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Plasticity and Power: How MEIS Transcription Factors Define Melanoma Aggressiveness

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Abstract

Melanoma is an aggressive cutaneous malignancy characterized by profound phenotypic plasticity and inherent therapy resistance. Recent evidence highlights the aberrant reactivation of developmental gene regulatory networks, particularly the TALE-class homeobox transcription factors MEIS1, MEIS2, and MEIS3, as master regulators of this oncogenic plasticity. This study investigates the molecular and clinical impact of MEIS dysregulation in melanoma pathogenesis and explores epigenetic editing as a targeted therapeutic strategy. Genomic, transcriptomic, and clinical survival data from the TCGA PanCancer Atlas (Skin Cutaneous Melanoma cohort) were systematically analyzed via cBioPortal and the Human Protein Atlas. Multi-pathway network mapping was employed to trace MEIS-driven hyperactivation of canonical survival cascades. Clinical analysis revealed that MEIS3 upregulation acts as a highly aggressive oncogenic driver, precipitating a severe collapse in patient overall survival (a 55-month reduction in median survival, p=0.000023). Mechanistically, MEIS factors integrate developmental signaling with the PI3K/AKT, MAPK, and TGF-β pathways to sustain a multidrug-resistant, neural crest stem-like state. Dismantling this transcriptional machinery through precision epigenetic engineering, specifically CRISPR interference (CRISPRi) utilizing a dCas9-KRAB system, offers a potent strategy to eradicate the melanoma stem cell reservoir and prevent metastatic relapse.

Keywords: MEIS transcription factors; phenotypic plasticity; CRISPRi; epigenetic editing; targeted therapy; PI3K/AKT pathway

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1. Introduction

1.1 Melanoma Pathogenesis and Phenotypic Plasticity

Melanoma represents the most aggressive and lethal form of cutaneous malignancy, originating from the malignant transformation of pigment producing melanocytes. Clinically and histopathologically, this disease is highly heterogeneous and is broadly classified into four primary subtypes. Superficial spreading melanoma constitutes the vast majority of cases, typically presenting as a radially expanding lesion [1]. Nodular melanoma represents a highly aggressive variant characterized by rapid vertical growth and deep dermal invasion from the very outset. Lentigo maligna melanoma primarily arises in chronically sun damaged skin of the elderly population, while acral lentiginous

melanoma develops on non hair bearing surfaces such as the palms, soles, and nail beds, presenting a unique pathogenesis that is largely independent of ultraviolet radiation exposure. Because normal melanocytes are embryologically derived from the highly migratory neural crest lineage, all subtypes of melanoma inherently possess a profound biological capacity for systemic dissemination, making the disease notoriously difficult to treat once it has metastasized beyond the primary site [2].

The World Health Organization further stratifies melanomagenesis into four distinct molecular cohorts driven by the acquisition of canonical oncogenic mutations. These functional classifications include the BRAF mutant, NRAS mutant, NF1 mutant, and the triple wild type genomic profiles. The most prevalent driver is the BRAF V600E amino acid substitution, which, alongside various NRAS mutations, leads to the constitutive and entirely ligand independent hyperactivation of the mitogen activated protein kinase (MAPK) signaling cascade. This continuously hyperactive signaling violently phosphorylates downstream MEK and ERK kinases, which subsequently translocate to the nucleus to aggressively drive unchecked cellular proliferation, immortalization, and the active evasion of intrinsic apoptotic triggers. Concurrently, the frequent genetic deletion or epigenetic silencing of crucial tumor suppressors, such as PTEN, heavily amplifies the parallel PI3K and AKT signaling axis. This dual pathway hyperactivation fundamentally cements the absolute survival capacity and metabolic dominance of the malignant cells within the harsh tumor microenvironment [3].

Despite monumental recent clinical advances utilizing highly targeted kinase inhibitors and immune checkpoint blockade therapies, metastatic melanoma exhibits a staggering rate of therapy resistance, leading to ultimately poor patient outcomes. This profound therapeutic failure is largely attributed to the extraordinary phenotypic plasticity of melanoma cells. Rather than relying solely on the slow acquisition of de novo genetic mutations to escape selective drug pressure, melanoma cells dynamically and rapidly rewire their epigenetic and transcriptional states to ensure immediate survival [4]. This dynamic state shift is heavily governed by the Microphthalmia associated transcription factor (MITF) rheostat model. While a high MITF transcriptional state promotes active cellular proliferation, robust melanin production, and cellular differentiation, targeted therapeutic stress forces a critical subpopulation of melanoma cells to drastically downregulate MITF expression. This acute downregulation triggers a massive, genome wide epigenetic reprogramming event. It causes the targeted cells to shed their differentiated melanocytic identity and adopt a dedifferentiated, highly invasive, and neural crest stem like phenotype that is intrinsically invisible and completely refractory to current targeted therapies [5].

This sophisticated and lethal phenotypic switching fundamentally relies on the chromatin level reactivation of dormant embryonic gene regulatory networks. Within this developmental paradigm, recent advanced molecular and transcriptomic studies have highlighted the paramount importance of developmental transcription factors in sustaining melanoma biology and driving multidrug resistance. In particular, members of the TALE class homeobox gene family, including MEIS1, MEIS2, and MEIS3, have emerged as highly influential master epigenetic regulators of this oncogenic plasticity.

1.2. MEIS Transcription Factors: Structure and Mechanisms in Melanoma

1.2.1 Dimerization with PBX/HOX and Chromatin Binding

Unlike classical homeodomain proteins, MEIS1, MEIS2, and MEIS3 (Myeloid Ecotropic Viral Integration Site) belong to the TALE (Three-Amino-Acid-Loop-Extension) family of transcription factors. This structural distinction is of critical biochemical importance for their oncogenic functions. While a classical homeodomain contains three alpha-helices that dock into the major groove of DNA, TALE proteins possess an additional three-amino-acid loop extension between the first and second alpha-helices. This highly flexible loop confers a unique steric adaptability to MEIS proteins, enabling them to establish robust protein-protein interactions (heterodimerization) with cofactors like PBX and HOX. At the core of this transcriptional complex lies the PBX-HOX interaction. HOX proteins feature an evolutionarily conserved hexapeptide motif that docks into a hydrophobic pocket on the PBX protein, forming a PBX-HOX dimer.

However, in highly aggressive cancer cells such as melanoma, this bipartite dimer may lack the necessary stability to robustly drive target gene activation on its own. This is precisely where MEIS proteins intervene [6].

MEIS forms a high-affinity bond with PBX, assembling a trimeric (three-part) complex. When this tripartite structure binds to DNA, PBX and HOX recognize adjacent target sequences, while the MEIS factor binds to specific motifs nearby. This multimeric binding strategy significantly expands the footprint of the complex on the DNA, widening the contact area and maximizing sequence specificity. This structural cooperation in melanoma is observed in the MJT1 melanoma cell line. In these cells, MEIS1 cooperates with PBX to dramatically enhance the stability and half-life of the HOX-PBX-DNA complex. This MEIS-driven stabilization ensures the continuous operation of a high-affinity transcriptional machinery that supports melanoma proliferation [7].

In melanoma cells, this cooperative binding is evident. For example, in the MJT1 melanoma cell line, MEIS1 together with PBX was shown to enhance the stability of a HOX–PBX–DNA complex. These MEIS/PBX/HOX assemblies bind to specific regulatory DNA motifs, with PBX/HOX recognizing adjacent sequences and MEIS often binding nearby sites, thereby widening the DNA contact and specificity of the complex. The net result is a high-affinity transcriptional complex that can robustly modulate target gene expression [8].

Disruption of these interactions destabilizes chromatin binding and impairs melanoma cell growth and proliferation. Peptide molecules, such as the HXR9, designed to antagonize HOX–PBX dimerization can disrupt the HOX/PBX/MEIS complex. The cell-permeable peptide HXR9 represents a pioneering strategy in this regard. HXR9 functions as a competitive antagonist, structurally mimicking the hexapeptide motif of HOX proteins. By selectively occupying the hydrophobic binding pocket on the PBX protein, HXR9 physically outcompetes endogenous HOX factors, effectively preventing HOX-PBX heterodimerization. Treatment with such peptides was shown to slow the growth of melanoma cells by preventing the formation of the active trimeric complex on DNA [9].

Consistently, an antagonist of HOX–PBX binding was able to block the proliferation in murine B16 melanoma models melanoma, showing dose-dependent cytotoxic or cytostatic effects, reducing tumor growth by approximately 30% and even trigger apoptosis in vitro and in vivo [10]. These findings indicates that intact MEIS/PBX/HOX complexes bound to chromatin are necessary to maintain the pro-tumor transcriptional programs in melanoma cells.

1.2.2 Downstream Target Gene Regulation and Oncogenic Pathways

As transcription factors, MEIS1/2/3 regulate gene expression programs that intersect with key oncogenic signaling pathways in melanoma. Through ChIP-seq and related approaches, MEIS proteins have been found to bind enhancer or promoter regions of genes that drive melanoma aggressiveness. For example, MEIS1 can directly bind to an enhancer of the MCAM gene (Melanoma Cell Adhesion Molecule, also known as CD146) and activate its transcription. ChIP-seq analyses demonstrate that MEIS1 selectively occupies an enhancer region upstream of the MCAM locus. However, binding alone is insufficient for robust transcriptional activation; it serves as a nucleating event for chromatin remodeling. Once bound, the MEIS-containing complex recruits essential co-activators, such as p300/CBP histone acetyltransferases (HATs), to the enhancer site. This enzymatic recruitment leads to the targeted acetylation of adjacent histone tails ,H3K27ac, transitioning the local chromatin into an open, transcriptionally permissive state. This active enhancer then loops to contact the MCAM promoter, driving high-level transcription and thereby equipping the melanoma cell with the necessary adhesive properties to facilitate motility, extracellular matrix invasion, and ultimate metastatic dissemination in vitro. This provides a clear example of a MEIS-driven target gene that promotes melanoma cell motility and metastasis [11]. Given the absolute requirement of this complex to sustain such aggressive phenotypes, its structural interface is a challenging therapeutic target. The most direct approach to dismantling this transcriptional machinery involves disrupting the highly conserved physical interactions between its core components. Since MEIS relies on the intact HOX-PBX dimer to form the stable trimeric structure on chromatin, the HXR9-mediated blockade fundamentally destabilizes the entire complex. Consequently, the complex is rapidly evicted from its DNA target sites. This structural collapse not only terminates the transcription of pro-metastatic targets like MCAM but also triggers a

rapid and profound apoptotic response in melanoma cells, validating the MEIS/PBX/HOX interaction interface as a critical vulnerability in metastatic melanoma [9,11].

Likewise, MEIS3 has been reported to bind to a CpG-rich site in the promoter of the oncogenic microRNA MIR-21, leading to increased miR-21 expression. Since miR-21 is a well-known oncomiR in melanoma that downregulates tumor suppressors (including the PI3K pathway inhibitor PTEN), MEIS3-driven miR-21 upregulation could enhance PI3K/AKT signaling and melanoma cell survival. Thus, MEIS factors can directly activate pro-tumor genes (like MCAM) or oncomiRs (like miR-21) by binding regulatory DNA, as evidenced by targeted ChIP analyses [12].

Beyond the regulation of individual genes, MEIS/PBX/HOX complexes orchestrate comprehensive transcriptional programs that establish and sustain critical oncogenic signaling loops in melanoma. The transition from early-stage to advanced metastatic melanoma is accompanied by a dynamic shift in the repertoire of TALE cofactors. In advanced melanoma cells, PBX2 emerges as the predominantly expressed PBX family member and preferentially pairs with HOXB7, a well-characterized oncogenic transcription factor in this lineage. To fully unleash its transactivation potential and securely anchor to target promoter regions, this HOXB7-PBX2 dimer is likely stabilized by MEIS cofactors, forming a highly active trimeric assembly [13].

