



Tumor Suppressor Gene Loss and Immune-Epigenetic Reprogramming

Nicholas Foley^{✉,1} Alexej Dick^{✉,2} Simon Cocklin^{✉,3,*}

¹ Department of Biological Chemistry and Molecular Pharmacology, Blavatnik Institute, Harvard Medical School, Boston, MA 02115, USA

² Drexel University College of Medicine, Philadelphia, PA 19102, USA

³ Chan Soon-Shiong Institute of Molecular Medicine at Windber, Windber, PA 15963, USA

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Abstract

Tumor suppressor gene (TSG) inactivation is a fundamental driver of tumorigenesis. Beyond disrupting cell-intrinsic regulatory functions, TSG inactivation profoundly remodels the tumor microenvironment (TME). Loss of TSG activity through genetic mutations, epigenetic silencing, or deletions often enables cancer cells to evade immune detection and reprogram neighboring stromal and immune cells, thereby creating an immunosuppressive environment and contributing to therapy resistance. In particular, TSG loss modulates interactions between tumor and immune cells by altering cytokine profiles, upregulating inhibitory immune checkpoints, and inducing epigenetic alterations that collectively impair antitumor immune responses. This mini-review explores how TSG inactivation influences immune modulation and epigenetic programming within the TME. The role of TSG loss in promoting immune evasion and “cold” tumor immune phenotypes is examined, along with its contribution to epigenetic alterations that sustain pro-tumorigenic gene expression patterns. The review further highlights emerging therapeutic strategies, including synthetic lethality approaches, epigenetic therapies, and immunomodulatory interventions designed to counteract the immune–epigenetic consequences of TSG loss. A deeper understanding of immune–epigenetic reprogramming induced by TSG inactivation highlights the importance of integrated therapeutic strategies that restore immune surveillance and promote tumor suppression within the complex TME.

Keywords:

tumor suppressor gene; tumor microenvironment; immune evasion; epigenetic reprogramming; immunotherapy; synthetic lethality

1. Introduction

TSGs serve as critical guardians of cellular homeostasis by restraining uncontrolled proliferation, facilitating DNA repair, and promoting the apoptosis of abnormal cells. Inactivation of TSGs through mutations, deletions, or epigenetic silencing abolishes their protective functions and triggers malignant transformation. Beyond cell-intrinsic consequences, TSG inactivation profoundly reconfigures the TME by disrupting immune surveillance and perturbing normal stromal–immune interactions [1]. TSG-deficient tumor cells can modify cytokine and chemokine signaling and induce stromal remodeling, including fibrosis and extracellular matrix reorganization,

thereby creating a microenvironment that promotes tumor immune evasion and progression [1]. For instance, mutations in TP53 or NF1 can promote the activation of cancer-associated fibroblasts and enhance extracellular matrix stiffness, thereby establishing a physical barrier that impedes T-cell infiltration. Simultaneously, TSG loss reshapes the immune landscape toward an immunosuppressive state by promoting the accumulation of regulatory T cells (Tregs) and tumor-associated macrophages (TAMs) while weakening cytotoxic T lymphocyte (CTL) responses. Through these mechanisms, the absence of tumor suppressors makes the TME more permissive to cancer growth and less responsive to treatment.

* Corresponding Author:

Simon Cocklin, Chan Soon-Shiong Institute for Molecular Medicine at Windber, Windber, PA 15963, USA, s.cocklin@wriwindber.org



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The influence of TSG inactivation on anti-tumor immunity is complex and context-dependent. In many solid tumors, TSG loss is associated with immune evasion, characterized by the absence of robust T-cell infiltration despite high neoantigen burden, a feature commonly referred to as a “cold” tumor phenotype. One of the best-characterized examples is the inactivation of the pivotal TSG TP53, which can shift the immune landscape toward increased accumulation of Tregs and M2-polarized macrophages, thereby protecting tumors from immune-mediated elimination. However, in certain contexts, TSG loss can paradoxically enhance tumor immunogenicity. Defects in DNA repair TSGs, such as BRCA1/2, or in mismatch repair genes, increase the tumor mutational burden and generate neoantigens capable of attracting T cells. Indeed, ARID1A mutations (loss-of-function mutations in a chromatin remodeling TSG) are associated with higher mutation loads and better responses to immune checkpoint inhibitors in certain cancers [2]. However, even under these conditions, compensatory mechanisms, such as the recruitment of myeloid-derived suppressor cells (MDSCs), can suppress immune responses. Therefore, TSG inactivation does not uniformly affect the TME. It can both suppress and, in certain contexts, enhance tumor immune visibility. This duality underscores the importance of elucidating the context-dependent immune and epigenetic consequences of TSG inactivation to enable the development of more effective therapeutic strategies.

2. Immune Evasion Driven by TSG Loss

TSG inactivation frequently promotes the establishment of an immunosuppressive TME, enabling cancer cells to evade immune-mediated elimination. Mechanistically, loss of a TSG can reprogram cytokine and chemokine networks to favor the recruitment of immunosuppressive leukocytes while limiting the infiltration and activity of effector lymphocytes [3]. A well-established example is TP53 loss, whereby TP53 mutation or deletion induces elevated production of interleukin-34 (IL-34), a cytokine that is normally suppressed by wild-type p53 [4]. IL-34 then binds the CSF-1 receptor on monocytes, promoting the differentiation of TAMs into an M2-like, “foam cell” phenotype that strongly suppresses CD8⁺ T-cell activity [4]. Through dysregulation of the p53–IL-34 axis, TP53-deficient tumors establish a protumorigenic, macrophage-rich niche that facilitates immune evasion and protects cancer cells from immune-mediated attack (Figure 1) [4].

Another key tumor suppressor, PTEN, provides a similar example, where its loss leads to hyperactivation of the PI3K–AKT pathway, resulting in increased secretion of immunosuppressive factors and recruitment of regulatory immune cells [3]. PTEN-null tumors are marked by abundant Tregs and MDSCs in the microenvironment, with a shortage of cytotoxic T cells [3]. Clinically, PTEN-deficient melanomas and lung cancers frequently exhibit a “non-T-cell-inflamed” phenotype and demonstrate limited responsiveness to PD-1 blockade immunotherapy [3].

Similarly, in non-small cell lung cancer, inactivation of the serine/threonine kinase LKB1 (also called STK11), which is frequently co-mutated with KRAS, has become a significant driver of “cold” tumor phenotypes. LKB1-mutant tumors are characterized by low T-cell infiltration and reduced PD-L1 expression, features that are strongly associated with primary resistance to immune checkpoint blockade [5]. Overall, these examples demonstrate how TSG loss can actively reshape the immune environment by promoting the entry and expansion of immunosuppressive cells (TAMs, Tregs, MDSCs) while deterring effector T and NK cells.

