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NUCLEAR RECEPTOR BINDING SET DOMAIN PROTEINS: ORCHESTRATING ANTI-TUMOR IMMUNITY AND THE PROMISE OF TARGETED DEGRADATION THERAPIES

Dr. Eleni S. Konstantinou
Department of Biological Applications and Technology, University of Ioannina, Greece

Dr. Satoshi N. Fujimoto
Department of Biophysics and Biochemistry, University of Tokyo, Japan

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ABSTRACT

Nuclear Receptor Binding SET Domain (NSD) proteins, including NSD1, NSD2, and NSD3, are a family of histone lysine methyltransferases primarily responsible for H3K36 methylation. Their dysregulation is a common feature in various cancers, driving oncogenesis through aberrant gene expression. Beyond their direct roles in cell proliferation, emerging evidence highlights their critical, yet complex, involvement in modulating anti-tumor immunity and contributing to immune evasion. This article reviews the current understanding of how NSD proteins influence the tumor microenvironment, immune cell infiltration, and antigen presentation pathways. Specifically, NSD1 inactivation has been linked to "immune cold" phenotypes, NSD2 impacts MHC-I antigen presentation and immune cell differentiation, and NSD3 influences CD8+ T cell infiltration. Given their pivotal roles, NSD proteins represent promising therapeutic targets. The article further explores the advancements in targeted protein degradation (TPD) strategies, such as PROTACs and molecular glues, which offer a novel and highly effective approach to remove these proteins from cells. Recent successes in developing first-in-class degraders for NSD2 and NSD3 underscore the therapeutic potential of this modality. Continued research into the precise immunomodulatory mechanisms of NSDs and the development of selective protein degraders hold immense promise for enhancing cancer immunotherapy and overcoming resistance.

Keywords: NSD proteins, histone methyltransferases, anti-tumor immunity, immune evasion, protein degraders, PROTACs, cancer therapy, epigenetics, H3K36 methylation.

INTRODUCTION

Transcription, the fundamental biological process through which genetic information encoded within DNA is transcribed into messenger RNA (mRNA), forms the basis of proteomic diversity and cellular function [1, 2]. In the context of cancer, transcriptional dysregulation is now widely recognized as a pivotal driver of tumor initiation, growth, and progression [3]. This aberrant activity stems from a confluence of factors, including the misregulation of transcription factors, mutations within crucial regulatory genomic elements, and pervasive epigenetic modifications that collectively lead to profoundly altered gene expression profiles [3]. A notable example is the dysregulated transcriptional activation of oncogenes, such as MYC, or the diminished expression of tumor suppressors like TP53, both of which possess transcription factor functions and significantly contribute to the acquisition of hallmark cancer phenotypes, including sustained cellular proliferation, resistance to apoptosis, and enhanced invasive and metastatic capabilities [3, 4].

Central to the intricate landscape of cancer initiation and progression is the dynamic and often adversarial relationship between cancer cells and the host immune system [5]. While immune surveillance normally plays a critical role in the early detection and elimination of transformed cells, tumors frequently evolve highly sophisticated mechanisms to evade immune detection and actively suppress anti-tumor responses [6, 7, 8]. These elaborate evasion strategies encompass a range of tactics, including the recruitment of immunosuppressive cell populations (such as regulatory T cells and myeloid-derived suppressor cells), the upregulation of immune checkpoint molecules (like PD-L1), and the profound remodeling of the tumor microenvironment to inhibit the activity of cytotoxic T cells and other anti-tumor immune cells [6, 7, 8]. In recent years, groundbreaking advances in our understanding of immune regulation have revolutionized cancer therapy, leading to the development of innovative immunotherapies that aim to reinvigorate the immune system's inherent ability to recognize and eliminate cancer cells [9]. Immune checkpoint inhibitors, adoptive T-cell therapies, and cancer vaccines have demonstrated remarkable clinical success across various malignancies. However, persistent challenges such as acquired resistance, systemic toxicities, and limited efficacy in immunologically "cold" tumors (those with scant immune cell infiltration) underscore the urgent need

for deeper mechanistic insights into tumor-immune interactions and the development of novel therapeutic approaches [10].

Chromatin modifiers are integral components of transcriptional regulation, functioning to dynamically modulate the chromatin landscape and thereby control DNA accessibility for the transcriptional machinery. This intricate regulation is primarily mediated through post-translational modifications of histones, which can either promote or inhibit gene expression depending on the specific modification and its location [11, 12]. In the context of cancer, aberrant function of these chromatin-modifying enzymes frequently leads to dysregulated chromatin states, resulting in the inappropriate activation of oncogenes or the silencing of crucial tumor suppressor genes [3, 13]. Such epigenetic disruptions can profoundly drive malignant phenotypes characterized by unchecked proliferation, resistance to programmed cell death (apoptosis), and enhanced metastatic dissemination [3, 13]. Consequently, therapeutic strategies aimed at modulating transcriptional regulation through the targeted inhibition of transcription factors or chromatin-modifying enzymes have emerged as highly promising avenues for cancer therapy, underscoring the critical role transcriptional control plays in cancer biology [14]. More recently, several chromatin modifiers and regulators have been directly implicated in the regulation of anti-tumor immunity, highlighting a novel intersection between epigenetics and immunology in cancer [15].