Once bound to chromatin, the MEIS/PBX2/HOXB7 complex directly feeds into the most notorious signaling cascade in melanoma: the mitogen-activated protein kinase (MAPK) pathway. Rather than altering the intracellular kinase cascade itself, this transcriptional complex amplifies the signal from the outside in. A primary target of this complex is the gene encoding basic fibroblast growth factor (bFGF) [14].

By robustly upregulating the expression and subsequent secretion of bFGF, MEIS-containing complexes establish a vicious autocrine mitogenic loop. The secreted bFGF binds to its cognate receptor tyrosine kinases (FGFRs) on the surface of the very same melanoma cells, inducing receptor dimerization and transphosphorylation. This receptor activation continuously funnels mitogenic signals into the RAS-RAF-MEK-ERK axis. In melanomas that may already harbor BRAF or NRAS mutations, this MEIS-driven bFGF supply acts as an additional accelerant, hyperactivating MAPK signaling to drive relentless cell cycle progression and proliferation [15,16].

Furthermore, the transcriptional influence of the MEIS/PBX2/HOXB7 complex extends directly into the extracellular space to facilitate metastasis. The complex upregulates the expression of matrix metalloproteinase-9 (MMP9) and angiopoietin-2 (Ang-2). The secretion of MMP9, a potent protease, degrades components of the basement membrane and extracellular matrix, physically clearing a path for tumor invasion. Concurrently, Ang-2 promotes the vascular remodeling and angiogenesis necessary to sustain the nutrient demands of the expanding tumor mass. Consistently, loss-of-function models demonstrate that silencing PBX cofactors in melanoma causes a rapid downregulation of HOXB7 and its downstream target genes, including bFGF, Ang-2, and MMP9, thereby causing impairing cell proliferation and invasiveness [14,17]

MEIS activity also intersects with the TGF-β and WNT signaling pathways that are crucial for melanoma cell plasticity. PBX proteins (MEIS partners) are known to modulate TGF-β/SMAD signaling and other developmental pathways. In lung cancer, for instance, MEIS2 was found to inhibit the expression of TGF-β type II receptor, preventing tumor supression effect of TGF-β signaling and contributing to oncogenesis. Although not yet directly shown in melanoma, this raises the possibility that MEIS dysregulation could alter TGF-β responses in melanoma as well, either by suppressing TGF-β tumor-suppressive effects in early-stage lesions or by modulating TGF-β-driven EMT and invasion in late-stage disease. Similarly, melanoma cells often exhibit activation of the WNT/β-catenin pathway when they adopt a stem-like or invasive phenotype. While direct regulation of WNT inhibitors by MEIS has not been reported in melanoma, it is noteworthy that epigenetic silencing of WNT antagonists (e.g DKK1) can occur during melanoma dedifferentiation [18].

1.2.3 Epigenetic Regulation and Chromatin Context

Epigenetic mechanisms both regulate MEIS expression and are employed by MEIS complexes to execute their functions. The expression of MEIS genes in melanoma may be influenced by epigenetic modifications such as DNA methylation. For example, analysis of primary cutaneous melanoma samples showed that the HOXA9 gene (a HOX factor functionally linked to MEIS) is frequently hypermethylated in melanoma relative to benign melanocytic nevi. HOXA9 promoter hypermethylation was observed across all stages of melanoma and is thought to contribute to tumor development [19].

This suggests that epigenetic silencing of certain homeobox genes accompanies melanoma progression. Although MEIS1/2/3 promoter methylation in melanoma has not been comprehensively reported, pan-cancer analyses indicate MEIS1 is generally downregulated in many tumors, raising the possibility that epigenetic silencing could be one mechanism (alongside transcriptional regulation by upstream factors) controlling MEIS levels. Indeed, MEIS1 was found to be significantly downregulated in skin cutaneous melanoma (SKCM) tumors compared to certain normal tissues. Future studies are needed to determine if DNA methylation or histone modifications at the MEIS loci contribute to this decreased expression in melanoma [20,21].

On the other hand, MEIS proteins themselves can recruit epigenetic modifiers to target genes. When MEIS3 binds to the MIR-21 promoter at a specific CpG site, it may influence the local DNA methylation state or chromatin accessibility, thereby sustaining miR-21 expression. MEIS/PBX/HOX complexes have been associated with super-enhancers and permissive chromatin in other cancers (for instance, MEIS1 co-binding with lineage-specific oncoproteins in Ewing sarcoma drives a super-enhancer that dysregulates transcription). In melanoma, it is conceivable that MEIS-bound enhancers coincide with regions of active chromatin (such as marked by H3K27ac) to maintain expression of melanoma subtype-specific genes [22].

Conversely, loss of MEIS binding could allow repressive marks to accumulate. In support of an epigenetic feedback loop, new evidence shows that pharmacological MEIS inhibitors (which displace MEIS from DNA) lead to reduced expression of MEIS target genes and even downregulate MEIS itself. Specifically, blocking MEIS DNA-binding with small molecules caused a decrease in MEIS1/MEIS2 levels and in known MEIS-driven genes like HIF-1α, HIF-2α, and CDKN1A (p21). This implies that MEIS proteins might autoregulate or sustain their target network partly via epigenetic circuits, and disrupting those circuits triggers widespread transcriptional repression of the MEIS program [23,24].

Finally, melanoma cells' ability to undergo phenotype switching (oscillating between a differentiated state and a stem-like, dedifferentiated state) is tightly linked to chromatin reprogramming. During the acquisition of a stem-like state, melanoma cells tend to repress differentiation genes (including certain lineage-specific transcription factors) and activate an embryonic crest-like program. Given that HOX gene clusters are canonical differentiation genes often kept silent in stem cells, the status of HOX/MEIS chromatin in melanoma may change with cell state. In a more differentiated (MITF-high) melanoma cell, MEIS-target genes might be less accessible or less needed, whereas in a dedifferentiated, invasive cell (MITF-low, NGFR-high), the chromatin at developmental gene loci (possibly including MEIS/PBX/HOX targets) could become activated [25].

Indeed, interferon-γ treatment in melanoma can induce a neural crest-like de-differentiation state accompanied by broad chromatin remodeling, potentially licensing developmental regulators like MEIS to be more active. Although direct maps of MEIS chromatin occupancy in different melanoma phenotypic states are lacking, these considerations highlight that MEIS function in melanoma is context-dependent and intertwined with epigenetic regulation. It will be important for future research to integrate ChIP-seq profiling of MEIS with chromatin state analyses (such as ATAC-seq or histone mark ChIP-seq) in melanoma subpopulations to fully understand how epigenetics govern MEIS activity and vice versa [26].

1.3. Roles of MEIS Factors in Melanoma Initiation and Progression

1.3.1 Tumor Initiation and Proliferation

MEIS transcription factors exhibit a potent tumor promoting role in the earliest stages of melanocytic neoplasia, acting as fundamental epigenetic architects that prepare the cellular landscape for malignant transformation. In established cutaneous tumorigenesis models utilizing two stage chemical skin carcinogenesis, the conditional deletion of Meis1 in epidermal stem cells severely impairs tumor initiation, leading to a drastically reduced tumor burden. Molecularly, MEIS1 acts as a critical pioneer factor in this context. It actively remodels and opens previously compacted chromatin regions, thereby pre conditioning the genomic landscape and making it highly permissible for primary oncogenic driver mutations, such as BRAF V600E or NRAS Q61R, to fully engage their downstream MAPK signaling cascades. Without MEIS1 to establish this permissive chromatin state, these initiating mutations fail to trigger robust clonal expansion[27]. In the melanocytic lineage, which shares this cutaneous niche, nascent melanoma cells absolutely depend on the intact HOX, PBX, and MEIS tripartite complex for their continued survival and initial proliferation. Functional disruption of this transcriptional axis using highly specific competitive peptide antagonists physically uncouples PBX from its HOX partners. This rapid structural dissociation strips the entire MEIS complex from its consensus DNA binding sites, which immediately halts the active transcription of crucial anti apoptotic guardians like BCL2 and MCL1. Consequently, treating early stage melanoma cells with these antagonists induces massive and rapid apoptosis, underscoring that these developmental transcription factors are not merely passive bystanders but active and indispensable drivers of melanoma cell survival from the very outset [28].

The expression dynamics of MEIS1 and MEIS2 are notoriously complex and frequently appear decreased in bulk primary melanomas when compared directly to adjacent normal melanocytes. However, this apparent overall downregulation masks the profound intratumoral heterogeneity inherent to melanoma progression. Extensive pan cancer gene expression analyses reveal that while the bulk tumor mass may downregulate MEIS through targeted promoter hypermethylation, virtually every cancer type harbors a distinct, dedifferentiated subpopulation with aberrantly high MEIS expression. In melanoma, this high MEIS subset heavily overlaps with the highly aggressive, drug resistant, and neural crest stem like cellular state, which is classically characterized by low MITF and high AXL expression. In these specific embryonic like reservoirs, MEIS1, MEIS2, and MEIS3 are robustly transcribed and actively function to maintain the primitive, undifferentiated transcriptional profile that is absolutely required to seed new tumor foci and drive continuous proliferation [29].

These specific high MEIS subpopulations directly correlate with highly aggressive clinical behavior and accelerated growth kinetics. As melanoma progresses, the stoichiometry of the available TALE cofactors fundamentally shifts, most notably through the marked upregulation of PBX2. When highly expressed in metastatic melanoma cell lines relative to early stage lines, PBX2 powerfully cooperates with MEIS1 and specific HOX genes to assemble a hyperactive transcriptional apparatus. A primary genomic target of this cooperating complex is the FGF2 gene, which encodes basic fibroblast growth factor (bFGF). By binding directly to the FGF2 promoter region, the MEIS and PBX complex drives massive autocrine growth factor production, fueling uncontrolled cell cycle progression via parallel hyperactivation of the MAPK and PI3K pathways [29].

Furthermore, MEIS proteins exert profound and nuanced control over critical cell cycle regulators, most notably the cyclin dependent kinase inhibitor p21, encoded by the CDKN1A gene. While traditionally viewed strictly as a nuclear tumor suppressor that halts the cell cycle, p21 exhibits a paradoxical and highly oncogenic dual role in advanced melanoma. MEIS1 directly transactivates the CDKN1A promoter to sustain high intracellular levels of p21 [30]. However, concurrent oncogenic kinase signaling phosphorylates this p21, forcing its rapid nuclear export and subsequent cytoplasmic accumulation. In the cytosol, p21 physically binds and neutralizes pro apoptotic signaling molecules such as ASK1 and specific executioner caspases. Thus, MEIS mediated regulation effectively converts a canonical cell cycle brake into a potent, anti apoptotic survival shield that facilitates senescence bypass and the maintenance of a slow cycling, incredibly resilient tumor state [30].

1.3.2 Invasion and Metastasis

During melanoma progression, profound changes in MEIS regulated epigenetic programs facilitate the physical transition from a localized primary tumor to a highly aggressive, invasive, and metastatic disease. Although direct, isolated studies of MEIS in the context of melanoma metastasis are still emerging, multiple lines of biochemical evidence suggest that MEIS target genes and their specific transcriptional cofactors are deeply embedded within the metastatic cascade. One critical downstream target is MCAM (also known as CD146), a transmembrane glycoprotein and cell adhesion molecule. The expression of MCAM on the surface of melanoma cells drastically enhances their physical tethering to endothelial cells and the surrounding extracellular matrix, thereby promoting tissue dissemination. At the molecular level, the cytoplasmic domain of MCAM directly interacts with ERM (ezrin, radixin, and moesin) scaffold proteins, physically linking the plasma membrane to the dynamic actin cytoskeleton. This linkage actively recruits focal adhesion kinase (FAK) and p130Cas to drive lamellipodia formation. The finding that MEIS1 can directly bind to and transactivate the MCAM enhancer via specific TGACAG consensus motifs in other oncogenic contexts raises the strong possibility that a parallel MEIS1 to MCAM regulatory axis operates in melanoma. If so, elevated MEIS1 nuclear localization in a dedifferentiated subset of melanoma cells could directly drive robust MCAM transcription, endowing those cells with the extreme migratory and invasive cytoskeletal capacity required for systemic spread [31,32].