In addition to actively promoting immunosuppressive cell populations, TSG inactivation can upregulate immune checkpoint molecules and other immune-evasion signals on tumor cells. For example, loss of PTEN or RB1 has been associated with increased PD-L1 expression on cancer cells, driven by sustained PI3K/AKT or MYC pathway activation (Figure 1) [3]. Such TSG-deficient tumor cells not only prevent T-cell infiltration but also directly suppress T-cell activity by overexpressing checkpoint ligands. Furthermore, TSG loss may induce chronic inflammation that can contribute to local and systemic immune dysfunction. NF- κ B activation resulting from specific TSG mutations (e.g., loss of CYLD or A20, negative regulators of NF- κ B) can lead to sustained production of inflammatory mediators, effector cell exhaustion, and, over time, recruitment of suppressor cells. This inflammation-driven state of immune tolerance further facilitates metastatic progression and contributes to resistance to immunotherapeutic interventions.

Importantly, the consequences of TSG loss are not uniformly immunosuppressive. As discussed previously, the loss of certain TSGs can, in specific contexts, enhance tumor immunogenicity and increase tumor visibility to the immune system. Deficiencies in DNA repair-associated TSGs provide a clear example. Tumors with mismatch repair gene silencing, such as MLH1 hypermethylation in colorectal cancer, frequently exhibit microsatellite instability and an elevated mutational burden, which can enhance tumor immunogenicity, promote T-cell responses, and increase sensitivity to PD-1 block-

ade. Tumors harboring BRCA1, BRCA2, or ARID1A alterations may exhibit an increased neoantigen burden and, in certain contexts, enhanced infiltration by tumor-infiltrating lymphocytes (Figure 1) [2]. However, even in these contexts, secondary immunosuppressive adaptations frequently undermine effective immune surveillance. For example, BRCA-mutant ovarian cancers, despite their elevated neoantigen burden, can promote the recruitment of MDSCs, which suppress cytotoxic T-cell activity and facilitate immune evasion. Therefore, even when TSG loss enhances tumor immunogenicity, tumors frequently

compensate by activating robust immune-evasion mechanisms. The balance between these opposing effects, immunogenic versus immunosuppressive, varies depending on tumor type and genetic context. Overall, in most TSG-deficient solid tumors, the predominant environment is pro-tumor, with immune-suppressive mechanisms overpowering any increase in immunogenicity. This immune-evasive phenotype poses a significant challenge to current immunotherapies, which are generally less effective in “cold” TME contexts driven by TSG inactivation [3].

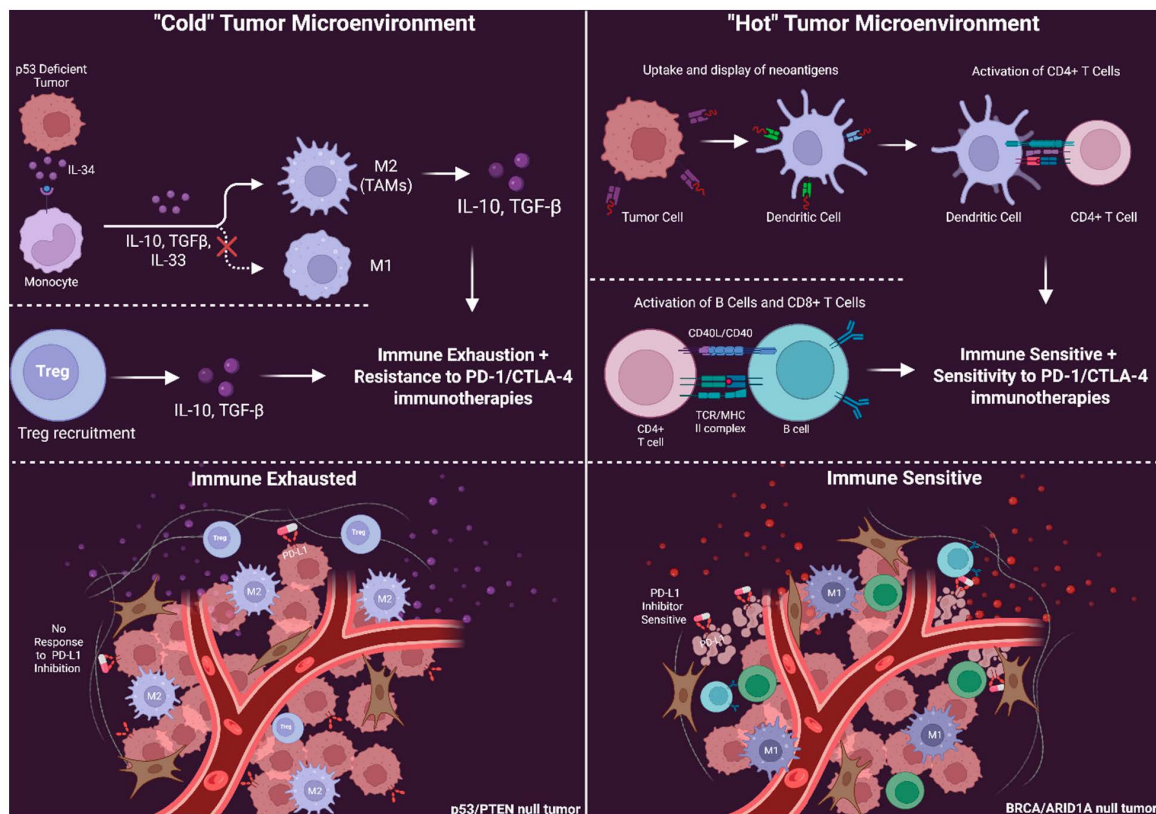


Figure 1: Loss of a tumor suppressor gene creates an immune “cold” or “hot” tumor microenvironment. While presented here as a dichotomy, these states represent two ends of a dynamic spectrum, and mixed phenotypes frequently occur depending on secondary mutations and the epigenetic landscape. The left panel displays an immune “cold” TME with increased M2 macrophage polarization and Treg recruitment, leading to increased secretion of immune-suppressive cytokines such as IL-10 and TGF- β . These immunosuppressive cytokines significantly reduce the effectiveness of immunotherapies, such as PD-1/CTLA-4 targeting. The right panel displays an immunologically hot TME with increased neoantigen production in tumors carrying a high mutational burden, including tumors harboring BRCA1, BRCA2, or ARID1A alterations. These neoantigens activate dendritic cells, which can stimulate immune responses from CD4+ T cells, B cells, and CD8+ T cells. This increase in immune activity greatly increases the effectiveness of immunotherapy. Created with [BioRender.com](https://www.biorender.com).

3. Epigenetic Reprogramming in TSG-Deficient Tumors

Loss of tumor suppressors is often linked to, and sometimes caused by, epigenetic changes that fundamentally alter gene expression in cancer cells. Epigenetic modifica-

tions, including DNA methylation and chromatin remodeling, can silence key genes without altering the DNA sequence, thereby functionally mimicking loss-of-function alterations in TSGs. For example, promoter hypermethylation of CDKN2A (p16) or MLH1 is a common way of inactivating TSGs across various cancers [6]. These epi-

genetic silencing events directly impact the immune microenvironment. Silencing of DNA repair genes, such as MLH1, can result in high levels of microsatellite instability and an increased neoantigen burden, whereas suppression of antigen-presentation machinery, including B2M or MHC class I genes, facilitates evasion of T-cell recognition [3]. Essentially, cancer cells use epigenetic reprogramming to turn off tumor-suppressive and immune-stimulating genes, promoting immune escape [1,7]. Aberrant DNA hypermethylation in tumors can suppress cytokine, chemokine, and antigen-presentation pathways that are essential for immune-cell recruitment and activation [1]. At the same time, global DNA hypomethylation (often associated with TSG loss) may activate oncogenes and pro-inflammatory genes indiscriminately, thereby contributing to a highly disorganized immune landscape within the TME [7,8].