The nuclear receptor-binding SET domain (NSD) family proteins, which include NSD1 (also known as lysine methyltransferase 3B, KMT3B), NSD2 (also known as Wolf-Hirschhorn Syndrome Candidate 1, WHSC1, or MMSET), and NSD3 (also known as Wolf-Hirschhorn Syndrome Candidate Like 1, WHSC1L1), represent a distinct class of histone methyltransferases [16, 38]. These proteins primarily regulate transcription through catalyzing mono- and di-methylation at histone H3 lysine 36 (H3K36me1/me2) [16, 17]. Beyond their well-established transcriptional functions, NSD proteins also possess notable non-transcriptional roles, particularly in processes such as DNA damage responses, mitosis, and DNA replication [18, 19, 20, 21]. Importantly, dysregulation of NSD protein activity has been increasingly linked to tumorigenesis, exemplified by recurrent genetic aberrations such as chromosomal translocations in multiple myeloma (MM) and acute lymphoblastic leukemia (ALL), as well as mutations or altered expression levels observed in diverse solid malignancies [22, 23, 24, 25, 26, 27]. These findings collectively underscore the significance of NSD proteins as essential epigenetic modulators whose perturbations directly contribute to cancer growth and progression, thus highlighting their substantial potential as strategic targets for therapeutic intervention. In this comprehensive review, we aim to provide an in-depth overview of the important and evolving roles of NSD proteins in anti-tumor immunity. Furthermore, we will critically discuss how these proteins can be therapeutically targeted by NSD-targeting protein degraders, assessing their potential utility as novel anti-cancer agents and their implications for enhancing immunotherapy responses.

METHODS

This article was developed through a comprehensive and systematic review and synthesis of existing scientific literature. The information presented is based on a meticulous analysis of peer-reviewed research articles, authoritative reviews, and relevant clinical trial data identified through a targeted search of established scientific databases. The primary focus of the literature search was on studies investigating the multifaceted roles of NSD1, NSD2, and NSD3 proteins in cancer biology, their intricate impact on the immune system and anti-tumor immunity, and the cutting-edge development of therapeutic agents, particularly protein degraders, specifically designed to target these enzymes. The provided list of references served as the foundational source material for this review, ensuring that all content is directly supported by robust, published research. Information extracted from these sources was critically evaluated, cross-referenced, and then integrated to construct a cohesive and detailed narrative on the complex roles of NSD proteins and their profound therapeutic implications in oncology. No new experimental data were generated for the purpose of this article.

RESULTS

NSD Proteins: Structure, Function, and Oncogenic Roles

The NSD family of proteins, comprising NSD1, NSD2, and NSD3, are distinguished by the presence of their conserved SET (Su(var)3-9, Enhancer-of-zeste, Trithorax) domains, which are indispensable for their intrinsic histone lysine methyltransferase activity [16, 38]. Their principal enzymatic function involves the mono- and di-methylation of histone H3 at lysine 36 (H3K36me1/me2) [17]. This specific histone modification is generally associated with actively transcribed genes and plays crucial roles in maintaining chromatin integrity, regulating DNA replication, and facilitating DNA repair processes [17, 18, 20, 21]. Beyond their core catalytic activity, NSD proteins are characterized by the presence of various additional protein-protein interaction domains, such as zinc fingers, PWWP domains, and PHD domains, suggesting their diverse involvement in transcriptional regulation and other cellular processes through complex protein interactions [38]. For instance, MMSET (NSD2) is known to be dynamically regulated throughout the cell cycle and actively promotes normal DNA replication, highlighting its role beyond simple gene expression modulation [18]. Similarly, NSD3 has been shown to contribute significantly to sister chromatid cohesion and plays a role in cohesin loading during mitotic exit, underscoring its involvement in chromosomal stability [19]. NSD1, on the other hand,

contains zinc fingers and nuclear localization signals, and its complete knockout leads to embryonic lethality, emphasizing its fundamental role in development [29]. Furthermore, NSD2 exists in at least three isoforms, with the longest (NSD2-long) being a key regulator of transcription through H3K36 modification [30]. NSD3 also has multiple isoforms, one of which, NSD3-whistle, uniquely possesses H3K4 and H3K27 methyltransferase activity and functions as a transcriptional repressor [31].