Beyond single targets, the tripartite MEIS, HOX, and PBX complexes masterfully regulate a broad host of genes that actively dismantle tissue boundaries to facilitate invasion. For example, the specific HOXB7 transcription factor, when physically partnered with MEIS and PBX cofactors on the DNA, synergistically induces the expression of MMP-9 (matrix metalloproteinase 9) and Ang2 (Angiopoietin 2). MMP-9 is a highly potent zinc dependent endopeptidase that specifically targets and cleaves Type IV collagen and gelatin, the primary structural components of the basement membrane. This proteolytic degradation creates physical corridors through the extracellular matrix, directly aiding tumor invasion into the surrounding stroma and facilitating intravasation into local blood vessels. Concurrently, the secreted Angiopoietin 2 acts as an antagonistic ligand for the Tie2 receptor tyrosine kinase on adjacent endothelial cells. By competing with Ang1, the tumor derived Ang2 disrupts endothelial VE-cadherin junctions, physically destabilizing the vascular endothelium and increasing local vascular permeability, which greatly eases the transendothelial migration of melanoma cells into the bloodstream [33].

By actively upregulating such structural and angiogenic effectors, MEIS containing complexes decisively contribute to the invasive phenotype. Furthermore, this transcriptional network exerts profound control over post transcriptional regulation. The HOXB7 and PBX2 heteromeric complex in melanoma has been shown to directly upregulate the transcription of the miR-221 and miR-222 cluster, a pair of highly conserved microRNAs that strongly promote metastasis and multidrug resistance. Chromatin immunoprecipitation studies have confirmed that HOX and PBX complexes physically occupy specific binding sites upstream of the miR-221/222 promoter region. Disrupting the HOXB7 and PBX2 interaction drastically reduces primary miR-221/222 biogenesis. Functionally, mature miR-221 and miR-222 are loaded into the RISC complex where they base pair with the 3' untranslated regions of critical tumor suppressor mRNAs, leading to their rapid nucleolytic degradation. A primary target of this cluster is the pro apoptotic factor c-FOS; silencing the miR-221/222 cluster results in the immediate re expression of c-FOS and subsequent caspase dependent cell death. Since miR-221/222 have established roles in driving melanoma cell migration by neutralizing suppressors like PTEN to hyperactivate PI3K signaling, the structural participation of MEIS within the HOXB7 and PBX2 complex links it indirectly, yet powerfully, to these pro metastatic microRNAs. In short, MEIS, through its physical cooperation with HOX and PBX proteins, orchestrates a comprehensive pro metastatic gene signature encompassing adhesion molecules, endopeptidases, angiogenic cytokines, and oncogenic microRNAs that collectively execute the multi step process of metastasis, including local invasion, intravasation, survival in the circulatory shear stress, extravasation, and ultimate colonization of distant organs [13].

The complex tumor microenvironment and the immune evasion mechanisms necessary for successful metastasis may also be directly sculpted by fluctuating MEIS levels. A recent pan cancer transcriptomic study reported that the high nuclear expression of MEIS2 and MEIS3 strongly correlates with an immune silent or immune cold tumor microenvironment phenotype, characterized by a severe lack of cytotoxic CD8+ T lymphocyte infiltration. In clinical melanomas, this immune cold state is a prerequisite for metastasis, as the tumor successfully evades immune mediated clearance. Thus, if a specific melanoma subpopulation exhibits high MEIS2 and MEIS3 activity alongside minimal immune cell presence, it strongly suggests that MEIS high tumors actively orchestrate localized immune exclusion to foster metastatic spread. While the direct modulation of immune related genes by MEIS in melanoma is still an active area of investigation, it is highly intriguing that MEIS1 overexpression was found to drastically reduce MHC class II expression in leukemia models by repressing the master regulator CIITA. In melanoma, a similar MEIS driven transcriptional repression could lead to reduced neoantigen presentation, rendering the invasive cells virtually invisible to circulating T cells. Furthermore, the localized TGF-β signaling network, a well known driver of both melanoma cell invasiveness and immune exclusion, is intricately modulated by MEIS activity. High expression of MEIS2 acts as a transcriptional repressor of the TGF-β type II receptor (TGFBR2), which dampens the cytostatic and growth inhibitory effects of TGF-β in early melanoma stages [34]. However, in advanced disease, this altered stoichiometry may license non canonical, SMAD independent signaling cascades, such as the RhoA and ROCK pathway, driving amoeboid migration while simultaneously maintaining a highly immunosuppressive cytokine profile in the surrounding stroma [35,36]

Finally, profound insights from developmental biology strongly support the fundamental involvement of MEIS in driving cellular invasion. During embryogenesis, MEIS3 is strictly required for the extensive invasion and migration of neural crest cells, specifically the precise mobilization of vagal neural crest cells into the developing enteric nervous system in zebrafish models. Because melanomas are inherently derived from the neural crest lineage, these malignant cells frequently hijack and reactivate these dormant embryonic migratory programs to execute metastasis. It is therefore highly tantalizing from a molecular standpoint to consider that MEIS3 acts as a pioneer transcription factor that epigenetically reawakens these specific neural crest networks, thereby enhancing the invasive motility of melanoma cells [37].

For example, MEIS3 likely upregulates critical EMT transcription factors such as SNAIL, TWIST, and ZEB1, coordinating the classic cadherin switch from E cadherin to N cadherin. By directly regulating the expression of specific integrin receptors and upstream cytoskeletal modulators originally utilized during embryonic neural crest migration, MEIS3 effectively repurposes these developmental tools for lethal metastasis. In summary, while direct experimental evidence within melanoma models continues to rapidly emerge, multiple converging strands of biochemical and developmental data definitively indicate that MEIS factors facilitate melanoma invasion and metastasis by aggressively upregulating pro metastatic effector proteins, orchestrating an immune evading microenvironment, and fundamentally reawakening silenced developmental migration pathways [29].

1.3.3. Cancer Stemness and Plasticity

1.3.3.1 Neural Crest Plasticity and Epigenetic Reversion

Melanoma exhibits an extraordinary degree of phenotypic plasticity, enabling tumor cells to dynamically oscillate between a differentiated, pigment-producing state and a dedifferentiated, stem-like state reminiscent of embryonic neural crest progenitors. This reversible phenotype switching is a non-mutational, epigenetically driven adaptation critical for survival under severe microenvironmental stress, such as targeted BRAF/MEK inhibition or immune-mediated cytokine attacks. For example, in response to immune cytokine IFN-γ or BRAF/MEK inhibitor therapy, melanoma cells can dedifferentiate into a neural crest-like state that is MITF-low and NGFR (CD271)-high [38].

In their baseline, highly proliferative state, melanoma cells are predominantly driven by the lineage-specific master regulator MITF (Microphthalmia-associated transcription factor). Within this MITF-high cellular context, broad embryonic gene expression programs, including specific HOX gene clusters and their corresponding MEIS cofactors, are frequently kept silent. This transcriptional silencing is enforced by restrictive epigenetic barriers, such as targeted

DNA hypermethylation at CpG islands and the accumulation of repressive histone modifications (such as H3K27me3 via Polycomb repressive complexes) at the MEIS and HOX loci [39].

However, when subjected to intense therapeutic or immune pressure, a subpopulation of melanoma cells undergoes a profound, genome-wide chromatin reprogramming. These cells rapidly downregulate MITF and concurrently upregulate neural crest stem cell markers, most notably NGFR (CD271), transitioning into a slow-cycling, multidrug-resistant state. During this critical transition to a MITF-low/NGFR-high phenotype, the repressive epigenetic landscape at developmental loci is actively actively dismantled. Enhancers and promoters governing the MEIS/PBX/HOX network transition into a highly accessible, open chromatin state (marked by H3K27ac) [40].

The reactivation of MEIS transcription factors within this dedifferentiated niche is highly strategic. By re-engaging these embryonic regulatory networks, MEIS proteins endow these stem-like cells with enhanced apoptotic resistance and the metabolic adaptability required to persist as minimal residual disease (MRD). Consequently, MEIS factors function not merely as passive remnants of embryogenesis, but as critical epigenetic linchpins that sustain the viability and therapeutic recalcitrance of the melanoma stem-cell reservoir [41].

One clue linking MEIS to melanoma stemness comes from metabolic and apoptotic vulnerabilities. When HOX/PBX/MEIS interactions are disrupted by peptides such as HXR9, not only do melanoma cells stop proliferating, but they undergo apoptosis even in the absence of other stresses. This suggests that a subset of melanoma cells relies on HOX/MEIS-mediated transcription for survival, a hallmark of cancer stem cells which are often more resistant to apoptotic stimuli. Additionally, miR-495, which as mentioned targets PBX3, can induce apoptosis in melanoma cells. Cells with more stem-like properties (slow cycling) might particularly depend on these developmental transcription factor networks for their persistence; hence knocking down PBX/MEIS hits them hard. It has been reported that subpopulations of melanoma can survive therapy in a dormant state and then give rise to relapse. If MEIS factors help maintain the viability of these dormant cells (for instance by inducing pro-survival signals like BCL2 or metabolic adaptations via HIF-1α/HIF-2α, which are known MEIS targets), then MEIS is indirectly supporting the melanoma stemness phenotype [42].

Furthermore, MEIS1/MEIS2 are implicated in normal stem cell and progenitor cell function in various tissues. MEIS1 is crucial for hematopoietic stem cell self-renewal, and interestingly, the recent small-molecule MEIS inhibitors were found to paradoxically expand hematopoietic stem cells when low doses were used. This indicates that modulating MEIS activity can have profound effects on stem cell populations. Translating this to melanoma: tweaking MEIS activity might alter the balance between differentiation and self-renewal in tumor cells. High MEIS levels in a melanoma cell might push a transcriptional program that confers partial differentiation (since MEIS often partners with differentiation-driving HOX genes), whereas intermediate MEIS activity might support a progenitor-like state. The exact relationship likely depends on which MEIS member and which HOX partners are expressed, a subject that warrants single-cell level analysis in melanoma [29].

In sum, while direct evidence of MEIS defining a melanoma stem cell subpopulation is still forthcoming, their known functions strongly suggest involvement. MEIS factors act at the nexus of developmental signaling and cell cycle/apoptosis control, which is exactly where mechanisms of stemness reside. A reasonable hypothesis is that melanoma cells that upregulate MEIS (and appropriate HOX/PBX partners) may gain a survival advantage under stress (such as chemo, targeted therapy), contributing to minimal residual disease and relapse. Conversely, melanoma cells in which MEIS/HOX programs are epigenetically silenced might be more differentiated and initially benign (as perhaps indicated by MEIS1 downregulation in many primary tumors). The plasticity of melanoma likely means cells can toggle MEIS on or off as needed. Targeting MEIS in combination with other therapies could therefore force melanoma cells out of the protected stem-like niche into a more vulnerable state.

1.3.3.2 MEIS-Mediated Modulation of TGF-β and WNT/β-catenin Pathways

Melanoma cells must engage specific developmental signaling cascades to physically dismantle their surrounding extracellular matrix and initiate migration following the epigenetic reversion to a neural crest like state, melanoma. The TGF-β and WNT/β-catenin pathways, canonical drivers of embryonic cell motility and tissue morphogenesis, are heavily co-opted in this malignant process. Within this context, MEIS transcription factors act as crucial modulators, fine tuning the molecular outputs of these cascades to favor cellular invasion [43].