In many cancers, tumor suppressor genes (TSGs) are integral components of the epigenetic machinery, and their loss triggers widespread transcriptional dysregulation. Notable examples include genes encoding chromatin remodelers and histone modifiers, which are critical regulators of chromatin architecture and gene expression. ARID1A, PBRM1, and SMARCA4 are TSGs that encode subunits of the SWI/SNF chromatin-remodeling complex. These genes are frequently mutated in solid tumors.

Loss of ARID1A has been shown to weaken the tumor immune response by impairing the expression of Th1-type chemokines that attract CD8⁺ T cells [2]. A recent study of gastric cancer demonstrated that ARID1A deficiency reduced CXCL9 and CXCL10 expression and was associated with a marked absence of intratumoral CD8⁺ T cells and enhanced tumor growth [2]. Additionally, tumors with ARID1A mutations showed decreased histone acetylation and chromatin accessibility at immune gene loci, linking these epigenetic changes to immune exclusion [2]. Importantly, restoration of epigenetic homeostasis through histone deacetylase inhibition has been shown to reverse ARID1A loss-mediated chemokine suppression, thereby promoting the re-infiltration of CD8⁺ T cells and substantially enhancing the efficacy of anti-PD-L1 therapy in preclinical models [2]. This demonstrates how epigenetic reprogramming downstream of TSG loss can be a critical factor in anti-tumor immunity.

Other chromatin regulatory TSGs also exhibit similar relationships with the immune microenvironment. In renal cell carcinoma, PBRM1 mutations have been associated in some studies with increased T-cell infiltration and enhanced sensitivity to PD-1 blockade [9], whereas in lung cancer, PBRM1 or ARID2 alterations may be linked to a non-inflamed tumor phenotype [9,10].

BAP1, a tumor suppressor encoding a nuclear deubiquitinase, provides another example in which its loss in mesothelioma has been shown to modulate the TME by upregulating interferon-responsive genes and enhancing immune cell infiltration [11]. Clinically, BAP1-deficient mesotheliomas seem to represent an immunogenic subtype that may respond better to checkpoint inhibitor immunotherapy [11]. These examples highlight that the epigenetic effects of TSG loss can either suppress or boost anti-tumor immunity, depending on which pathways are affected.

A unifying theme is that TSG inactivation frequently establishes an epigenetic landscape that promotes tumor progression while impairing effective antitumor immunity [1]. Aberrant promoter methylation, histone modifications such as EZH2-mediated H3K27 trimethylation, and loss of chromatin-regulating factors collectively silence genes involved in immune recognition, including genes governing antigen presentation, chemokine signaling, and cell adhesion. These alterations can also permit the expression of genes that promote proliferation, metastasis, and immune tolerance [1,7]. For example, promoter hypermethylation of Th1-attracting chemokines or genes involved in antigen processing can render tumors less visible to cytotoxic T cells. At the same time, epigenetic upregulation of immune checkpoint ligands (such as PD-L1, which can be increased through chromatin changes in some TSG-null environments) effectively suppresses residual effector T-cell activity [3]. Importantly, unlike DNA mutations, epigenetic alterations are potentially reversible. This inherent plasticity provides a therapeutic opportunity to reprogram the cancer epigenome and thereby modulate the TME, as discussed in Section 5. Additionally, epigenetic alterations often serve as intermediaries connecting TSG loss to immune effects—acting as a molecular “memory” that sustains an immune-evasive state. Recognizing these interconnections is essential, as targeting epigenetic dysregulation may enable reactivation of silenced TSG pathways and immune-stimulatory genes in tumor cells, thereby restoring antitumor immune function [1].

4. Crosstalk Between Immune Evasion and Epigenetic Dysregulation

The bidirectional relationship between immune modulation and epigenetic reprogramming in TSG-deficient tumors underscores a dynamic interplay in which epigenetic abnormalities within tumor cells actively shape the immune landscape of the TME. By regulating specific gene networks, cancer-cell-intrinsic epigenetic changes

determine which immune-related molecules (cytokines, chemokines, checkpoints) are expressed [1]. For instance, loss of a tumor suppressor that induces epigenetic silencing of chemokine genes can reduce immune cell infiltration, whereas epigenetic activation of immune checkpoint ligand genes can locally suppress T-cell activity. In this way, the abnormal epigenome of TSG-deficient cancer cells shapes the local immune environment, enabling it either to fail in recognizing the tumor or, in some contexts, to actively support tumor progression [1]. Importantly, recent single-cell studies have shown strong links between the chromatin accessibility landscape of tumor cells and the makeup of immune infiltrates [1]. Regions of open chromatin in cancer cells are enriched for genes encoding secreted factors, including chemokines, which regulate immune cell migration and differentiation [1]. Therefore, the epigenetic environment can assist in the tumor's ability to attract immunosuppressive or immunogenic cells.

In addition to modulating immune cell recruitment within the TME, tumor-derived signals can also reprogram the epigenetic landscape of immune cells residing in the TME. As immune cells infiltrate a tumor, they face chronic antigen stimulation, suppressive cytokines (e.g., IL-10, TGF- β), and metabolic stress, all of which can induce stable epigenetic changes in these cells. For example, exhausted T cells in cancer develop a distinct epigenetic and transcriptional profile that keeps them in a dysfunctional state. Likewise, TAMs and myeloid-derived suppressor cells (MDSCs) within TSG-deficient tumors can acquire stable chromatin alterations that reinforce M2 polarization and sustain their immunosuppressive functions. Once immune cells enter the TME, they modify their histone marking and DNA methylation patterns to survive the tumor's hostile, inflammation-rich environment [1]. Because immune cell plasticity is intrinsically regulated by epigenetic modifications essential for normal lineage specification and memory formation, this inherent adaptability can be co-opted as a vulnerability within the tumor context [12]. This epigenetic adaptation gives tumor-associated immune cells a "fitness advantage," effectively conditioning them to tolerate or even support the tumor [1]. For instance, TAMs in a p53-null, IL-34-rich environment may acquire stable chromatin states that sustain their immunosuppressive phenotype. Importantly, cancer therapies can also modulate immune cell epigenetics. Immune checkpoint blockade and cytokine-based therapies can reprogram epigenetic states in T and NK cells, while epigenetic agents, such as DNA methyltransferase inhibitors and histone deacetylase inhibitors, can act on both tumor cells and immune cells within the TME, thereby reshaping their functional states [1,13]. Thus, immune-epigenetic crosstalk is dynamic. Tumor-derived, epigenet-

ically regulated signals influence immune-cell functions, while immune cells undergo epigenetic adaptation in response, which may further affect tumor behavior.

