p300/CBP activity, thereby triggering G_0/G_1 arrest and senescence in melanoma (101). Mechanistically, ITCs orchestrate a pleiotropic epigenetic reprogramming landscape through reducing the total HDAC activity, modulating the expression of histone-modifying enzymes (HDACs, HATs and methyltransferases), and altering acetylation-methylation crosstalk on histones H3/H4 (102,103). This multifaceted activity positions ITCs as ideal partners for kinase inhibitor combinations in refractory melanoma. Looking beyond their role as direct acetylation modifiers, targeting stress-responsive nodes, such as pseudokinase TRIB3, reveals novel metabolic-epigenetic interdependencies. Li *et al* (104) found that treatment with metformin led to melanoma growth and metastasis via reducing TRIB3 expression. Mechanistically, metformin was shown both to suppress SMAD3 phosphorylation and to weaken the interaction between the histone acetylase KAT5 and SMAD3, which, in turn, reduces KAT5-mediated acetylation of SMAD3, leading to a decrease in SMAD3 transcriptional activity and subsequent TRIB3 expression, and thereby antagonizing melanoma progression.

Beyond HDACi, targeting HATs, utilizing natural compounds, or employing repurposed drugs are diverse strategies for modulating acetylation against melanoma. These substances often exhibit poly-pharmacology (namely, the design and use of a single drug that simultaneously acts on multiple biological targets to achieve a therapeutic effect), which may lead to complex biological effects and potential off-target risks; however, their *in vivo* antitumor activity, pharmacokinetic properties, bioavailability and synergistic potential with standard therapies require systematic evaluation in models that closely resemble the clinical setting. Examples such as Rg3 and metformin suggest that modulating acetylation might represent an essential component of their known antitumor mechanisms, providing novel insights into their modes of action, especially in the case of some established agents (or 'old drugs'). However, translating these findings into effective clinical treatment regimens necessitates addressing challenges that are associated with optimal dosing, routes of administration, and how best to integrate these non-canonical epigenetic agents within standard therapeutic frameworks.

6. Prospects and perspectives

Acetylation, a critical post-translational modification, has been increasingly recognized for its profound impact on the progression and metastasis of melanoma. Given the critical role of acetylation in melanoma pathogenesis, targeting this modification has emerged as a promising therapeutic strategy. Various HDACi have been developed, ranging from pan-HDACi that target multiple HDAC isoforms, to more selective inhibitors targeting specific HDACs. Despite the promise that they hold, the clinical application of HDACi in melanoma treatment continues to face several challenges. The efficacy and safety profiles of these compounds require further validation through extensive clinical trials.

First, one of the primary challenges in the clinical application of HDACi is the heterogeneity of melanoma tumors, and the variability in acetylation patterns among patients. This heterogeneity may lead to variable responses to HDACi treatment, which would necessitate personalized approaches to therapy. Secondly, the redundancy and context-dependence of acetylation networks (such as the dual pro-oncogenic/tumor-suppressive roles of different sirtuins or HDACs) necessitate the development of more precise targeting strategies. The toxicity and side effects of pan-inhibitors limit their application, highlighting the urgent need to develop highly selective inhibitors (targeting specific HDAC/HAT isoforms or even specific acetylation sites). Thirdly, numerous preclinical findings to date that hold promise for clinical applications in the future have yet to achieve widespread success in clinical trials. Key reasons for this include: i) model limitations; specifically, that cell lines and genetically engineered mouse models are generally not suitable for fully recapitulating human tumor heterogeneity and microenvironment complexity; ii) toxicity management, due to the fact that the toxicity of HDACi limit their sufficient dosing within combination regimens; and iii) lack of patient selection, given that there is an absence of reliable predictive biomarkers for response to acetylation-targeted therapies. Finally, emerging evidence highlights the significance of other lysine acylations, particularly lactylation, in cancer biology (105). Lactylation involves the transfer of a lactate-derived lactyl group to lysine residues on histones and non-histone proteins, which is analogous to the transfer of an acetyl group in acetylation (106). Histone lactylation has been shown to regulate gene expression programs that are distinct from acetylation, influencing multiple physiological and pathological processes (107). Mechanistically, the enzymes involved in adding or removing lactyl marks are still being identified, although evidence already exists to suggest potential interplay or competition with acetylation pathways, given that both modifications target lysine residues (108,109). This presents a compelling future direction-namely, to explore the potential crosstalk and hierarchy between different types of acylation reactions (for example, acetylation and lactylation) that shape melanoma pathogenesis. Therefore, future studies should not only continue to delineate the acetylation-specific networks but also map the landscape of lactylation and other novel modifications in melanoma, which will serve to identify their convergent and unique roles in oncogenesis.

In conclusion, acetylation modifications fulfill a crucial role in the pathogenesis and progression of melanoma. Understanding the molecular mechanisms underlying these modifications may provide insights into novel therapeutic strategies. Future studies should focus on a number of different aspects, including developing isoform-selective HDACi to minimize toxicity, validating acetylation-based biomarkers in large clinical cohorts for patient stratification, and elucidating subtype-specific acetylation patterns in acral and mucosal melanoma. Through harnessing the power of epigenetics, we will be able to pave the way for more effective and personalized treatments for this devastating disease.

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Availability of data and materials

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Authors' contributions

JW and XC wrote the first draft of the manuscript. JW, XC and CH created the images. ZZ, XL, KZ and CW performed literature review. CH and BY provided advice in revising the manuscript and supervised the study. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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