The TGF-β signaling network typically presents a paradoxical role in oncology. It acts as a cytostatic tumor suppressor in early stages by inducing cell cycle arrest through the upregulation of p21 and p15, but it ultimately switches to a potent driver of an epithelial to mesenchymal transition (EMT) like phenotype in advanced disease. MEIS factors intricately manipulate this signaling axis to facilitate tumor progression at the chromatin level. For instance, high expression of MEIS2 has been shown to directly repress the transcription of the TGF-β type II receptor, known as TGFBR2. Mechanistically, the MEIS2 and PBX complex binds to specific consensus motifs within the TGFBR2 promoter region, subsequently recruiting histone deacetylases and corepressors to establish a transcriptionally silent state. In the context of early melanoma, this targeted receptor downregulation effectively desensitizes the tumor cells to the growth inhibitory signals of the microenvironment [18].

Conversely, as the melanoma progresses into a dedifferentiated stem like subpopulation, the intricate balance of TALE cofactors shifts. This new stoichiometry potentially licenses non canonical TGF-β signaling, bypassing traditional SMAD2 and SMAD3 phosphorylation. Instead, it activates alternative kinase cascades such as the RhoA and ROCK pathway, which directly promotes the actomyosin contractility and amoeboid invasive behaviors that are highly characteristic of neural crest cell migration during embryogenesis [44].

Simultaneously, the hyperactivation of the WNT/β-catenin pathway stands as a hallmark of the invasive melanoma phenotype. In a quiescent state, canonical WNT signaling is actively suppressed by a multiprotein destruction complex composed of Axin, APC, and the kinase GSK3β. This complex constitutively phosphorylates intracellular β-catenin at specific serine and threonine residues, primarily Ser33, Ser37, and Thr41, marking it for rapid ubiquitination and subsequent proteasomal degradation. However, during melanoma dedifferentiation, the profound epigenetic reprogramming that reactivates the MEIS network also coordinates the DNA hypermethylation and silencing of critical secreted WNT antagonists, most notably DKK1. MEIS complexes are thought to act as genomic anchors that guide DNA methyltransferases to the DKK1 promoter, ensuring its stable repression [45].

By maintaining these antagonists in a locked state, the MEIS machinery indirectly allows exogenous WNT ligands to freely bind to Frizzled and LRP5/6 receptors. This receptor engagement triggers the phosphorylation of Dishevelled, which rapidly dismantles the destruction complex. Freed from continuous degradation, unphosphorylated β-catenin safely accumulates in the cytoplasm and translocates into the nucleus. Once nuclear, it displaces Groucho repressors and binds to TCF and LEF transcription factors. This active transcriptional complex powerfully drives the expression of target genes such as matrix metalloproteinases, specifically MMP2 and MMP9, which are responsible for degrading the collagen rich basement membrane. Concurrently, it orchestrates the transcriptional downregulation of E-cadherin, effectively dismantling intercellular adherens junctions and upregulating cytoskeletal dynamics. Ultimately, this MEIS supported WNT hyperactivation physically mobilizes the melanoma stem like cell for widespread metastatic dissemination [46].

1.3.3.3 Survival Under Stress: MEIS3-Driven PI3K/AKT Activation via MIR-21

To survive the cytotoxic onslaught of targeted therapies or immunotherapies, the dedifferentiated melanoma subpopulation must rapidly fortify its intrinsic anti apoptotic defenses. In this high stress context, MEIS factors, particularly MEIS3, emerge as critical survival determinants by fundamentally rewiring the PI3K/AKT signaling axis. Rather than modulating kinase activity directly, MEIS3 operates upstream at the deepest epigenetic and transcriptional levels. Functioning as a master regulatory pioneer factor, MEIS3, often in concert with PBX and HOX cofactors, selectively occupies a CpG rich regulatory element within the promoter region of MIR-21, which encodes a highly potent oncogenic

microRNA. By physically anchoring to this specific genomic locus, the MEIS complex recruits histone acetyltransferases such as p300 and CBP. This targeted recruitment deposits active H3K27ac marks and prevents localized DNA hypermethylation, thereby sustaining an open and accessible chromatin architecture that guarantees the continuous, robust RNA polymerase II dependent transcription of primary miR-21 (pri-miR-21) [12].

Following its initial transcription, pri-miR-21 undergoes a complex, multi step biogenesis pathway to become a functional oncomiR. Within the nucleus, the microprocessor complex, consisting of Drosha and DGCR8, cleaves the primary transcript into a hairpin precursor known as pre-miR-21. This precursor is subsequently exported to the cytoplasm via Exportin 5, where the RNase III enzyme Dicer processes it into a mature microRNA duplex. The functional guide strand is then rapidly loaded into Argonaute 2 (AGO2) to form the core of the RNA induced silencing complex (RISC). Once assembled, this mature miR-21 complex exerts its potent oncogenic effect primarily by seeking out and targeting the 3' untranslated region (3' UTR) of PTEN mRNA. By establishing complementary base pairing specifically through its nucleotide seed sequence (nucleotides 2 through 8) with the PTEN transcript, miR-21 physically blocks ribosomal scanning to induce translational repression. Furthermore, the AGO2 complex recruits deadenylases like the CCR4 NOT complex, which removes the poly-A tail and triggers the rapid nucleolytic degradation of the PTEN mRNA [47].

Since PTEN is the canonical lipid phosphatase responsible for actively dephosphorylating PIP3 back into PIP2, its profound functional neutralization by the MEIS3 and miR-21 regulatory loop completely removes the primary inhibitory constraint on the entire PI3K pathway. Without PTEN to counteract it, the catalytic p110 subunit of PI3K operates unchecked, continuously phosphorylating the inositol ring of membrane bound PIP2. Consequently, PIP3 accumulates at massive concentrations along the inner leaflet of the plasma membrane. This hyperaccumulation creates an abundance of essential lipid docking sites for proteins harboring Pleckstrin Homology (PH) domains, most notably the serine/threonine kinases PDK1 and AKT. This precise and forced membrane recruitment physically aligns AKT with its upstream activators, facilitating a sustained and entirely ligand independent phosphorylation cascade. AKT is first phosphorylated at the Thr308 residue within its activation loop by PDK1, followed immediately by a critical secondary phosphorylation at the Ser473 residue within its hydrophobic motif by the mTOR complex 2 (mTORC2), bringing AKT to its state of maximum catalytic hyperactivity [48].

The fully activated AKT subsequently orchestrates a comprehensive and multi tiered anti apoptotic response to ensure absolute cellular persistence. In the cytoplasm, AKT directly phosphorylates pro apoptotic executioner proteins such as BAD, typically targeting the Ser136 residue. This specific phosphorylation event creates a high affinity consensus binding site for 14-3-3 chaperone scaffold proteins. The 14-3-3 complex completely sequesters BAD, effectively isolating it from the outer mitochondrial membrane. This sequestration frees crucial anti apoptotic guardians like BCL-2 and BCL-XL to bind and neutralize the pore forming proteins BAX and BAK. By preventing BAX and BAK oligomerization, the cell effectively blocks Mitochondrial Outer Membrane Permeabilization (MOMP), thereby stopping the release of cytochrome c into the cytosol and preventing the subsequent assembly of the APAF1 apoptosome and Caspase 9 activation [49].

Simultaneously, active AKT translocates to the nucleus to phosphorylate FOXO family transcription factors, specifically FOXO1 and FOXO3a. This phosphorylation forces their immediate export and cytoplasmic retention, permanently shutting down their ability to drive the transcription of lethal BH3 only cell death genes like BIM, PUMA, and FasL. Beyond sheer apoptotic evasion, this expansive MEIS driven signaling network actively supports severe metabolic adaptation. By phosphorylating targets that inhibit the proteasomal degradation machinery, AKT signaling heavily stabilizes hypoxia inducible factors, specifically HIF-1alpha and HIF-2alpha. This stabilization drives a massive transcriptional shift toward glycolysis, upregulating enzymes like Hexokinase 2 and Lactate Dehydrogenase A, which enables the cell to maintain strict energy homeostasis and bypass senescence within the extremely harsh, nutrient deprived, and hypoxic tumor core [50].

Ultimately, this magnificent and intricate molecular circuitry preserves a dormant, multi drug resistant pool of cells, defined clinically as the minimal residual disease (MRD), that remains perfectly shielded and poised to drive aggressive clinical relapse the moment therapeutic pressure is withdrawn.

1.4 Therapeutic Targeting of MEIS in Melanoma

Transcription factors like MEIS have historically been challenging to target with traditional small molecule drugs. However, given their central role in melanoma malignancy, there is growing interest in therapeutic strategies to inhibit MEIS function. Below we discuss both experimental and conceptual approaches, including direct gene silencing and interference with MEIS protein interactions or DNA binding. It is worth noting that while some of these strategies have shown efficacy in preclinical models, including other cancers, their application to melanoma is a prospective endeavor. The ultimate goal is to disable the MEIS, PBX, and HOX transcriptional machinery in melanoma cells, thereby crippling the tumor's growth and invasive capacity.

1.4.1 CRISPR Interference (CRISPRi) Approaches

One precise way to downregulate MEIS genes is via CRISPRi, which uses a catalytically inactive Cas9 (dCas9) fused to a repressive domain, such as KRAB, to epigenetically silence target genes. Recent pharmacological advancements have yielded highly potent tools to disrupt the TALE cofactor complexes, most notably competitive peptides like HXR9 and targeted small molecule inhibitors such as MEISi 1 and MEISi 2. While these agents successfully dismantle the MEIS, PBX, and HOX transcriptional machinery to induce rapid melanoma cell apoptosis in vitro, their translation into systemic clinical application presents a profound and potentially lethal pharmacological challenge: severe off target developmental toxicity. MEIS proteins are not exclusively oncogenic elements; they are absolute biochemical requirements for the maintenance, self renewal, and differentiation of normal adult stem cell populations, most critically the hematopoietic stem cell compartment residing within the bone marrow. Systemically flooding a patient with small molecules that universally disable all MEIS complexes across all tissues would inevitably trigger catastrophic bone marrow failure, severe cytopenias, and widespread developmental toxicity.

To safely navigate this exceptionally narrow therapeutic window, CRISPR interference emerges not merely as an alternative, but as a vastly superior, precision guided epigenetic engineering tool. By designing single guide RNAs (sgRNAs) to MEIS1, MEIS2, or MEIS3 promoter regions, one can recruit the dCas9 KRAB to these loci. Once securely tethered, the KRAB domain induces heterochromatin formation by acting as a highly active epigenetic nucleation center. It directly recruits the KAP1 corepressor, which serves as a massive macromolecular scaffold to assemble an extensive chromatin remodeling apparatus. This includes histone deacetylases that rapidly strip away active transcriptional acetylation marks, and crucially, the SETDB1 histone methyltransferase. These recruiting factors deposit highly repressive histone H3 lysine 9 trimethylation (H3K9me3) marks and methylate DNA, thereby permanently blocking transcription of the MEIS gene.

CRISPRi has been successfully used to knock down oncogenic transcription factors in research settings, with high specificity. For example, in an acute leukemia model driven by HOXA9 and MEIS1, dCas9 KRAB was targeted to a HOXA9 and MEIS bound enhancer, resulting in reduced expression of downstream leukemia oncogenes and impairment of leukemic cell proliferation [51]. By analogy, a dCas9 KRAB could be directed to critical MEIS bound enhancers or to the MEIS gene promoters in melanoma cells to achieve a potent and durable silencing. This CRISPRi strategy offers a way to functionally inactivate MEIS without permanently altering the genome, which is advantageous if considering therapeutic windows. Although not yet reported specifically for melanoma, CRISPRi could be delivered via gene therapy vectors or lipid nanoparticles to melanoma tumors in the future. The expectation is that silencing MEIS transcription would downregulate the whole network of pro tumor genes MEIS controls, leading to tumor suppression. Notably, because MEIS may influence the tumor immune microenvironment, CRISPRi mediated MEIS knockdown might even synergize with immunotherapies by reversing immune silencing effects. This remains speculative but is an exciting avenue for research.