This close interplay indicates that immune evasion and epigenetic dysregulation are mutually reinforcing processes in many cancers. Tumors with TSG loss may epigenetically silence genes to evade immune detection, while concurrently recruiting immunosuppressive cell populations that subsequently acquire stable epigenetic modifications sustaining their suppressive functions. The result is a self-perpetuating cycle that sustains an immune-evasive, tumor-friendly environment. Disrupting this cycle is challenging but presents important therapeutic opportunities. Strategies that concurrently target the epigenetic states of both tumor and immune cells, along with suppressive immune signaling pathways, may achieve improved therapeutic efficacy when used in combination. For example, epigenetic reprogramming of tumor cells using pharmacological agents may induce the expression of chemokines that promote effector T-cell recruitment. However, the activity of these T cells may still be constrained by immune checkpoint signaling. Accordingly, combining epigenetic therapies with immune checkpoint inhibitors may achieve greater therapeutic efficacy than either approach alone [1]. Overall, the immune environment and the epigenetic landscape should be seen as interconnected systems in TSG-inactivated cancers. Effective therapies are likely to be those that reactivate silenced immune pathways in tumors while reducing immune-cell suppression, thereby improving antitumor immunity.

4.1. A Unifying Framework: Trajectories and Hierarchies

To understand why certain tumors are predisposed toward immune "hot" or "cold" phenotypes, a unifying framework is proposed. The immune-epigenetic consequences of TSG loss can be viewed as progressing through a four-stage hierarchy. The primary event (genetic inactivation) drives a secondary event (epigenetic rewiring of the tumor cell). This epigenetic rewiring can act as a bridge to the tertiary event (altered cytokine/chemokine secretion). This ultimately culminates in a quaternary event characterized by the epigenetic adaptation of infiltrating immune cells, resulting in stable immune suppression within the TME.

As detailed by Kondilis-Mangum and Wade [14], normal adaptive immune cells depend on dynamic epigenetic regulation, including targeted DNA methylation and histone modifications at specific cytokine loci, to drive differentiation and stabilize effector or memory states. It is increasingly apparent that TSG-deficient tumors can exploit these intrinsic epigenetic mechanisms. In this

model, the altered immunosuppressive cytokine profile of the TME (the tertiary event) serves as an extrinsic stimulus that drives epigenetic adaptation in infiltrating T cells and macrophages. By providing persistent suppressive cues, the tumor promotes stable, epigenetically repressed immune states (such as T-cell exhaustion or M2-like macrophage polarization), maintaining immune evasion.

As discussed in Section 2, immunosuppression is not the only possible immune trajectory, as tumors may exhibit immunologically cold, hot, or intermediate phenotypes. These states are not absolute, and epigenetic adaptations can give rise to mixed or intermediate phenotypes. A summary of the influence of tumor suppressor genes on immune trajectories is provided in Table 1.

Table 1: Predictive rules and trajectories of TSG-driven immune reprogramming.

TSG	Primary Gatekeeper Function	Dominant Immune Trajectory	Generalizability vs. Tumor Specificity	Clinical Inconsistencies/Contradictory Studies
TP53	Cell cycle control, apoptosis	Often cold/suppressive, via myeloid and Treg-skewed immune evasion	Broadly generalizable, but highly context-dependent across tumor types	Some TP53-mutant tumors show high mutational burden and potential immunogenicity, yet many remain ICI-resistant because suppressive myeloid programs dominate [15] PTEN loss is associated with immune exclusion, but
PTEN	PI3K/AKT signaling restraint	Commonly cold/suppressive, with reduced T-cell inflamed phenotypes	Largely generalizable, especially in melanoma and prostate cancer	single-agent PI3K-pathway inhibition often does not fully restore immune responsiveness in practice [16]
LKB1/STK11	Metabolism and AMPK signaling	Typically, cold/immune desert	More tumor-specific, with strongest evidence in NSCLC, often in KRAS-co-mutant disease	Preclinical metabolic targeting is promising, but clinical benefit is often incomplete and variable [17]
ARID1A/PBRM1	SWI/SNF chromatin remodeling	Mixed/bifurcated, depending on tumor context	More context-specific than universal; PBRM1 is especially studied in RCC and NSCLC [18]	PBRM1 has been linked to ICI response in RCC and resistance in other settings; ARID1A can correlate with increased immune activity but also suppression of chemokine programs like CXCL9/10 [9]
MLH1/BRCA	DNA repair	Often hot/immunogenic, especially in MSI-H or homologous recombination-deficient tumors	Broadly generalizable for mismatch repair deficiency and related neoantigen load [19]	Even when T-cell infiltration is high, some tumors still need combination therapy because responses are not always durable [18]

5. Therapeutic Strategies
Targeting the Immune–Epigenetic Axis

Given the significant immune and epigenetic changes caused by TSG loss, new therapeutic strategies are being developed to address these effects. Below, key approaches aimed at restoring tumor suppressor functions or targeting vulnerabilities in TSG-deficient tumors are de-

scribed, with particular emphasis on strategies that modulate the immune–epigenetic axis.

5.1. Synthetic Lethality and TSG-Directed Vulnerabilities

One therapeutic strategy for tumors with TSG loss involves the identification of synthetic lethal interactions, wherein specific genetic or functional dependencies become essential for tumor cell survival in the absence of

a given TSG. Synthetic lethal strategies do not directly restore the lost TSG. Instead, they target compensatory pathways on which cancer cells become dependent for survival. As illustrated in **Figure 2**, this concept spans both biological discovery and therapeutic application. At a fundamental level, discovery-based synthetic lethality identifies natural vulnerabilities in which the loss of two parallel pathways (e.g., two redundant DNA repair genes) results in cell death (**Figure 2A**). Clinically, this concept has been translated by targeting a compensatory protein or pathway that becomes essential following the loss or alteration of a cancer-associated gene (**Figure 2B**). A well-

established example is the use of PARP inhibitors in tumors harboring BRCA1/2 mutations. Loss of homologous recombination due to BRCA1/2 deficiency leads to accumulation of DNA double-strand breaks, which are normally detected and processed through PARP-mediated repair pathways. Consequently, PARP inhibitors such as olaparib cause the accumulation of replication-associated DNA damage that BRCA-deficient cells cannot repair through homologous recombination, resulting in selective tumor-cell death (**Figure 2**). This concept has already led to approved therapies for BRCA-mutant breast and ovarian cancers [20].