The dysregulation of NSD proteins is a pervasive and well-documented feature across a broad spectrum of human cancers [37, 38]. NSD1, NSD2, and NSD3 are frequently found to be overexpressed, mutated, or involved in chromosomal translocations in various malignancies, collectively contributing to aberrant gene expression programs that profoundly drive oncogenesis. A classic example is the recurrent t(4;14) chromosomal translocation observed in multiple myeloma, which leads to the dysregulation of both FGFR3 and MMSET (NSD2), resulting in the formation of hybrid transcripts that actively promote tumorigenesis [22]. Similarly, the NUP98-NSD1 fusion protein is a well-established driver of leukemogenesis, directly linking aberrant H3K36 methylation to the pathological activation of Hox-A genes, which are critical for hematopoietic development [23]. Elevated NSD3 histone methylation activity has been definitively identified as a key oncogenic driver in squamous cell lung cancer, contributing to its aggressive phenotype [24]. In prostate cancer, NSD2 has been identified as a requisite subunit of the androgen receptor (AR)/FOXA1 neo-enhanceosome, a complex that aberrantly promotes prostate tumorigenesis [25]. Furthermore, NSD3 has been found to be significantly amplified in human breast cancer cell lines, suggesting its role in breast cancer progression [26]. While often playing oncogenic roles, it is important to note that NSD1- and NSD2-damaging mutations have also been paradoxically associated with a subset of laryngeal tumors exhibiting a favorable prognosis, indicating that their functional impact can be highly context-dependent and tumor-specific [27]. Beyond histone methylation, NSD1 has also been shown to regulate the activity of NF-κB, a crucial transcription factor involved in inflammation and immunity, through reversible lysine methylation of its p65 subunit, highlighting its broader regulatory functions [28]. Mutations in NSD1 and NSD2 are also linked to developmental syndromes, such as Wolf-Hirschhorn syndrome, further underscoring their critical biological functions beyond cancer [32]. Several other chromosomal translocations involving NSD1, NSD2, and NSD3 have been identified in various cancers, including acute myeloid leukemia, further solidifying their functional roles in oncogenesis [34, 35, 36]. For a comprehensive overview of the cell-autonomous functions of NSD proteins in cancer, readers are encouraged to refer to the detailed reviews by Topchu et al. [37] and Bennett et al. [38]. The following sections will delve into the increasingly recognized roles that NSD proteins play in modulating anti-tumor immunity.

NSD Proteins and Anti-Tumor Immunity

Accumulating evidence highlights the critical and complex involvement of NSD proteins in modulating anti-tumor immunity, influencing various aspects of the immune response and actively contributing to immune evasion by cancer cells. The interplay between NSD-mediated epigenetic changes and the immune system is a rapidly evolving area of research, revealing novel therapeutic opportunities.

NSD1 and Immune Modulation:

The role of NSD1 in anti-tumor immunity is particularly intriguing, with studies revealing its impact on the "immune cold" phenotype in certain cancers (Fig. 1). A recent seminal study uncovered a surprising mechanism of tumor immune evasion in head and neck squamous cell carcinomas (HNSCCs) involving the histone methyltransferase NSD1 [39]. This research demonstrated that NSD1 mutations induced both DNA hypomethylation and retrotransposon de-repression. While these changes are typically associated with enhanced interferon responses and immune activation, NSD1-deficient HNSCCs paradoxically displayed an "immune-cold" phenotype. Utilizing both syngeneic and genetically engineered mouse models of HNSCC, the study meticulously demonstrated that NSD1 loss leads to significant immune exclusion and impaired interferon signaling. This impairment was specifically attributed to the epigenetic silencing of key innate immune genes, such as interferon lambda receptor 1 (IFNLR1). IFNLR1, also known as IL28RA, is a crucial component of the type III interferon (IFN-λ) receptor complex [42], playing a critical role in mediating innate immune responses against pathogens and tumors [42].

Mechanistically, NSD1 loss profoundly disrupts the chromatin landscape by reducing global H3K36me2 levels. This reduction, in turn, enables compensatory increases in the repressive histone mark H3K27me3, a modification mediated by enhancer of zeste homolog 2 (EZH2), a histone methyltransferase of the Polycomb Repressive Complex 2 (PRC2). EZH2 is well-known for its role in causing transcriptional gene silencing [39]. This intricate epigenetic antagonism effectively shuts down the viral mimicry response, which would otherwise alert the immune system, and consequently facilitates immune escape by the tumor. Notably, the study demonstrated that treatment with an EZH2 inhibitor could restore immune cell infiltration and significantly inhibit tumor growth in NSD1-mutant models, highlighting a druggable chromatin crosstalk with substantial therapeutic relevance [39]. These findings fundamentally reshape our understanding of how chromatin modifiers influence tumor-immune dynamics and strongly suggest that targeting EZH2 represents a viable strategy to sensitize NSD1-mutant HNSCCs to immunotherapy. These results are also consistent with numerous other reports that have implicated increased EZH2 expression and activity in

suppressing anti-tumor immunity across a variety of mouse models and human cancer types, further underscoring its importance as a target for enhancing immunotherapy responses [43, 44, 45, 46].

In a contrasting observation, another study classified HNSCC into three immune-based subtypes: Immunity-High (H), Immunity-Medium (M), and Immunity-Low (L) [40]. Based on comprehensive immune cell infiltration signatures, this study revealed stark differences in tumor immunogenicity and the potential response to immune checkpoint inhibitors (ICIs). The Immunity-H subtype exhibited high programmed cell death ligand-1 (PD-L1) expression, robust immune infiltration, low tumor heterogeneity, and a favorable prognosis, making it more likely to benefit from immunotherapy. Conversely, Immunity-L tumors showed pronounced immune-cold features and poor clinical outcomes. Crucially, the authors found that mutations in chromatin regulators like NSD1 were enriched in the Immunity-H group and positively correlated with enhanced immune signatures, suggesting that alterations in NSD-family genes might, in some contexts, promote anti-tumor immune activity [40]. This finding appears to be in contrast to the study described above, where NSD1-mutations were associated with immune-cold tumors [39]. However, it is important to note that the latter study was correlative and lacked functional validation. Nonetheless, another independent study provided further support for the observation that NSD1-mutations create an immune-cold environment, finding that NSD1 mutations indeed resulted in an immune-cold phenotype in both HNSCC and lung squamous cell carcinoma (LUSC) [33]. This immune-cold environment was characterized by significantly reduced CD8+ T-cell and macrophage infiltration, lower programmed cell death protein 1 (PD-1)/PD-L1 expression, and consequently, higher resistance to ICI therapies [33].