1.4.2. Peptide and Small Molecule Inhibitors

An alternative to gene silencing is directly targeting the MEIS protein or its critical interactions. One of the pioneering efforts in this area has been the use of cell permeable peptides that disrupt the interaction between HOX and PBX, which indirectly affects the HOX, MEIS, and PBX complex. The prototype peptide, HXR9, competes for the conserved hexapeptide motif through which HOX proteins bind PBX, thereby preventing HOX PBX dimerization. In melanoma models, HXR9 treatment triggered rapid apoptosis of melanoma cells both in vitro and in mouse xenografts. By breaking apart HOX PBX, HXR9 functionally disables the larger HOX, PBX, and MEIS transcription complex that is needed for target gene activation. A related peptide, CXR9, which is a control peptide with a scrambled sequence, does not induce apoptosis, highlighting the specificity of HXR9 action on the HOX and PBX interface. These peptides essentially act as indirect MEIS inhibitors, because without the HOX PBX dimer, MEIS has nothing to stabilize and cannot execute its transcriptional role. While HXR9 is a useful laboratory tool, peptides have limitations as drugs, including stability and delivery. Nonetheless, this approach validates the TALE cofactor complex as a drug target in melanoma.

More recently, there has been progress in developing small molecule inhibitors that target MEIS or PBX more directly. One strategy has been to prevent PBX from binding DNA, which would affect any PBX partner, including HOX or MEIS, from regulating target genes. In 2018, a series of small molecules was described that bind to PBX1 at its DNA binding homeodomain, blocking PBX1 DNA interaction. These molecules disrupt the transcription of PBX dependent genes and are more drug like, having greater stability and cell permeability than peptides. Another breakthrough has been the development of MEIS specific inhibitors. Using structure based design and high throughput screening, researchers identified two novel compounds, termed MEISi 1 and MEISi 2, that bind to the MEIS homeodomain and prevent MEIS from binding DNA. Crystallographic analyses confirmed that these molecules have high affinity for the MEIS homeodomain and do not significantly bind other related homeodomains, conferring a degree of specificity. Functionally, MEISi 1 and MEISi 2 were shown to block MEIS driven transcription, they prevent transactivation of MEIS target genes by dislodging MEIS from its DNA sites [23,52].

Treatment of cells with these MEIS inhibitors led to downregulation of MEIS1 and MEIS2 expression itself and of known downstream effectors like HIF 1alpha, HIF 2alpha, and p21. Importantly, these compounds had cellular effects in the low nanomolar range and could penetrate cells efficiently. While these MEIS inhibitors have primarily been tested in leukemia and normal stem cell models where they influenced hematopoietic stem cell function, they represent a proof of concept for directly targeting MEIS in cancer. It is reasonable to hypothesize that MEISi 1, MEISi 2, or future derivatives could be applied to melanoma cells with aberrant MEIS activity. If melanoma cultures are treated with MEIS inhibitors, we would anticipate a reduction in their viability and invasiveness, similar to the effects seen with HOX and PBX disruption. Testing these compounds on melanoma cell lines, especially those with high MEIS3 or MEIS2 expression, would be an important next step. These are also under consideration include RNA based approaches such as siRNA or shRNA to knock down MEIS transcripts, as well as antisense oligonucleotides. RNA interference against MEIS1 has been used in research contexts to delineate its function, and a systematic shRNA screen identified MEIS1 as a driver of malignant progression in an engineered skin tumor model. Delivering siRNAs or antisense oligos to melanoma in patients is challenging but not impossible; nanoparticle carriers or conjugates to tumor homing peptides could be employed. Additionally, decoy oligonucleotides, which are short DNA fragments containing MEIS and PBX binding motifs, could be used to soak up MEIS, PBX, and HOX complexes, preventing them from binding to endogenous gene promoters. This approach has been tried for other transcription factors with some success. In the context of MEIS, a decoy containing a high affinity MEIS and PBX consensus site might lure the complex away from actual target genes, thus acting as a sink for the transcriptional activity. While these methods are still in early stages, they expand the arsenal of indirect MEIS inhibition tactics.

In deploying MEIS targeted therapies for melanoma, a few considerations arise. First, patient stratification will be key: tumors with evidence of MEIS upregulation or dependence, for example via gene expression profiling or looking

at a panel of MEIS target genes, would likely benefit the most. Second, combination therapy strategies should be explored. For instance, combining a MEIS inhibitor with a BRAF and MAPK pathway inhibitor might produce a more durable response by preventing the tumor from switching to a developmental, drug resistant state. There is also a potential to combine MEIS inhibition with immunotherapy. If high MEIS correlates with an immune cold microenvironment, then MEIS inhibition could potentially reverse some immunosuppressive mechanisms, making the tumor more responsive to anti PD1 or other immune checkpoint blockade. Finally, toxicity must be considered: MEIS proteins play roles in normal stem cells and tissue homeostasis, so systemic inhibition could have side effects, for example, hematopoietic or cardiac, since MEIS1 is involved in cardiogenesis and HSC maintenance. An ideal therapeutic design might be one that delivers the MEIS suppressing agent specifically to melanoma cells, for example, using a melanoma specific promoter to drive a CRISPRi construct, or an antibody linked nanoparticle targeting a melanoma surface antigen to deliver a small molecule inhibitor.

2. Materials and Methods

2.1 Genomic Data Acquisition and in silico Cohort Selection

The comprehensive evaluation of genomic and transcriptomic alterations was conducted utilizing publicly available, large-scale multi-omics datasets, thereby requiring no additional institutional ethical approval. The primary clinical and genomic cohort was systematically retrieved from The Cancer Genome Atlas (TCGA) PanCancer Atlas. Specifically, the Skin Cutaneous Melanoma (SKCM) study population was isolated to analyze the mutational landscape and copy number variations. Data extraction and interactive visualization were executed via the cBioPortal for Cancer Genomics platform (https://www.cbioportal.org/). The selected cohort strictly included patient samples profiled for mutations, putative copy-number alterations (from GISTIC algorithms), and structural variants, ensuring a robust statistical foundation for downstream analyses.

2.2 Pathway Network Construction and Genomic Alteration Mapping

To determine the mechanistic disruption of specific developmental and survival signaling cascades, complex multi pathway network analyses were performed. The genomic alteration frequencies, encompassing missense mutations of unknown or putative significance, truncating mutations, deep deletions (homozygous loss), and robust mRNA upregulation, were mapped onto established signaling topologies. mRNA expression z scores relative to all samples (log RNA Seq V2 RSEM) were utilized to accurately define expression anomalies. Curated pathway architectures for the WNT, TGF-β, PI3K/AKT/mTOR, and canonical cell cycle/RTK signaling cascades were constructed using the integrated signaling library within the cBioPortal environment. This approach allowed for the visual and statistical assessment of how individual genetic lesions converge to dysregulate entire molecular networks, driving the dedifferentiated and proliferative phenotypic states in melanoma.

2.3 Transcriptomic Profiling and Clinical Survival Analysis

The prognostic significance and clinical translation of the identified genomic anomalies were rigorously assessed through Overall Survival (OS) analyses. For alterations mapped via cBioPortal (specifically the MEIS2 and MEIS3 gene loci), Kaplan Meier survival probability plots were generated to compare the longitudinal survival trajectories between the genetically altered and unaltered patient cohorts.

To independently validate the prognostic impact of bulk transcript abundance without the confounding effects of mutational status, orthogonal RNA sequencing survival data for MEIS2 were accessed via the Human Protein Atlas (HPA) pathology database (https://www.proteinatlas.org/). Transcriptomic data were normalized using the pTPM (protein coding transcripts per million) metric to account for sequencing depth and gene length variations. An

algorithmically optimized expression cut off threshold of 5.32 pTPM was utilized to effectively stratify the patient population into discrete high and low expression cohorts.

Statistical significance for all clinical survival data was calculated utilizing the Log rank (Mantel Cox) test to determine the exact p values (e.g., p=0.349 for overall MEIS2 alterations, p=0.000023 for MEIS3 upregulation), mathematically confirming the probability that the observed differences in median survival times (reported in months) were not due to random chance.

3. Results

3.1 Genomic Alterations and Transcriptomic Landscape of MEIS2

The profound phenotypic plasticity of melanoma is strongly supported by clinical genomic datasets evaluating the MEIS2 transcription factor. According to the TCGA PanCancer Atlas cohort, MEIS2 exhibits a genomic alteration frequency of 8%, indicating a highly heterogeneous disruption involving mutations, deep deletions, and robust mRNA upregulation. The functional impact of these alterations translates into a clinically relevant reduction in overall survival, with the altered cohort experiencing a median survival of 64.44 months compared to 80.68 months for the unaltered group. (Figure 1)

Furthermore, transcriptomic survival analysis using optimized RNA sequencing data from the Human Protein Atlas (cut-off: 5.32 pTPM) reveals a paradoxical yet highly mechanistic dynamic. Patients harboring low bulk MEIS2 expression experienced a severely accelerated mortality rate, plummeting to a 0% three-year survival probability. This severe clinical deterioration aligns perfectly with the model of melanoma dedifferentiation, where widespread epigenetic reprogramming and the shedding of melanocytic identity drive the tumor into a highly invasive, neural crest-like state. (Figure 2)