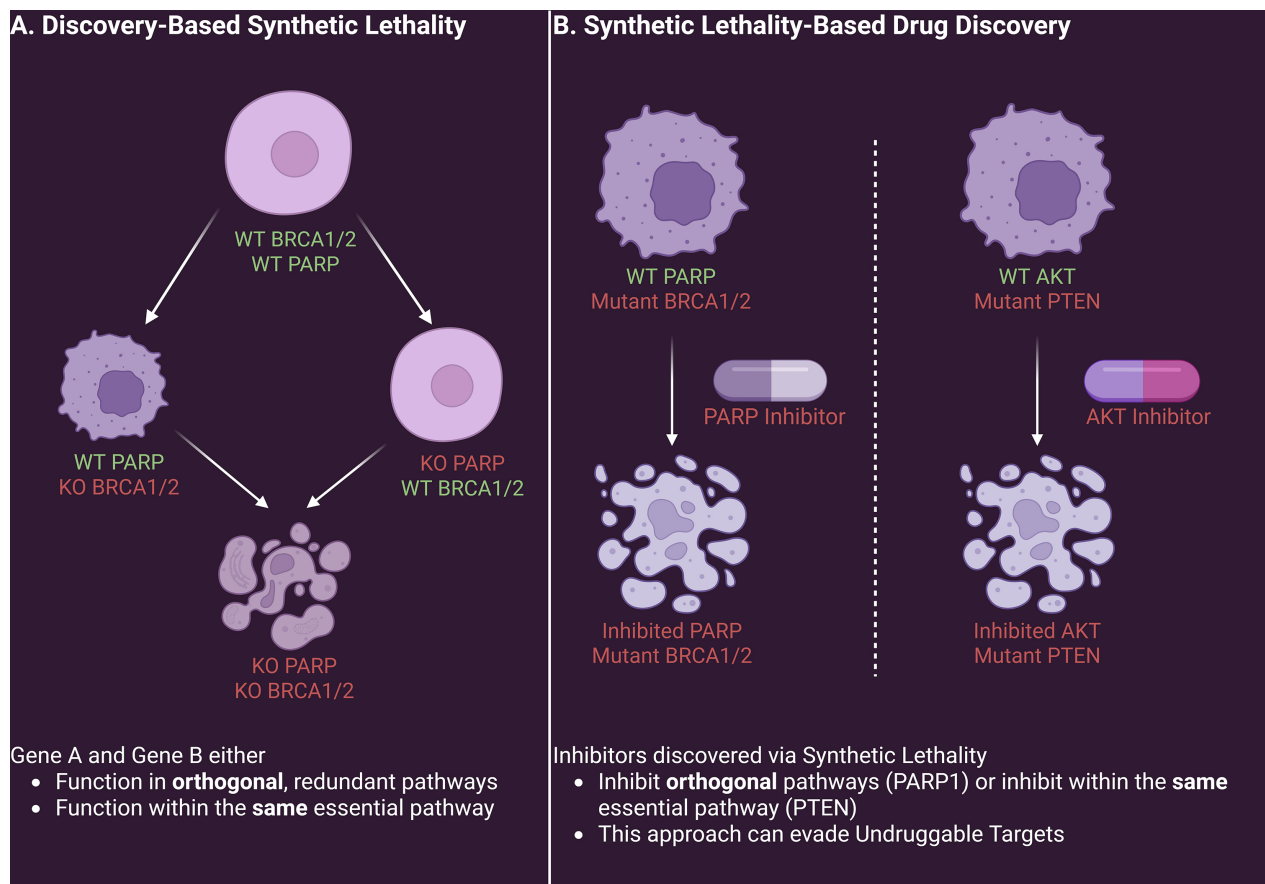


Figure 2: An overview of synthetic lethality in drug discovery. Panel (A) displays discovery-based synthetic lethality, in which genes in the same pathway or in orthogonal pathways are mutated, turning a nonlethal knockout into a lethal double-knockout. Panel (B) illustrates therapeutic synthetic lethality, in which a protein or pathway that becomes essential following a cancer-associated genetic alteration is pharmacologically inhibited, leading to selective tumor-cell death. This approach can create a much wider therapeutic window and enable drugs to target previously undruggable mutants. Created with [BioRender.com](https://www.biorender.com).

Beyond PARP, numerous emerging synthetic lethal targets are being investigated across diverse TSG defects. For example, deficiency of the bromodomain protein Polybromo-1 (PBRM1) in renal carcinoma cells has been associated with increased sensitivity to specific DNA damage response inhibitors [3]. Chabanon

et al. demonstrated that loss of PBRM1 (a SWI/SNF subunit) causes synthetic lethality with ATR and PARP inhibitors, suggesting these drugs could be effective in PBRM1-mutant tumors [21]. Likewise, PTEN loss causes sustained PI3K-AKT-mTOR signaling and may create therapeutic dependence on components of this pathway.

AKT and mTOR inhibitors are therefore being evaluated in PTEN-deficient cancers (e.g., NCT03072238 [IPATentia150, ipatasertib], NCT02121639 [ProCAID, capivasertib]). Synthetic lethal screens using CRISPR/Cas9 have identified many targetable gene pairs for TSG-mutant contexts. For example, ARID1A mutations sensitize cancer cells to EZH2 inhibition, reflecting functional antagonism between the SWI/SNF and PRC2 chromatin-remodeling complexes [22].

The main advantage of synthetic lethality is that it transforms a tumor's weakness (TSG loss) into its Achilles' heel. Moreover, synthetic lethal targeting of tumor cells can confer immunological advantages. For example, PARP inhibitors not only induce cancer cell death but also activate type I interferon signaling and promote immunogenic cell death, thereby enhancing immune cell recruitment to the tumor site [23–25]. Evidence suggests that combining PARP inhibition with PD-1/PD-L1 blockade enhances anti-tumor immunity in preclinical models by revealing neoantigens and activating dendritic cells [26]. Therefore, synthetic lethal treatments may work synergistically with immunotherapy, especially in tumors where TSG loss initially attenuates antitumor immune responses. Ongoing clinical trials are evaluating combinations such as PARP inhibitors with anti-PD-1 agents and ATR inhibitors with anti-CTLA-4 therapy to determine whether targeting TSG-associated vulnerabilities can also restore effective immune engagement.

5.2. Epigenetic Modulation: Reprogramming Tumor Cells and TME

Given the central role of epigenetic dysregulation in TSG-inactivated tumors, epigenetic therapies represent a rational component of therapeutic strategies. By targeting DNA methyltransferases (DNMTs), histone deacetylases (HDACs), or other epigenetic enzymes, these therapies aim to reverse the silencing of TSGs and immune-regulatory genes. DNMT inhibitors such as azacitidine and decitabine can demethylate gene promoters, restoring the expression of tumor suppressors and improving immune visibility [1,8]. Notably, low-dose DNMT inhibitors have been shown to induce the expression of endogenous retroviral elements and interferon-stimulated genes in tumor cells, thereby generating a “viral mimicry” state that activates antitumor immune responses. They can also increase the expression of MHC class I and PD-L1 on cancer cells. Increased MHC class I expression may improve antigen presentation, while increased PD-L1 can create a therapeutically targetable checkpoint dependence when combined with PD-1/PD-L1 blockade. Preclinical studies have demonstrated that demethylating agents can increase PD-L1 expression and sensitize previously un-

responsive tumors to PD-1/PD-L1 blockade [27]. Similarly, histone deacetylase (HDAC) inhibitors can modulate tumor immunophenotypes by remodeling chromatin accessibility and gene expression programs. By increasing histone acetylation, HDACi promote a more open chromatin structure, which can induce the expression of Th1-type chemokines, pro-apoptotic genes, and antigen presentation pathways. HDAC inhibition can increase the expression of death receptors and their ligands, including Fas, Fas ligand, and TRAIL-associated pathways, while restoring MHC class I antigen presentation on tumor cells. These effects may increase susceptibility to T-cell-mediated and natural killer-cell-mediated cytotoxicity. In addition, romidepsin has been shown to induce NKG2D ligand expression on transformed cells, further enhancing immune recognition and tumor cell clearance [28–31] (Figure 3). In ARID1A-mutant tumors discussed earlier, HDAC inhibition successfully restored CXCL9/10 production and enhanced infiltration of CD8⁺ T cells, especially when combined with PD-L1 blockade [2].