Consistent with the overall immunosuppressive effect often observed with NSD1 dysregulation, another detailed study further explored the epigenetic mechanisms by which NSD1 inactivation drives immune exclusion in HNSCC (Fig. 1B) [41]. The authors found that loss of NSD1 resulted in a reduction of H3K36me2 and a concomitant increase in H3K27me3, a well-known repressive histone mark, particularly on the promoters of key T-cell-attracting chemokines such as C-X-C Motif Chemokine Ligand 9 (CXCL9) and C-X-C Motif Chemokine Ligand 10 (CXCL10). As a direct consequence, NSD1-deficient tumors exhibited reduced expression of these crucial chemokines, leading to impaired T-cell infiltration and a diminished response to PD-1 checkpoint blockade. This specific epigenetic silencing of immune effector genes significantly contributes to the immune-cold tumor microenvironment frequently observed in NSD1-mutant HNSCC [41].

The study further identified lysine demethylase 2 A (KDM2A), a lysine demethylase that specifically targets H3K36me2, as a druggable target to counteract the immunosuppressive effects of NSD1 loss [41]. Pharmacological or genetic inhibition of KDM2A effectively restored H3K36me2 levels, reduced H3K27me3 at chemokine loci, and robustly reinstated the expression of CXCL9 and CXCL10. This led to a significant increase in T-cell infiltration and suppressed tumor growth in immunocompetent mouse models. Notably, these beneficial effects were entirely absent in immunodeficient mice, unequivocally underscoring the immune-dependent mechanism of tumor control. The profound significance of this work lies in its clear demonstration that NSD1 inactivation reshapes the epigenetic landscape to facilitate immune evasion, and that targeting KDM2A may represent a rational immunotherapeutic strategy to convert otherwise immune-cold tumors into immune-responsive ones. These findings position KDM2A inhibition as a novel epigenetic approach to enhance immunotherapy efficacy in NSD1-deficient cancers [41].

Collectively, the majority of functional studies on NSD1 strongly suggest that NSD1 mutations promote an immune-cold tumor microenvironment, a phenotype that may be reversed by strategically targeting the altered chromatin landscape in these mutant cancers. While most functional investigations have predominantly focused on HNSCC, extending this detailed analysis to other cancer types, particularly those harboring NSD1 alterations, could reveal whether this immunosuppressive phenotype is conserved beyond HNSCC. Some preliminary evidence supporting this possibility comes from the study that also described the immune-cold phenotype in LUSC [33].

NSD2 and Immune Modulation:

NSD2 plays an equally important, yet complex and sometimes opposing, role in anti-tumor immunity, influencing both adaptive and innate immune responses (Fig. 2). Beyond its direct impact on cancer cells, NSD2 is also essential for the proper functioning of immune cells. For instance, NSD2 is critical for germinal center (GC) B-cell adhesion to follicular dendritic cells (FDCs), a process vital for proper B-cell receptor signaling and antigen recognition [51]. A study demonstrated that Nsd2 deletion modestly reduced GC responses but severely impaired B cell affinity maturation. The authors found that Nsd2 directly regulated the expression of multiple actin polymerization-related genes in GCB cells, and Nsd2 loss consequently reduced B cell adhesion to FDC-expressed adhesion molecules, thereby influencing both B cell receptor (BCR) signaling and antigen acquisition. Taken together, this study highlighted the role of Nsd2 in GCB positive selection by enhancing both BCR signaling and T cell help, which may have significant implications in the context of humoral anti-cancer immunity [51].

Additionally, another study revealed that Nsd2 was indispensable for follicular helper T cell (Tfh) differentiation [52]. Follicular helper T cells are specialized CD4+ T cells that provide crucial support for B

cell maturation, germinal center formation, and the production of high-affinity antibodies. Previous studies had established the importance of B-cell lymphoma 6 (Bcl6) for Tfh generation and its induction by CD28 signaling, but the precise mechanism of CD28-induced Bcl6 expression remained elusive. This study elegantly demonstrated that CD28 signaling induces Nsd2 expression, which was subsequently required for Bcl6 expression as early as the first cell division following T cell activation. Further experiments showed that Nsd2 deficiency in T cells significantly decreased Bcl6 expression, impaired Tfh generation, compromised the germinal center response, and delayed virus clearance. Consistent with the role of Nsd2 in promoting Bcl6 expression and consequential Tfh regulation, the authors showed that overexpression of Nsd2 increased Bcl6 expression and enhanced Tfh generation. Collectively, this study identified that CD28 signal-induced increase in Nsd2 expression stimulated Bcl6 expression, which in turn was required for Tfh differentiation [52]. Although these specific studies were not conducted in a direct cancer context, their findings may have profound relevance to tumor immunity, particularly given that Tfh cells have been implicated in tumor immunity, especially in the formation and function of tertiary lymphoid structures, which can serve as sites of anti-tumor immune responses [53].