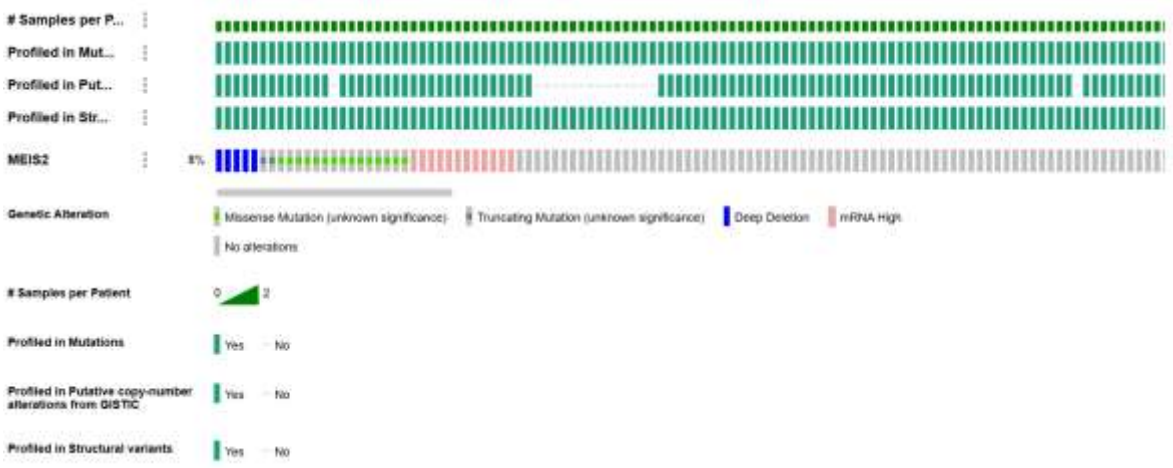

Figure 1A

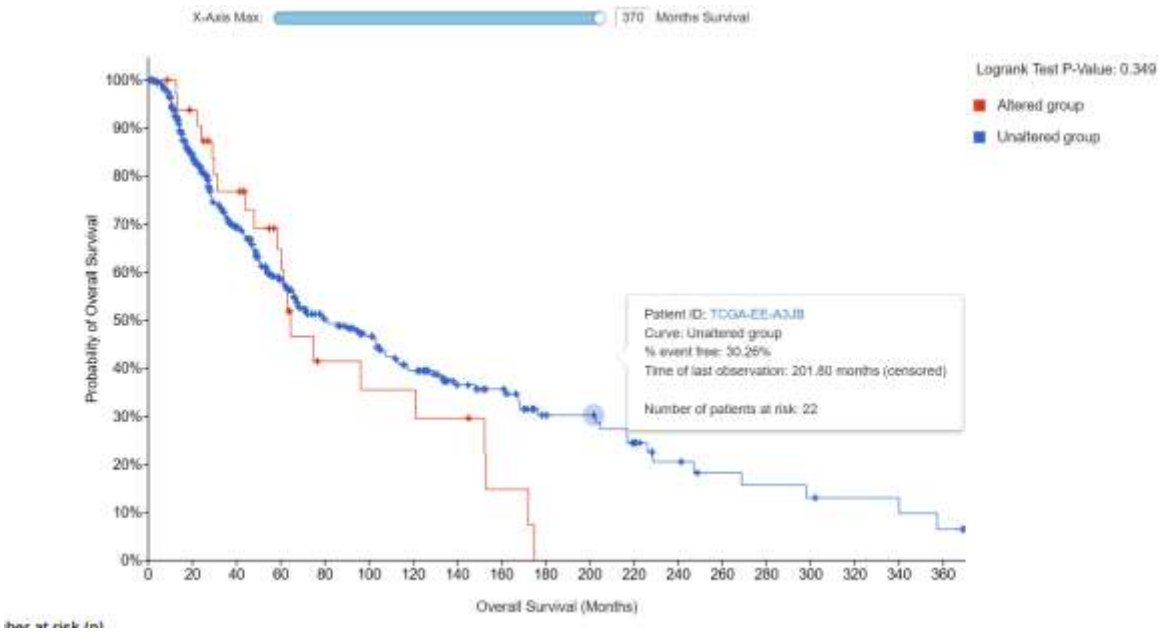

Figure 1B

Number at risk (n)

Altered group	33	29	22	15	7	6	6	5	2	0	0	0	0	0	0	0	0	0
Unaltered group	393	280	193	137	101	83	63	43	37	23	22	16	10	7	6	5	4	4	2

Survival plot summary

	Number of Cases, Total	Number of Events	Median Months Overall (95% CI)
Altered group	33	21	64.44 (58.52 - 152.81)
Unaltered group	393	189	80.68 (65.88 - 107.14)

Figure 1C

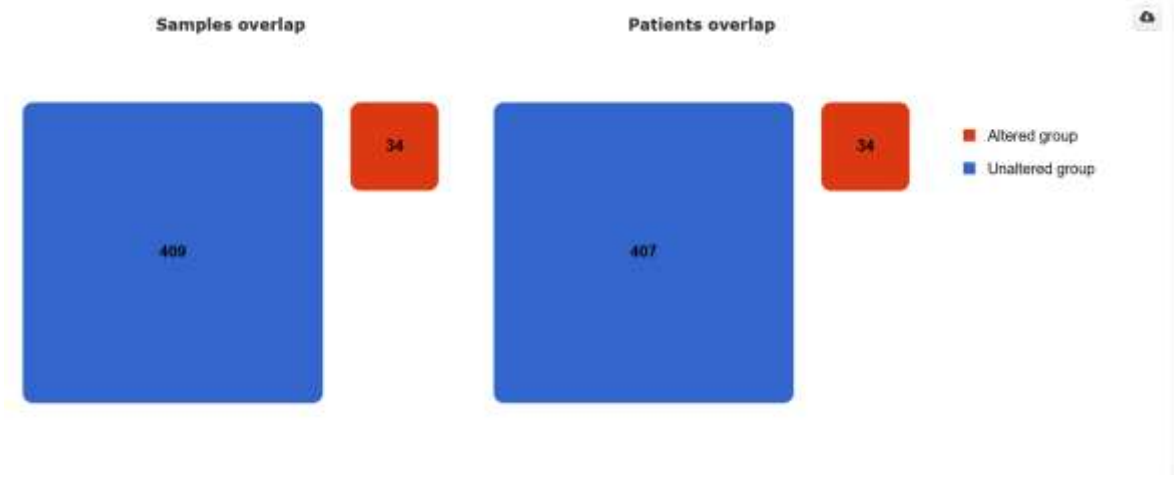

Figure 1D

Figure 1. Genomic alterations and clinical survival analysis of MEIS2 in Skin Cutaneous Melanoma. Data were systematically retrieved and analyzed from the TCGA PanCancer Atlas utilizing the cBioPortal for Cancer Genomics platform. (A) OncoPrint visualization detailing the overall genetic alteration frequency of the MEIS2 gene at exactly 8 percent across the 443 profiled patient samples. This 8 percent altered cohort is heterogeneous, encompassing a combination of missense mutations, deep deletions, and robust mRNA upregulation. (B) Overlap analysis confirming the distribution of the 34 altered versus 407 unaltered patient samples. (C) Kaplan Meier survival probability plot comparing the overall survival trajectory between the MEIS2 altered patient group (red curve) and the unaltered patient group (blue curve).

(D) Comprehensive survival plot summary table directly indicating a severely reduced median overall survival of 64.44 months for the altered cohort (n = 33 events) versus an extended 80.68 months for the unaltered cohort (n = 393 events), with a calculated Logrank test p value of 0.349.

Survival analysis	
Current cut off[i] :	5.32
Best expression cut off[i] :	5.32
Median expression[i] :	6.35
Median follow up time[i] :	1.23
P score[i]	0.098
3-year survival high[i]	53%
3-year survival low[i]	0%

Figure 2A

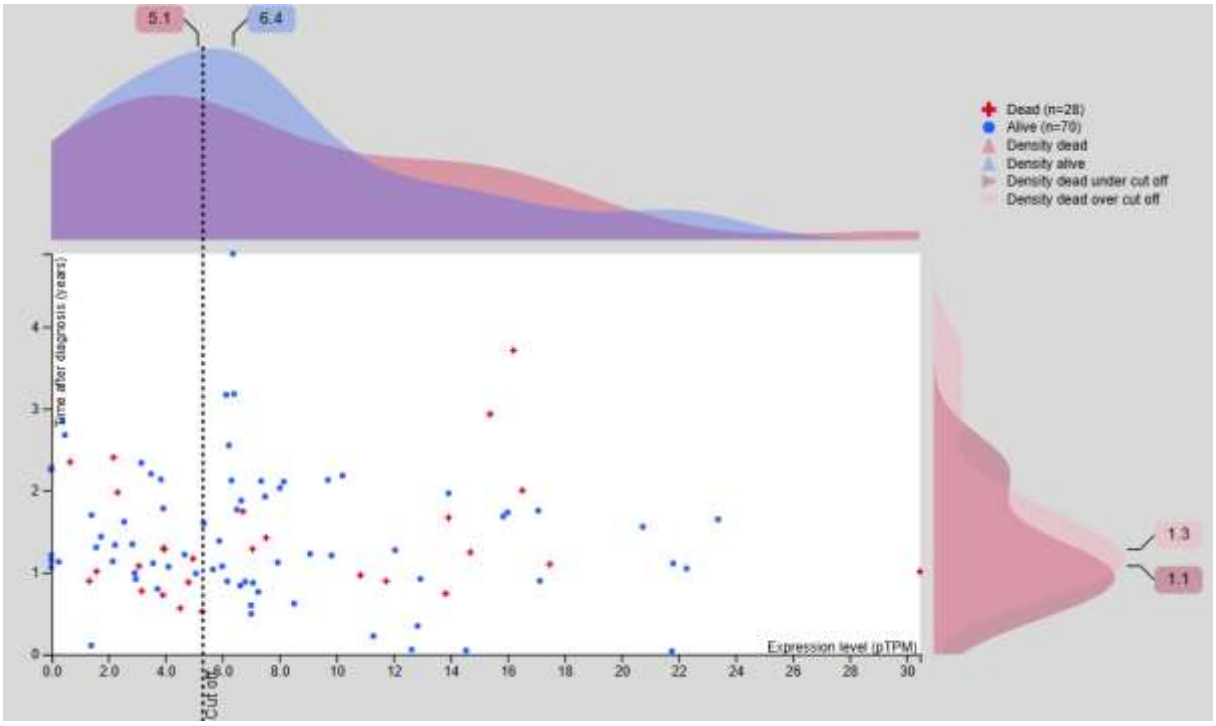

Figure 2B

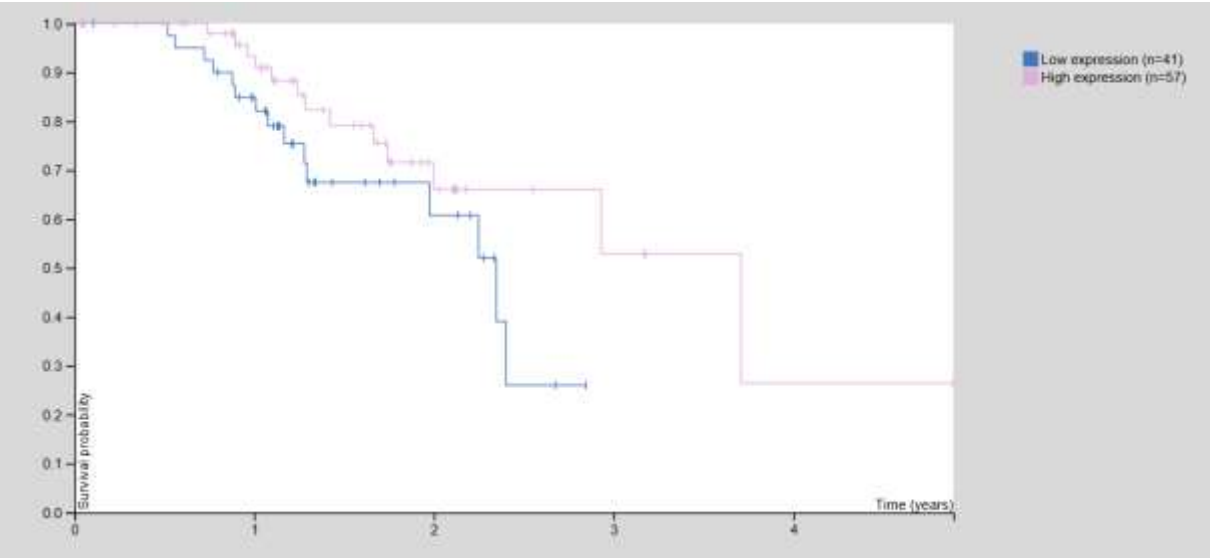

Figure 2C

Figure 2. Transcriptomic survival analysis of MEIS2 expression in Skin Cutaneous Melanoma. Data were systematically obtained from the Human Protein Atlas utilizing the TCGA patient cohort. (A) Survival analysis summary detailing the optimal expression cut off at 5.32 pTPM, highlighting a stark contrast in three year survival probabilities between the high expression cohort (53 percent) and the low expression cohort (0 percent), with an associated p value of 0.098. (B) Scatter and density plot correlating patient survival time in years with MEIS2 expression levels, visually separating living patients (blue dots) and deceased patients (red crosses) across the established cut off threshold. (C) Kaplan Meier survival curve illustrating the severely accelerated mortality and decreased survival probability of the low expression cohort (blue line, n = 41) compared to the high expression cohort (pink line, n = 57) over a five year observation period.