There is growing interest in agents targeting specific epigenetic regulators that exhibit synthetic lethality in the context of TSG loss. For example, EZH2 inhibitors in ARID1A-mutant cancers have been explored for their ability to reverse aberrant PRC2-mediated gene repression [32], while BET bromodomain inhibitors in TP53-mutant tumors may suppress MYC-driven transcriptional programs that become dysregulated following p53 loss [33]. Epigenetic drugs may also affect stromal and immune cells within the tumor microenvironment. Low-dose DNMT inhibitors can reduce the suppressive activity of tumor-associated macrophages and MDSCs by inducing them to express genes that stimulate immune responses (Figure 3) [34]. Overall, epigenetic modulation offers multiple strategies to reprogram both the tumor and its microenvironment from an immune-silent to an immune-active state. Early-phase clinical trials combining DNA hypomethylating agents or HDAC inhibitors with checkpoint inhibitors have shown promising results in melanoma and lung cancer that had progressed on immunotherapy alone—including entinostat plus pembrolizumab in anti-PD-(L)1-refractory NSCLC and melanoma (NCT02437136, ENCORE-601) and guadecitabine plus ipilimumab in advanced melanoma (NCT02608437, NIBIT-M4) [34,35]. These combinations aim to convert “cold” tumors—often characterized by TSG loss and epigenetic silencing of immune genes—into “hot” tumors filled with T cells and receptive to immune attack. Although challenges related to toxicity, dosing, and treatment sequencing remain, epigenetic therapies are emerging as potential complements to immunotherapy in TSG-mutant cancers [1].

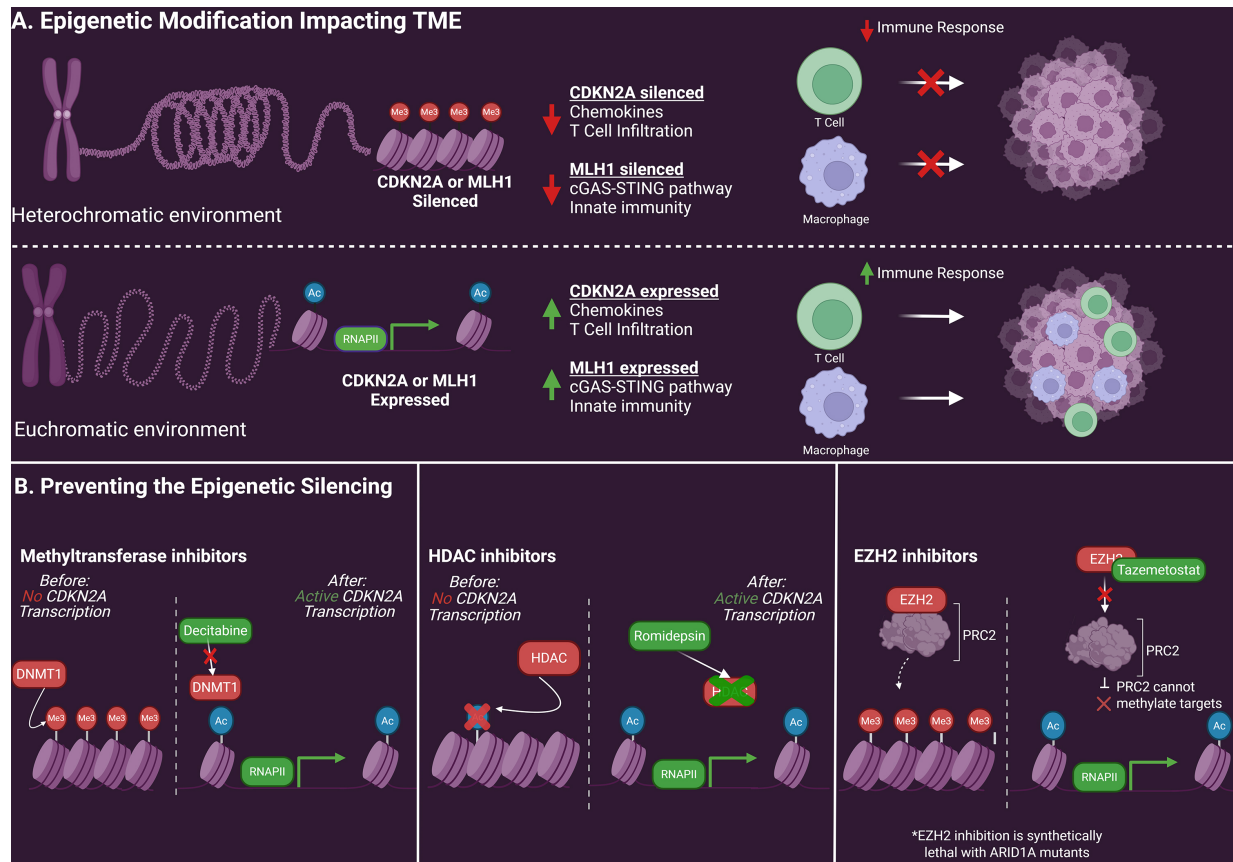


Figure 3: Panel (A) illustrates how repressive epigenetic alterations, including promoter DNA hypermethylation and repressive histone modifications, can silence genes involved in tumor suppression and immune regulation, thereby reducing immune-cell recruitment within the TME. Panel (B) shows how epigenetic drugs can reverse gene silencing and enhance antitumor immune responses by inhibiting DNA methyltransferases or histone deacetylases in tumor and immune cells. Figure created with [BioRender.com](https://www.biorender.com).