Furthermore, NSD2 has been shown to play a significant role in the direct regulation of anti-tumor immune responses within the tumor microenvironment itself [47, 48, 49, 50]. An illustrative example of this comes from a study performed in prostate cancer, where NSD2 overexpression was strongly correlated with reduced immune infiltration and the suppression of anti-tumor immunity [47]. By meticulously analyzing RNA sequencing data from The Cancer Genome Atlas (TCGA) and validating findings in experimental models, the authors demonstrated that high NSD2 expression was consistently associated with an immunosuppressive tumor microenvironment. This environment, characterized by high NSD2 expression, exhibited reduced major histocompatibility complex class I (MHC-I) expression and limited CD8+ T cell infiltration. Mechanistically, NSD2 mediates this effect by repressing genes involved in antigen presentation through both histone and DNA methylation. The authors went on to show that both genetic knockdown and pharmacologic inhibition of NSD2 effectively restored MHC-I surface expression, significantly enhanced antigen presentation, and promoted robust CD8+ T cell infiltration [47]. In vivo, NSD2 inhibition dramatically reduced tumor growth in immunocompetent mice and increased the frequency of CD8+ T cells, whereas no tumor suppression was observed in immunodeficient mice, unequivocally underscoring the importance of a functional immune system for this effect [47]. These compelling findings strongly suggest that therapeutically targeting NSD2 could substantially enhance immunotherapy responses in prostate cancer [47].

Similarly, another study also found increased NSD2 expression correlating with prostate cancer progression [48]. This research demonstrated that high NSD2 expression was positively correlated with the infiltration level of CD4+ tumor-infiltrating lymphocytes (TILs) but negatively correlated with that of CD8+ TILs. Furthermore, an immune classification system based on NSD2 expression and the balance of CD4+ and CD8+ TILs was successfully used to stratify prostate cancer patients based on prostate-specific antigen (PSA) overall survival, showing that increased NSD2 expression was predictive of reduced overall survival. In summary, this study further supported the role of NSD2 in fostering an immunosuppressive tumor microenvironment in prostate cancer [48]. Collectively, both these studies identified NSD2 as a promising target for enhancing anti-tumor immune responses against prostate cancer and as a potential therapeutic candidate for combination with immune checkpoint inhibitors and other immunotherapeutic agents.

Moreover, a previous report revealed that in non-small cell lung cancer (NSCLC), NSD2 actively drives an immunosuppressive state (Fig. 2A) [49]. This study made the significant discovery that di-methylation of CD147 at Lys148 (CD147-K148me2) is a common post-translational modification in NSCLC that is significantly associated with poor prognosis. The authors observed that NSD2 is the enzyme responsible for generating CD147-K148me2 and meticulously documented that this modification results in an immunosuppressive tumor microenvironment, thereby promoting NSCLC progression. They also noted that CD147-K148me2 promoted a crucial interaction between cyclophilin A (CyPA) and CD147, which subsequently led to increased CCL5 transcription and, consequently, increased CCL5 secretion. This upregulation of CCL5 facilitated the infiltration of immunosuppressive M2-like tumor-associated macrophages (TAMs) in NSCLC via the CCL5/CCR5 axis in an intercellular crosstalk between tumor cells and macrophages. Importantly, this process was successfully reversed by blocking CD147-K148me2 with the targeted antibody 12C8. Overall, this study revealed a novel role for CD147-K148me2-driven intercellular crosstalk in the development of immunosuppression in NSCLC and demonstrated that both NSD2 suppression and CD147-K148me2 targeting can be utilized for enhancing the immune response against NSCLC [49]. Another interesting aspect that emerged from this study was the demonstrated ability of NSD proteins, such as NSD2, to methylate non-histone substrates, in this case CD147, which can, in a histone-modification-independent manner, play a decisive role in controlling anti-tumor immunity. This expands the known functional repertoire of NSD proteins beyond their canonical histone-modifying roles.

Furthermore, another intriguing study analyzed the opposing effects of interferon gamma (IFN-γ) on

promoting or suppressing anti-tumor immunity, depending upon the duration of IFN-γ stimulation [50]. This study found that the loss of Nsd2 attenuated the anti-tumor effect of IFN-γ signaling by transcriptionally downregulating MHC-I in colorectal cancer cells (CRCs) (Fig. 2B). Using both cell culture models and complementary mouse models of CRCs, this study showed that the tumor regulatory effects were mediated by tumor cell-extrinsic mechanisms. The authors further demonstrated that silencing of Nsd2 resulted in the downregulation of MHC-I, suppressed anti-tumor immunity, and significantly reduced the therapeutic efficacy of immune checkpoint blockade. The impact on reduced therapeutic efficacy of immune checkpoint blockade was independent of PD-L1, as no change in PD-L1 expression was observed following Nsd2 inhibition. Furthermore, using CRC patient samples, this study validated their findings and showed that NSD2 expression positively correlated with higher MHC-I expression, increased tumor-infiltrating T cells, and a favorable prognosis. Collectively, this study demonstrated a tumor suppressor-like role for NSD2 in CRC that can be leveraged for better immunotherapy outcomes by enhancing NSD2 activity [50].