3.2 Comprehensive Genomic Disruption of Proliferation and Cell Cycle Networks

The transition to this aggressive dedifferentiated state is facilitated by an exceptionally destabilized genomic background. Multi-pathway network analysis reveals massive hyperactivation of the RTK/RAS signaling axis, heavily dominated by BRAF (58.1%) and NRAS (33.7%) driver mutations. To bypass oncogene-induced senescence and maintain uncontrolled proliferation, melanoma cells exhibit profound genetic disruption of the TP53 pathway. The canonical tumor suppressor CDKN2A is altered in 39.1% of cases, while TP53 itself is altered in 26.0% of the cohort. This complete dismantling of the apoptotic and cell cycle checkpoints is further exacerbated by bypass mechanisms, including E2F3 alterations (28.3%) and the constitutive activation of the MYC signaling cascade. (Figure 3)

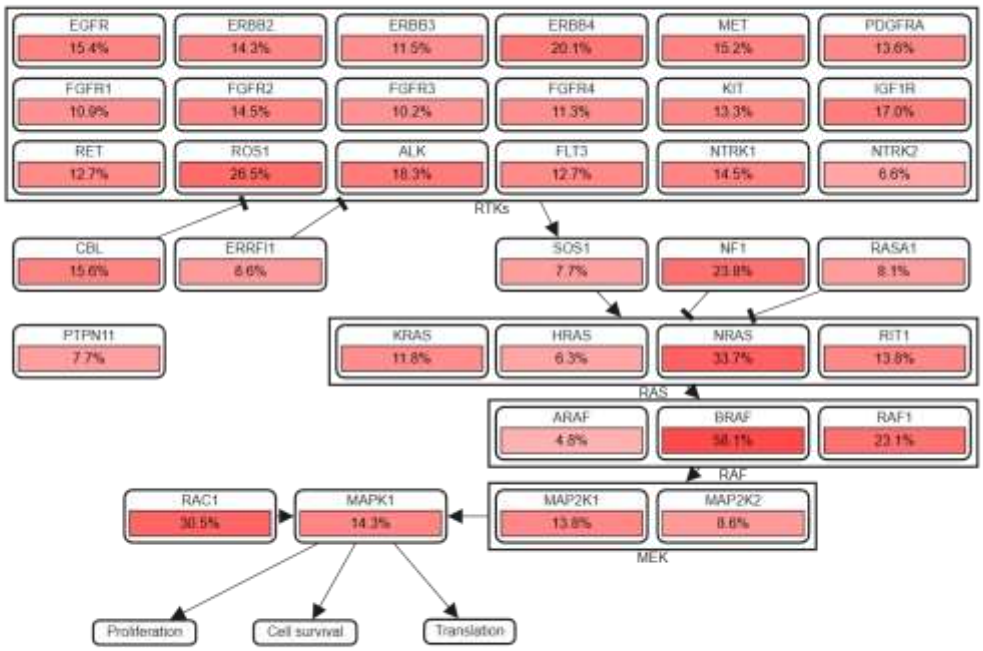

Figure 3A

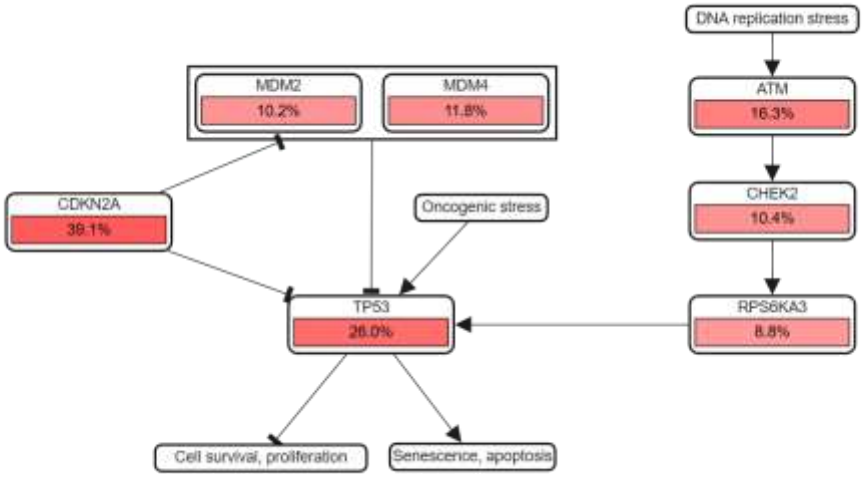

Figure 3B

Figure 3C

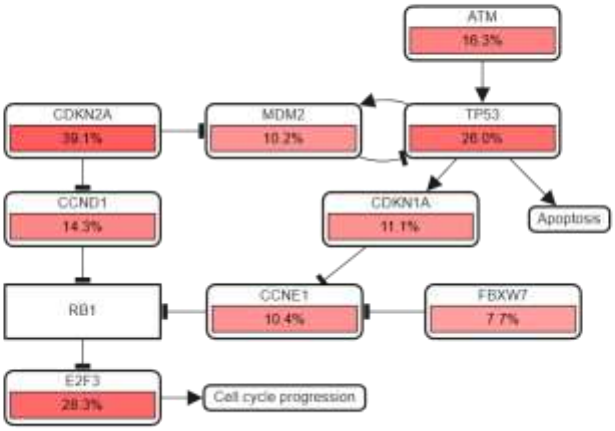

Figure 3D

Figure 3. Comprehensive genomic networks driving melanoma proliferation and cell cycle progression. **(A)** RTK and RAS signaling axis dominated by exceptionally high BRAF and NRAS mutation rates. **(**B) TP53 pathway illustrating massive CDKN2A and TP53 genetic disruption. **(C)** Cell cycle progression network revealing critical bypass mechanisms through E2F3 alterations. **(D)** MYC signaling cascade supporting unrestrained tumor cell growth.

3.3 Multi-Pathway Network Dysregulation: TGF-β and WNT Cascades

The critical role of MEIS-associated networks in driving the invasive, stem-like phenotype is corroborated by profound anomalies within the TGF-β and WNT signaling pathways. The TGF-β network exhibits high frequencies of alteration in upstream receptors (TGFBR2 at 8.1%, ACVR2A at 7.9%) and essential downstream SMAD effectors (SMAD2 at 13.6%, SMAD4 at 12.9%), converging to drive a proliferation and stem/progenitor phenotype. Concurrently, the WNT signaling cascade shows significant instability within dual receptor complexes and CTNNB1 (15.6% alteration frequency). These widespread network anomalies create a heavily dysregulated signaling environment that synergizes with MEIS epigenetic dysregulation to facilitate metastasis and invasiveness. (Figure 4 and 5)

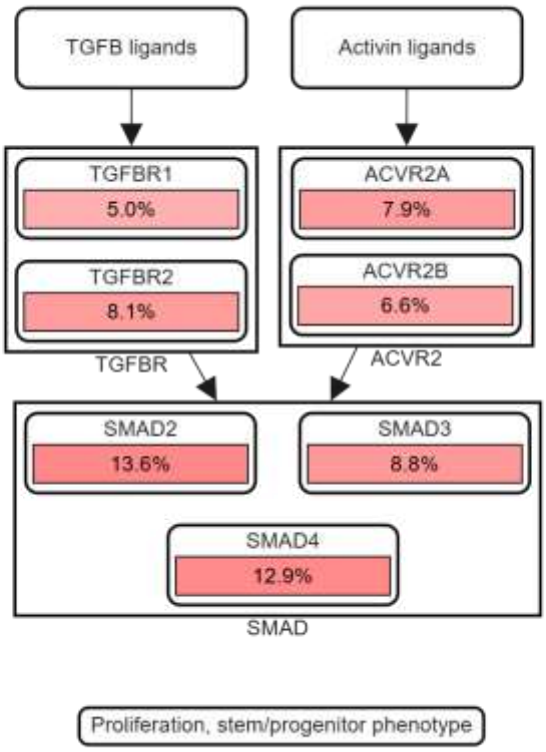

Figure 4. Genomic alteration network of the TGF-β signaling pathway in melanoma. Data obtained via cBioPortal detailing SMAD and receptor complex anomalies driving the stem progenitor phenotype.

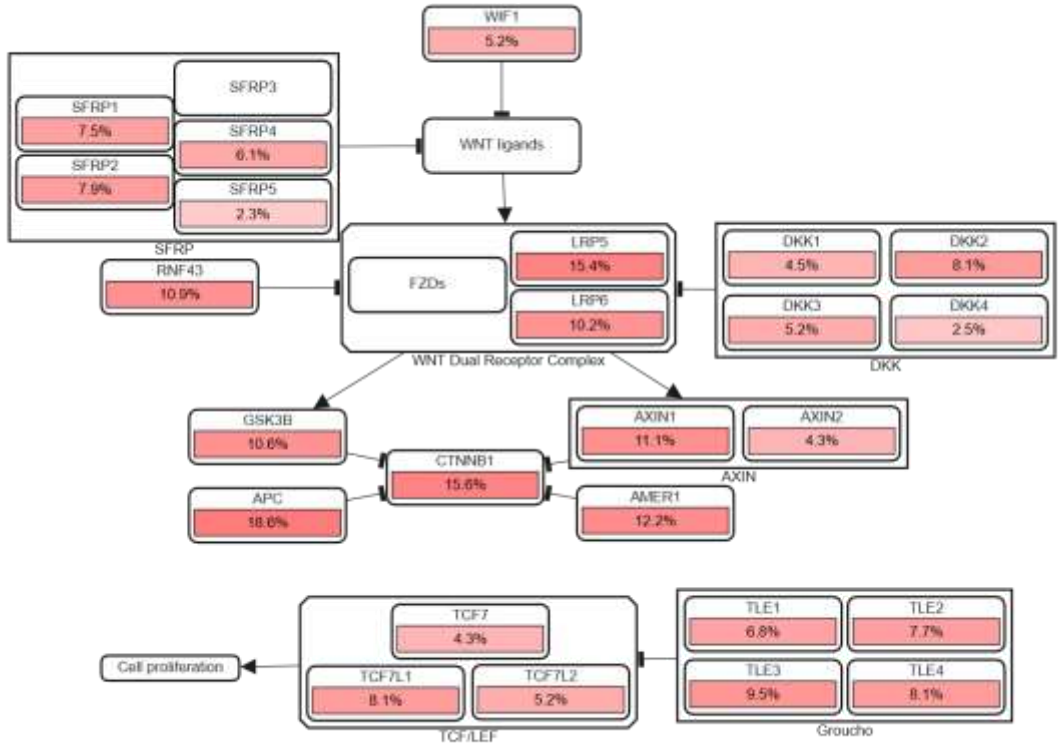

Figure 5. Genomic alteration network of the WNT signaling pathway in melanoma. Data detailing dual receptor and CTNNB1 alterations facilitating invasiveness.

3.4 Apoptotic Evasion and the PI3K/AKT Survival Axis via MEIS3

To survive the cytotoxic onslaught of targeted therapies, aggressive melanoma subpopulations fundamentally rewire the PI3K/AKT survival axis. Genomic network mapping of this pathway highlights a devastating paradigm for apoptosis evasion. The core tumor suppressor PTEN, which directly antagonizes PI3K, exhibits a severe alteration frequency of 22.2%. This primary loss of inhibitory control is accompanied by massive downstream genomic amplifications, including AKT3 (20.8%) and the master metabolic regulator MTOR (23.5%). (Figure 6)

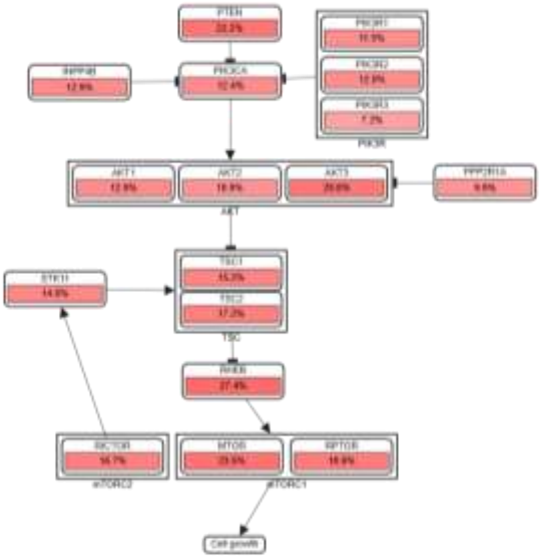

Figure 6. Genomic alteration network of the PI3K survival pathway in melanoma. Data highlighting significant PTEN loss alongside MTOR and AKT3 amplification, corroborating apoptosis evasion mechanisms.