5.3. Immunomodulatory Strategies to Restore TME Balance

To specifically counteract immune evasion driven by TSG loss, various immunomodulatory therapies are under investigation. Immune checkpoint inhibitors (ICIs), including anti-PD-1 and anti-CTLA-4 antibodies, have become standard therapies for multiple cancer types; however, their efficacy is often limited in TSG-deficient tumors characterized by an immune-cold phenotype. One strategy to improve outcomes is to combine ICIs with agents targeting immunosuppressive factors induced by TSG loss. A recent and compelling example is provided by TP53-null tumors: as discussed in [Section 2](#), loss of p53 leads to upregulation of the tumor-associated macrophage-promoting cytokine IL-34. In 5-week-old female C57BL/6 mice bearing orthotopic or subcutaneous Trp53^{-/-} (Trp53/Pten-driven) liver tumors that were refractory to anti-PD-1 alone, Nian et al. showed that intratumoral blockade of IL-34 combined with anti-PD-1 produced complete tumor regression in 9/10 (subcu-

taneous) and 7/9 (liver in situ) treated mice (n = 9–10 per group), with protection against tumor re-challenge indicating durable antitumor immunity [4]. This combination acts by simultaneously alleviating macrophage-mediated immunosuppression through IL-34/CSF1R pathway inhibition and restoring T-cell activity via PD-1 blockade [4]. Similar dual approaches are currently being evaluated in clinical settings. For example, in STK11/LKB1-mutant lung adenocarcinomas, which are typically resistant to PD-1 monotherapy, the addition of CTLA-4 blockade or other immunostimulatory agents has shown potential in overcoming the immune-desert phenotype [5, 36]. Chemotherapy or radiation can also be employed to modulate the TME. Low-dose chemotherapy can reduce myeloid-derived suppressor cell (MDSC) populations or deplete regulatory T cells (Tregs), thereby potentially enhancing subsequent immunotherapy responses in TSG-mutant tumors enriched with immunosuppressive cell populations. Cytokine therapies (such as IL-2 or IL-15 agonists) might help expand effector lymphocytes in environments where TSG loss has diminished their numbers.

Another approach involves targeting metabolic and stromal pathways that contribute to immune suppression. For instance, tumors with PTEN or LKB1 loss often exhibit abnormal metabolism, such as high lactate production, which hampers T-cell function. In such cases, agents that normalize tumor metabolism—such as PI3K inhibitors, AMPK activators, or lactate transport inhibitors—may indirectly enhance immune cell persistence and functional activity within the TME [37,38]. Additionally, therapies targeting TME components such as fibrosis and blood vessels may promote immune cell infiltration. TSG-deficient tumors frequently exhibit elevated TGF- β production as a consequence of the loss of TGF- β pathway suppressors or p53, thereby promoting fibrosis and immune exclusion. TGF- β inhibitors, currently in trials, aim to dismantle these physical and chemical barriers and have been shown to increase T-cell penetration when combined with checkpoint blockers. Similarly, CSF-1R inhibitors can deplete TAMs, and IDO inhibitors can block tryptophan metabolism, thereby starving T cells. Both strategies aim to break down key immunosuppressive mechanisms in TSG-altered TMEs [3]. Although single-agent IDO inhibitors have encountered clinical setbacks, they nevertheless underscore the rationale for targeting immunosuppressive metabolites within the TME.

Finally, advanced cellular therapies are being explored, including CAR T-cell and TCR-engineered T-cell approaches designed to target neoantigens or aberrant proteins selectively expressed in TSG-mutant cancers. For example, tumors with mismatch repair deficiency resulting from epigenetic loss of MLH1 often express frameshift peptides that may serve as potential targets for CAR T-cell therapy. Moreover, adoptive cell transfer of tumor-infiltrating lymphocytes (TILs) might be more effective when combined with epigenetic reprogramming to prevent exhaustion. While these personalized strategies are complex, they aim to reset the immune-TME balance so that the patient's immune system can better suppress the tumor.

The most promising immunomodulatory strategies for TSG-deficient tumors involve combination approaches that pair immune checkpoint inhibitors with complementary agents, including cytokine blockers, metabolic modulators, or epigenetic therapies, which collectively target the underlying mechanisms driving immune evasion in these tumors [4,36]. Early clinical evidence suggests that multimodal therapeutic strategies will be required to convert immunologically resistant, TSG-deficient cancers into tumors that can be effectively controlled by the immune system.

6. Challenges and Future Directions

Despite advances in understanding and targeting the immune–epigenetic consequences of TSG loss, significant challenges remain. Tumors and their microenvironments show substantial interpatient and intratumoral heterogeneity, complicating the development of broadly applicable therapeutic strategies [1]. The TME consists of a dynamic mix of cell types (multiple immune subsets, fibroblasts, endothelial cells) that can vary across space and time [1]. TSG mutations add another layer of heterogeneity; for example, two TP53-deficient tumors may exhibit markedly different immune landscapes, with one displaying pronounced myeloid infiltration and the other presenting an immune-desert phenotype driven by distinct co-mutation patterns. This diversity means that therapies effective in one context may not work in another. An ongoing challenge is identifying reliable biomarkers that accurately reflect the state of the immune-epigenetic TME, such as gene expression signatures of T cell-inflamed versus non-inflamed tumors, or methylation profiles indicating loss of antigen presentation. Comprehensive multi-omics profiling, integrating genomics, epigenomics, transcriptomics, and proteomics, will likely be required to classify tumors according to specific patterns of TSG inactivation and associated TME characteristics. This stratification could guide personalized combinations, such as identifying which patients need an IL-34/CSF1R inhibitor added to immunotherapy (those with p53 loss and TAM infiltration), or which might benefit most from DNMT inhibitor priming (those with substantial TSG promoter methylation and low T-cell gene signatures).

Another challenge is the emergence of compensatory resistance mechanisms. Tumors are highly adaptable; when one immune-evasion pathway is inhibited, alternative mechanisms are often activated. A TSG-deficient tumor suppressed by a specific population (e.g., Tregs) might switch to a different mode (e.g., upregulating alternative checkpoints or recruiting other suppressor cells) once Tregs are depleted. Similarly, epigenetic therapies may exert off-target effects and induce tumor plasticity, whereby transient re-expression of specific genes is followed by their re-silencing through alternative epigenetic mechanisms. The timing, dosing, and sequencing of combination therapies (such as immunotherapy with epigenetic modulators) need to be optimized to reduce adaptive resistance. There are also important safety considerations. Broad reactivation of silenced genes by epigenetic therapies may impact normal tissues, while widespread immune activation can increase the risk of autoimmune-related adverse effects. Balancing effectiveness with tol-

erability remains a key concern, especially when considering multi-agent regimens.

Furthermore, a persistent gap remains between pre-clinical efficacy and clinical translation. While murine models often demonstrate pronounced therapeutic responses, including complete tumor regression with combined epigenetic priming and immune checkpoint blockade, clinical outcomes in human trials have been considerably more variable and less consistent. Therefore, moving from a descriptive understanding to a predictive clinical model requires rigorous investigation into optimal dosing, sequential timing, and the precise biomarker landscapes that dictate patient-specific responses.

From a therapeutic development perspective, a key limitation of TSG-targeted strategies lies in the nature of TSG loss itself, which is often not directly druggable, as missing or inactivated proteins cannot readily be restored using conventional small-molecule approaches. Therefore, therapeutic approaches often rely on indirect strategies, as discussed above, which may not fully recapitulate the complete tumor-suppressive functions of the lost gene. Gene-therapy and gene-editing approaches aimed at restoring TSG function, including CRISPR-based gene correction, remain largely experimental. Nevertheless, these strategies hold considerable transformative potential in the long term, provided that current technical challenges can be overcome. In the near term, engineering immune cells to better handle the suppressive TME is a promising approach. For example, researchers are exploring the development of CAR T cells resistant to TGF- β or adenosine by knocking out the relevant receptors, which could render them effective even in TSG-loss TMEs rich in these suppressive factors.