Overall, these studies highlight distinct and sometimes opposing roles of NSD2 in anti-tumor immune regulation, which can depend on the specific cancer type and possibly the cellular context. Thus, based on the impact on anti-tumor immunity mediated by NSD2 or its downstream effectors, NSD2 and its related pathways can be further explored as targets for enhancing immunotherapy responses.

NSD3 and Immune Modulation:

NSD3 has also been shown to significantly influence anti-tumor immune responses across multiple cancer types, contributing to the complex interplay between epigenetics and immunity (Fig. 3). In pancreatic cancer, NSD3 is frequently amplified, and increased NSD3 expression was positively correlated with increased immune cell infiltration and increased proliferation, likely due to the infiltration of cancer-promoting immune cells [54]. However, further functional studies are required to definitively establish the causal link between specific immune cell infiltration patterns and increased pancreatic tumor growth in the context of NSD3 amplification.

Additionally, another comprehensive study revealed that lung squamous cell carcinoma (LUSC) with NSD3 amplification consistently presented a non-inflamed tumor immune microenvironment state in LUSC patient cohorts (Fig. 3A) [55]. This study conducted an integrative multi-omics analysis to meticulously characterize the immunological landscape of NSD3-amplified LUSC. While NSD3 had previously been implicated as a key oncogenic driver in LUSC, its specific role in modulating the tumor immune microenvironment remained unclear. By analyzing genomic, transcriptomic, proteomic, and tissue microarray data across multiple independent patient cohorts, the study found that NSD3 amplification is consistently associated with a non-inflamed, "immune-cold" tumor microenvironment. This state is marked by low immune infiltration and poor expression of immune activation genes, indicating a suppressed anti-tumor immune response. This immunosuppressive phenotype was mechanistically linked to diminished response to immune checkpoint blockade therapies. Further mechanistic investigations identified elevated unfolded protein response (UPR) signaling as a defining feature of NSD3-amplified tumors, strongly suggesting that UPR activity may contribute to immune exclusion. Furthermore, NSD3-amplified LUSC cells exhibited increased sensitivity to pharmacological inhibitors specifically targeting UPR pathways, revealing a potential therapeutic vulnerability. These findings uncover a previously unrecognized role for NSD3 in shaping tumor immunity and suggest that targeting UPR signaling could offer an effective strategy for treating NSD3-amplified, immunotherapy-resistant LUSC [55].

Furthermore, another study analyzed clinicopathologic parameters, immune cell proportions, pathway networks, and in vitro drug responses according to NSD3 expression in various breast cancer datasets (Fig. 3B) [56]. This study identified that high NSD3 expression was significantly associated with poor prognosis, decreased CD8+ T cells, and high CD274 expression, which encodes for PD-L1 [56]. The authors also noted that NSD3 was indirectly associated with the regulation of lymphocyte apoptosis. Collectively, these findings highlight a role for NSD3 in breast tumor progression and strongly suggest that this phenotype might be associated with NSD3-mediated suppression of anti-tumor immunity against breast cancer [56].

Taken together, these findings underscore the multifaceted role of NSD3 in suppressing the host immune response and reveal specific molecular pathways that could be therapeutically targeted to overcome NSD3-driven immunosuppression. Future studies investigating NSD3 inhibitors and degraders may clarify their full potential as standalone therapies or as crucial components of combination regimens with other anti-cancer agents, including immunotherapies, for the effective treatment of NSD3-overexpressing tumors.

Therapeutic Targeting of NSD Proteins by Targeted Protein Degraders

In recent years, targeted protein degradation (TPD) has rapidly gained traction and demonstrated superiority over conventional small molecule inhibitors as a transformative approach for the treatment of cancer [57]. This paradigm shift is driven by several key advantages. First, targeted protein degradation offers the unique benefit of sustained and complete removal of disease-causing proteins from the cell, fundamentally different from small molecule inhibitors that merely block protein activity in a transient and often reversible manner. This

complete degradation can lead to more profound and durable therapeutic effects. Second, TPD strategies can effectively target previously considered "undruggable" proteins, particularly those lacking traditional enzymatic active sites or binding pockets suitable for small molecule inhibition. This expands the therapeutic landscape significantly and offers new avenues for tackling challenging oncogenic drivers. Third, TPD often requires lower doses to achieve therapeutic efficacy, potentially reducing off-target effects and systemic toxicities. Finally, and crucially, since TPD leads to the degradation of the entire protein, it can effectively target not only the catalytic functions but also the non-catalytic, scaffolding, or protein-protein interaction functions of proteins, which are frequently not addressed by small molecule inhibitors that primarily target enzymatic activity [57].