This heavily mutated PI3K environment is further exploited by MEIS3. As an extreme oncogenic driver, MEIS3 (altered in 5% of cases via mRNA upregulation) acts as a master epigenetic orchestrator. Patients harboring MEIS3 alterations experience a precipitous collapse in overall survival, with median survival dropping drastically to 33.73 months (Log-rank p-value: 0.000023). This profound statistical significance strongly suggests that MEIS3 upregulation continuously fuels pro-survival cascades, likely by driving oncomiRs that abolish residual PTEN activity and unleashing the heavily mutated downstream AKT/mTOR effectors to sustain therapy resistance. (Figure 7)

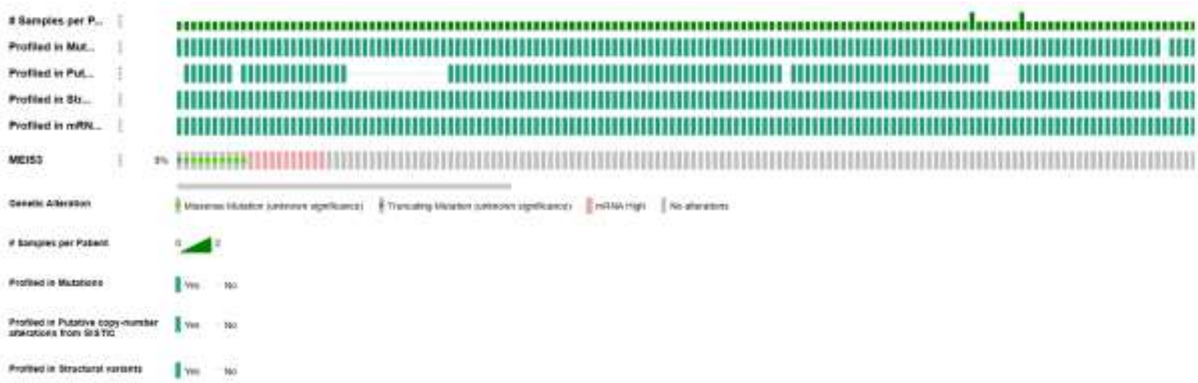

Figure 7A

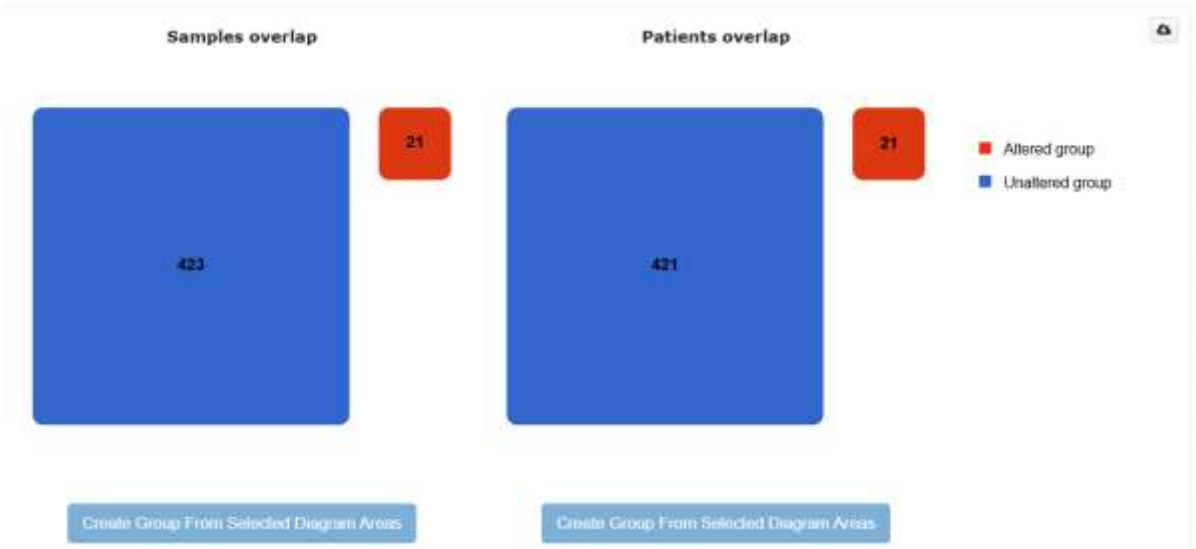

Figure 7B

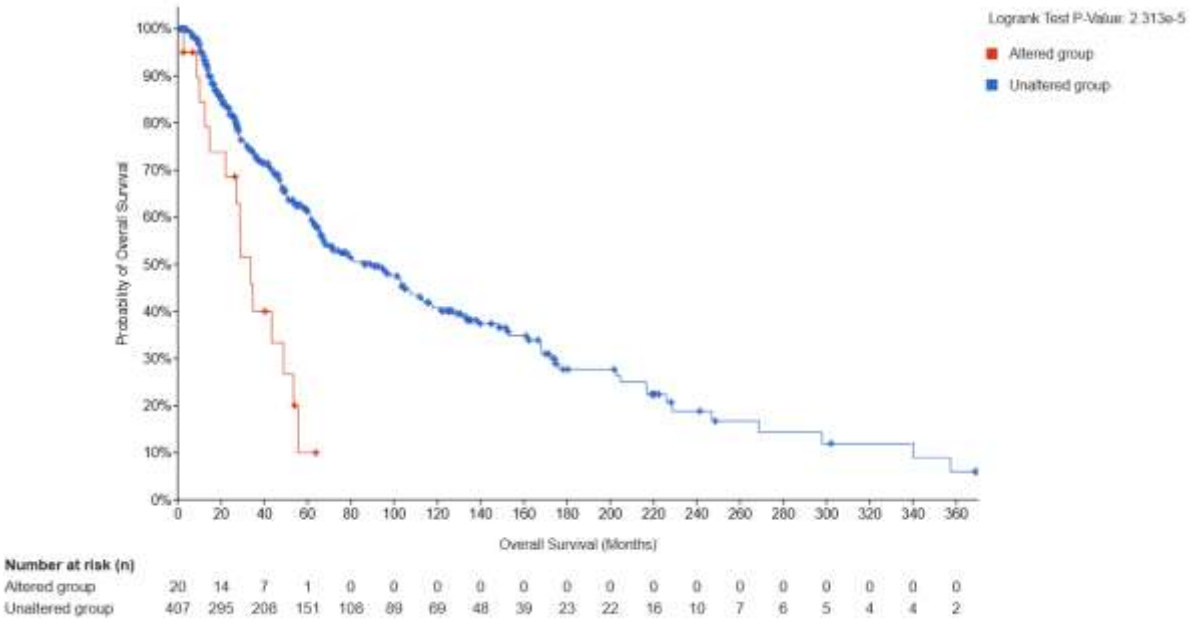

Figure 7C

Survival plot summary

	Number of Cases, Total	Number of Events	Median Months Overall (95% CI)
Altered group	20	15	33.73 (26.99 - NA)
Unaltered group	407	196	89.13 (66.74 - 111.09)

Figure 7D

Figure 7. Genomic alterations and highly significant clinical survival analysis of MEIS3 in Skin Cutaneous Melanoma. Data were systematically retrieved from the TCGA PanCancer Atlas utilizing the cBioPortal platform. (A) OncoPrint visualization detailing the genetic alteration frequency of the MEIS3 gene, predominantly characterized by mRNA upregulation in approximately 5 percent of the profiled clinical samples. (B) Overlap analysis confirming the distribution of the 21 altered versus 421 unaltered patient samples. (C) Kaplan Meier survival probability plot demonstrating a highly significant, precipitous drop in overall survival for the MEIS3 altered patient group (red curve) compared to the unaltered group (blue curve), highlighted by an extreme Logrank test p value of 0.000023. (D)

Comprehensive survival plot summary table explicitly indicating a severe collapse in median overall survival down to 33.73 months for the altered cohort versus 89.13 months for the unaltered cohort.

4. Discussion

The integration of existing developmental biology literature with our bioinformatics analyses solidifies the premise that MEIS1, MEIS2, and MEIS3 are not mere bystander anomalies but central drivers of melanoma oncogenesis. Through their ability to form robust multimeric complexes with PBX and HOX proteins, MEIS factors serve as linchpin transcriptional regulators that reconnect melanoma cells to dormant embryonic gene expression programs. The evidence synthesized in this review, corroborated by our multi-pathway network analyses, indicates that MEIS proteins influence nearly every stage of melanoma pathogenesis. They facilitate the initial expansion of tumor cells, promote invasive traits by activating pro-migratory genes (such as MCAM, MMP9, and Ang2), and sustain a multidrug-resistant, stem-like subpopulation.

Crucially, the clinical data analyzed from the TCGA and HPA cohorts reveal that MEIS dysregulation occurs in a profoundly destabilized signaling environment. The significant survival collapse observed in patients harboring MEIS3 alterations, a reduction of over 55 months in median overall survival, strongly supports the hypothesis that MEIS factors act as master epigenetic orchestrators, overriding canonical apoptotic checkpoints via mechanisms such as miR-21-mediated PTEN suppression. Furthermore, the paradoxical finding that low bulk MEIS2 transcription correlates with accelerated mortality underscores the extreme phenotypic plasticity of melanoma, where widespread epigenetic reprogramming drives the tumor into a highly invasive, dedifferentiated neural crest-like state.

From a therapeutic standpoint, the absolute dependency of aggressive melanoma cells on MEIS/HOX/PBX complexes represents a critical vulnerability. The development of precision epigenetic engineering, specifically CRISPR interference (CRISPRi) technology utilizing the dCas9-KRAB system, alongside novel small-molecule inhibitors (MEISi-1/2) that disrupt transcription factor-DNA binding, opens the door to interventions that were previously considered unattainable. These approaches, whether deployed as monotherapies or in combination with standard targeted kinase inhibitors, possess the potential to dismantle the MEIS-dependent transcriptional drive. By shifting the therapeutic focus from downstream kinases to the apex epigenetic regulators, it may be possible to force melanoma cells out of their protected stem-like niche, thereby eradicating minimal residual disease and preventing metastatic relapse.

5. Conclusions

In conclusion, MEIS1–3 transcription factors represent critical molecular threads connecting melanoma to its developmental origins. They reinforce oncogenic signaling loops across the PI3K/AKT, MAPK, and TGF-\β cascades, foster cellular plasticity, and enable the tumor to adapt and thrive under immense therapeutic pressure. Targeting these factors strikes at the fundamental core of tumor cell identity and survival. Ongoing and future research must aim to fully map MEIS-regulated networks in melanoma subpopulations at the single-cell level and refine MEIS-targeted therapeutics. By advancing these epigenetic editing strategies, we may uncover highly innovative treatments that dismantle melanoma's stem-like architecture, ultimately transforming long-term clinical outcomes for patients afflicted with this formidable malignancy.

Data Availability Statement: Publicly available datasets were analyzed in this study. The genomic and clinical data from the TCGA Skin Cutaneous Melanoma cohort can be accessed via the cBioPortal for Cancer Genomics (https://www.cbioportal.org). Transcriptomic survival data can be found at the Human Protein Atlas (https://www.proteinatlas.org).

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