Finally, the complexity of conducting trials with multi-component therapies presents a practical challenge. The large number of potential therapeutic combinations makes it difficult to evaluate all rational strategies in clinical settings. Accordingly, robust preclinical models that faithfully recapitulate the immune and epigenetic landscape of TSG-deficient human tumors are essential for prioritizing and refining candidate approaches. Mouse models with specific TSG knockouts, such as TP53-null or PTEN-null tumors, have been invaluable for mechanistic studies; however, species-specific differences between murine and human immune systems can limit the translational relevance of these findings. Advanced models, such as organotypic cultures, humanized mice, or systems biology simulations, may help predict the most effective strategies to advance to clinical trials.

Addressing TSG loss in cancer requires a nuanced, personalized approach that targets both the inherent vulnerabilities of cancer cells and the external support from the

reprogrammed microenvironment. Although challenges related to heterogeneity, adaptive resistance, and safety remain substantial, they may be addressed through continued research and innovative clinical trial designs. The field is increasingly equipped with tools such as single-cell omics, CRISPR screens, and computational modeling to analyze immune-epigenetic interactions and identify key intervention points. The insights gained will not only benefit patients with TSG-deficient tumors but also inform broader strategies for converting immunologically “cold” tumors into “hot,” therapy-responsive phenotypes.

7. Conclusions

TSG loss is a central feature of some of the most therapy-resistant cancers, largely due to the immune evasion and epigenetic reprogramming it drives. The inactivation of these genes often establishes a microenvironment that promotes tumor progression by suppressing antitumor immune responses and facilitating adaptation through epigenetic plasticity. Addressing this issue requires an integrated treatment strategy. As highlighted in this review, current research efforts are increasingly focused on integrated therapeutic strategies, including the combination of immune checkpoint inhibitors with epigenetic agents to target alternative dependencies in TSG-deficient cells while reactivating suppressed immune pathways, as well as harnessing the immune system to compensate for the loss of tumor suppressor function. Early results from these methods are promising and suggest new therapeutic avenues at the intersection of tumor genetics, epigenetics, and immunology. In the future, a more comprehensive understanding of the immune–epigenetic landscape of individual tumors will facilitate the development of precision therapeutic strategies, including the customization of treatment combinations based on specific TSG alterations and TME characteristics. By reactivating silenced tumor-suppressive pathways where possible, exploiting synthetic lethal vulnerabilities, and restoring immune surveillance, integrated therapeutic strategies may achieve more durable tumor control. Success in this endeavor would represent a significant advancement in translating molecular insights into TSG biology into meaningful clinical benefits for patients. Although considerable challenges remain, multidisciplinary efforts spanning genomics, immunology, and epigenetics are rapidly uncovering novel therapeutic opportunities.

List of Abbreviations

AKT	Protein Kinase B
AMPK	AMP-Activated Protein Kinase

ARID1A	AT-Rich Interaction Domain 1A	PBRM1	Polybromo-1
ARID2	AT-rich Interaction Domain 2	PRC2	Polycomb Repressive Complex 2
ATR	Ataxia Telangiectasia and Rad3-Related	PTEN	Phosphatase and Tensin Homolog
B2M	Beta-2-Microglobulin	RCC	Renal Cell Carcinoma
BAP1	BRCA1-Associated Protein 1	RB1	Retinoblastoma 1
BET	Bromodomain and Extra-Terminal domain	SMARCA4	SWI/SNF related, Matrix-associated, Actin-dependent Regulator of Chromatin Subfamily A member 4
BRCA1/2	Breast Cancer Gene 1/2	STK11	Serine/threonine Kinase 11 (also LKB1)
CAR	Chimeric Antigen Receptor	SWI/SNF	SWItch/Sucrose Non-Fermentable
Cas9	CRISPR-Associated Nuclease 9	TAM	Tumor-Associated Macrophage
CD4	Cluster of Differentiation 4	TCR	T-cell Receptor
CD8	Cluster of Differentiation 8	TGF- β	Transforming Growth Factor Beta
CDKN2A	Cyclin-Dependent Kinase Inhibitor 2A (p16)	TIL	Tumor-Infiltrating Lymphocyte
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats	TME	Tumor Microenvironment
CSF-1R	Colony-Stimulating Factor 1 Receptor	TP53	Tumor Protein p53
CTL	Cytotoxic T Lymphocyte	TRAIL	TNF-Related Apoptosis-Inducing Ligand
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4	Treg	Regulatory T cell
		TSG	Tumor Suppressor Gene
CXCL9	C-X-C Motif Chemokine Ligand 9	Author Contributions	
CXCL10	C-X-C Motif Chemokine Ligand 10	Conceptualization: S.C.; Methodology: N.F. and S.C.; Investigation: N.F., A.D. and S.C.; Writing—original draft preparation: N.F. and S.C.; Writing—review and editing: N.F., A.D. and S.C.; Visualization: N.F. and S.C.; Supervision: S.C. All authors have read and agreed to the published version of the manuscript.	
CYLD	Cylindromatosis Gene	Conflicts of Interest	
DNMT	DNA Methyltransferase	S.C. serves as Chief Scientific Advisor for Regenova Pharmaceuticals and is a co-founder of Bespoke Patient Solutions, LLC, the platform company for the Pocket Patient Advocate healthcare application. These affiliations did not influence the conception, content, analysis or interpretation of this review. The remaining authors declare no competing interests.	
DNA	Deoxyribonucleic Acid	Funding	
EZH2	Enhancer of Zeste Homolog 2	The study did not receive any external funding and was conducted using only institutional resources.	
HDAC	Histone Deacetylase	Acknowledgments	
HDACi	Histone Deacetylase Inhibitor	The authors thank the Chan Soon-Shiong Institute for Molecular Medicine at Windber for institutional support.	
ICI	Immune Checkpoint Inhibitor	AI Declaration	
IDO	Indoleamine 2,3-Dioxygenase	Portions of this manuscript were refined using AI-assisted tools (e.g., ChatGPT Plus with data sharing disabled and Grammarly). No AI-generated content was used without verification. All data interpretation and conclusions are original to the authors.	
IL-2	Interleukin-2		
IL-10	Interleukin-10		
IL-15	Interleukin-15		
IL-34	Interleukin-34		
KRAS	Kirsten Rat Sarcoma Viral Oncogene Homolog		
LKB1	Liver kinase B1 (also STK11)		
MDSC	Myeloid-Derived Suppressor Cell		
MHC	Major Histocompatibility Complex		
MLH1	MutL Homolog 1		
MSI-H	Microsatellite Instability-High		
mTOR	Mechanistic Target of Rapamycin		
NF1	Neurofibromin 1		
NF- κ B	Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells		
NKG2D	Natural Killer Group 2, Member D		
NK cell	Natural Killer Cell		
NSCLC	Non-Small Cell Lung Cancer		
PARP	Poly(ADP-ribose) Polymerase		
PD-1	Programmed Cell Death Protein 1		
PD-L1	Programmed Death-Ligand 1		
PI3K	Phosphoinositide 3-Kinase		

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