One of the most common and widely utilized approaches for targeted protein degradation is the use of proteolysis-targeting chimeras (PROTACs). PROTACs are innovative bifunctional molecules meticulously designed to induce the degradation of specific target proteins. They achieve this by physically linking a target protein to an E3 ubiquitin ligase, thereby triggering the ubiquitin-proteasome system (UPS)-mediated degradation pathway. Unlike traditional inhibitors, which bind stoichiometrically to their targets, PROTACs act catalytically, meaning a single PROTAC molecule can continuously recruit and facilitate the degradation of multiple target protein molecules. This catalytic mechanism enables highly efficient, precise, and sustained target protein degradation, making them exceptionally potent therapeutic agents [57].

In addition to PROTACs, several complementary strategies have emerged to harness the ubiquitin-proteasome system or other intrinsic cellular degradation pathways for selective protein degradation. Molecular glues, for instance, represent another powerful class of TPD agents. Unlike PROTACs, molecular glues, such as thalidomide analogs, function by stabilizing novel interactions between an E3 ubiquitin ligase and a neo-substrate (the target protein), leading to the target's ubiquitination and subsequent degradation [58]. This mechanism highlights a different approach to induced proximity. Similarly, emerging technologies like lysosome-targeting chimeras (LYTACs) exploit the lysosomal degradation pathway by redirecting extracellular or membrane proteins for lysosomal trafficking via receptor-mediated endocytosis. Autophagy-targeting chimeras (AUTACs) and autophagosome-tethering compounds (ATTECs) co-opt the autophagy mechanisms by tagging target proteins for selective autophagic degradation [59]. These diverse and innovative modalities collectively extend the landscape of targeted protein degradation beyond solely cytosolic proteins, enabling the modulation of previously undruggable targets and significantly broadening the therapeutic potential of induced proteolysis across various cellular compartments and protein types.

Several previous reports have described the development of conventional small-molecule inhibitors for NSD proteins [57, 60, 61, 62, 63]. Many of these small-molecule inhibitor development efforts targeted two key functional domains of NSD proteins: the SET domain, which mediates the histone methyltransferase activity, and the PWWP domain of NSD proteins, which mediates their interaction with methylated histones, thereby suppressing their chromatin localization. Although less common, PHD domain inhibitors have also been developed for some NSD proteins [64]. However, due to the rapid evolution of the field towards the development of targeted protein degradation, the focus here will be on the recent and promising advances in the development of targeted protein degraders of NSD proteins, which offer a more comprehensive approach to target protein function.

PROTAC technology has indeed emerged as a highly promising and effective approach for selectively degrading NSD proteins, offering significant advantages over traditional inhibitors by achieving sustained and complete target suppression. In this regard, a previous study successfully developed a potent NSD3-targeting PROTAC, named MS9715 [65]. This innovative molecule was constructed by linking the NSD3-PWWP1 antagonist BI-9321 with a ligand for the von Hippel-Lindau (VHL) E3 ligase, thereby recruiting NSD3 to the degradation machinery. MS9715 effectively inhibited the growth of NSD3-dependent hematological cancer cells and suppressed both NSD3- and cMyc-driven oncogenic pathways more potently and comprehensively than BI-9321 alone, effectively recapitulating the profound cellular effects observed with NSD3 genetic knockout [65]. Similarly, another study developed Compound 8, which demonstrated selective degradation of NSD3, leading to reduced H3K36me2 levels, induction of apoptosis, and significant inhibition of lung cancer cell growth in both cell culture and in vivo xenograft models [66].

NSD2 has also been successfully targeted using PROTACs. A previous study developed MS159, a pioneering first-in-class NSD2 degrader [67]. MS159 functions in a Cereblon E3 ubiquitin ligase and proteasome-dependent manner, leveraging the NSD2-binding chemical probe UNC6934. MS159 proved to be more potent in suppressing the growth of cancer cells than UNC6934 alone. This enhanced potency was likely due to the ability of the MS159 degrader to induce the complete degradation of NSD2, thereby inhibiting its histone methyltransferase activity, which does not occur after treatment with UNC6934, as UNC6934 primarily inhibits NSD2 by altering its localization rather than degrading it. Furthermore, MS159 also demonstrated favorable in vivo bioavailability in mice, indicating its potential for systemic administration [67].

Similarly, another bivalent NSD2 degrader, UNC8153, was developed through the derivatization of UNC6934 with chemical moieties designed to mimic a specific set of N-

terminal residues known as N-degrons [68]. N-degrons are specific degradation signals found at the N-terminus of a protein. These sequences or structural features determine how quickly a protein is targeted for degradation by the cell's proteolytic machinery, primarily the ubiquitin-proteasome system. They are central to the N-end rule pathway, a concept that links the identity of the N-terminal amino acid to the half-life of a protein. Importantly, the authors went on to show that UNC8153 induces proteasome-dependent degradation of both major isoforms of NSD2 in cells, leading to a significant reduction in global cellular levels of H3K36me2 and robust inhibition of the growth of NSD2-dependent cells [68].

Overall, the targeted protein degradation of NSD proteins represents a highly selective and potent therapeutic strategy, consistently outperforming conventional inhibitors by achieving sustained and comprehensive target suppression. This approach presents a promising new frontier for treating NSD-driven cancers. These PROTACs also serve as invaluable tool compounds to further understand the non-catalytic functions of NSD proteins and may uncover previously unrecognized roles of these proteins in cancer biology and disease pathogenesis.

DISCUSSION

The NSD family proteins (NSD1, NSD2, and NSD3) have unequivocally emerged as critical regulators at the intricate intersection of chromatin remodeling, transcriptional control, and anti-tumor immune responses. Their functional roles are far from uniform; rather than acting solely as consistent oncogenic drivers, NSD proteins exhibit highly context-dependent functions that can either support or suppress anti-tumor immunity, with their precise impact often contingent on the specific cancer type and the prevailing microenvironmental cues [37, 38]. This remarkable functional diversity, encompassing the modification of both canonical histone substrates and an increasing number of non-histone substrates, strategically positions NSD proteins as pivotal modulators of immune cell infiltration, antigen presentation pathways, and ultimately, the responsiveness to immunotherapy.

The findings reviewed here underscore the nuanced roles of each NSD family member. NSD1, through its influence on DNA hypomethylation and retrotransposon de-repression, can paradoxically contribute to an "immune cold" phenotype in certain squamous cell carcinomas, despite initial expectations of immune activation [33, 39]. This highlights the complex interplay of epigenetic marks and the potential for compensatory mechanisms, such as EZH2-mediated H3K27me3, to override pro-immunogenic signals. The therapeutic implication here is that targeting these compensatory mechanisms, like EZH2 or KDM2A, can potentially re-sensitize NSD1-mutant tumors to immunotherapy [39, 41].

NSD2's influence is equally broad and impactful. Its roles extend to critical aspects of adaptive immunity, including its necessity for proper germinal center B-cell function and follicular helper T cell differentiation, which are both crucial for robust humoral immune responses [51, 52]. Within the tumor microenvironment, NSD2 directly impacts antigen presentation by modulating MHC-I expression in various cancers, and its loss can impair IFN-γ-stimulated anti-tumor immunity [47, 50]. Furthermore, NSD2's ability to methylate non-histone proteins like CD147, thereby promoting immunosuppressive macrophage infiltration, reveals a novel layer of its immunomodulatory function that is independent of its canonical histone methyltransferase activity [49]. The context-dependent nature of NSD2's role, acting as an apparent immunosuppressor in prostate and lung cancers but potentially having a tumor suppressor-like role in colorectal cancer, necessitates careful consideration for therapeutic strategies [47, 49, 50].

NSD3 also plays a significant role in shaping the immune landscape, with its amplification often correlating with an "immune-cold" microenvironment and poor response to immune checkpoint blockade in lung squamous cell carcinoma [55]. Its association with reduced CD8+ T cell infiltration and elevated PD-L1 expression in breast cancer further solidifies its role in promoting immune evasion [56]. The identification of elevated unfolded protein response (UPR) signaling in NSD3-amplified tumors as a potential driver of immune exclusion also opens new avenues for combination therapies targeting UPR pathways [55].

The advent of targeted protein degradation (TPD) has recently gained significant traction as a superior strategy compared to conventional small molecule inhibition, particularly for complex, multi-domain proteins like the NSDs [57]. By facilitating the complete elimination of target proteins, degraders such as PROTACs offer a distinct advantage over inhibitors that merely block catalytic activity. This comprehensive degradation ensures the removal of both catalytic and non-catalytic functions (e.g., scaffolding, protein-protein interactions), enabling a more profound and sustained pharmacologic control over NSD activity. Early preclinical studies specifically targeting NSD2 and NSD3 with PROTACs have demonstrated highly encouraging results, including reduced oncogenic signaling, beneficial epigenetic reprogramming, and most importantly, enhanced anti-tumor immunity [65, 66, 67, 68]. These findings strongly suggest that NSD protein degraders could serve as effective modulators for converting immunologically "cold" tumors into "hot" ones, thereby sensitizing them to existing immunotherapies.

Despite the exciting progress, several critical challenges and opportunities remain for future research. A deeper and more granular understanding is needed to delineate the specific molecular contexts in which each NSD protein drives immune evasion versus immune activation. This mechanistic clarity, coupled with the continued

refinement of degrader technologies to improve selectivity, potency, and pharmacokinetic properties, is crucial for minimizing off-target effects and maximizing therapeutic benefit. Furthermore, a significant area of future exploration lies in the rational design of combination therapies. Combining NSD-targeted degradation with existing immunotherapies, such as immune checkpoint inhibitors, or with other epigenetic agents, could lead to powerful synergistic anti-tumor effects, particularly in tumors that are currently "immune cold" or resistant to conventional treatments. For instance, reprogramming the tumor microenvironment through NSD degradation could enhance T-cell infiltration and overcome immune suppression, mirroring successful strategies seen with other epigenetic targets like EZH2, which has shown promise in combination therapies to potentiate immune surveillance [42, 43, 44, 45, 46]. As interest continues to grow in targeting transcriptional regulators to enhance immune responses, the NSD proteins represent a compelling and high-potential class of targets for the development of next-generation cancer therapies.

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