Protein S-palmitoylation in T cell-mediated antitumor immunity: Context-dependent mechanisms and therapeutic opportunities (Review)

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Abstract. S-palmitoylation is a critical post-translational regulator of protein function; however, its role in T cell-mediated antitumor immunity remains unclear. The present review summarizes emerging evidence that redefines T cell biology and its implications for antitumor immunity. The regulatory functions of S-palmitoylation in T cell receptor signaling, activation, proliferation, differentiation, exhaustion and apoptosis are first outlined, highlighting the distinct roles of the zinc finger Asp-His-His-Cystype family of palmitoyl acyltransferases and depalmitoylating enzymes in modulating the membrane localization, stability and signal transduction of key T cell signaling regulators. How S-palmitoylation of immune checkpoints, such as programmed death-ligand 1, and the components of antigen presentation shape the tumor immune microenvironment were further examined. Additionally, the recent advances in therapeutic strategies targeting S-palmitoylation, including small-molecule inhibitors, peptide-based interventions and nanoparticle delivery systems, were highlighted, and their potential to enhance T cell antitumor immunity, particularly in combination with immune checkpoint blockade, was discussed. Finally, the current challenges, including the suboptimal selectivity of pharmacological agents, technical limitations of existing delivery systems and the intrinsic heterogeneity and immunosuppressive nature of the tumor microenvironment were discussed, and future directions for advancing S-palmitoylation-targeted immunotherapies were proposed. Collectively, the present review highlights S-palmitoylation as a promising regulatory axis for antitumor immunity and provides a foundation for the future development of targeted immunotherapies.

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Contents

1. Introduction
2. Fundamentals and methodological considerations in protein S-palmitoylation
3. T cell-intrinsic S-palmitoylation during TCR signaling, activation, differentiation, exhaustion and apoptosis
4. Tumor-cell-intrinsic S-palmitoylation regulating T cell immunity
5. S-palmitoylation in dendritic cells (DCs) and other antigen-presenting or myeloid cells
6. Metabolism-S-palmitoylation crosstalk in the TME
7. Therapeutic strategies, supporting evidence and translational barriers
8. Conclusions and perspectives

1. Introduction

In recent years, T cell-mediated cancer immunotherapies, notably immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR) T cell-based therapies, have markedly transformed the therapeutic landscape of oncology, yielding durable clinical responses and sustained survival benefits in a subset of patients (1-3). However, their broader clinical application remains limited by intrinsically heterogeneous response rates, the development of primary and acquired resistance as well as immune-related and off-tumor toxicities (4-6). These challenges are largely shaped by the tumor microenvironment (TME), which extensively reprograms the functional states of tumor-infiltrating T cells, driving exhaustion and impairing effector capacity and phenotypic plasticity, collectively limiting effective antitumor immunity (7,8). Therefore, deciphering the molecular networks that orchestrate T cell state transitions and developing strategies for precise, reversible immune reprogramming represents critical priorities for advancing next-generation cancer immunotherapies.

Within the signaling networks that orchestrate T cell activation and cell-state transitions, the subcellular localization of signaling proteins represents an actively regulated and functionally decisive layer of signal control, rather than a passive spatial feature (9,10). Among the diverse post-translational modifications that regulate protein distribution and spatial organization, S-palmitoylation has emerged as a reversible lipid modification in which palmitic acid (C16:0) is covalently conjugated to cysteine residues via thioester bond formation (11). This process is primarily mediated by the zinc-finger Asp-His-His-Cys (ZDHHC) family of palmitoyl acyltransferases, whose catalytic activity is regulated by transcriptional regulation, post-translational modification and dynamic membrane compartmentalization (12,13). Their expression patterns, subcellular distribution and enzymatic properties are precisely controlled by integrated transcriptional, translational and post-translational regulatory networks, enabling selective and context-dependent modulation of substrate S-palmitoylation events (14,15). By enhancing protein hydrophobicity and membrane association, S-palmitoylation functions as a reversible regulatory mechanism that facilitates the targeting of proteins to specialized membrane microdomains, promotes the formation of membrane-proximal signaling assemblies and fine-tunes the activation and propagation of intracellular signaling pathways (16-18). Conversely, the dynamic removal of palmitoyl groups by acyl-protein thioesterases (APTs), including APT1 and APT2, establishes a reversible acylation-deacylation cycle that permits rapid and stimulus-dependent reorganization of protein localization, stability and signaling activity (17,19,20). Collectively, the coordinated regulation of S-palmitoylation and depalmitoylation provides a molecular framework that confers spatiotemporal precision to immune receptor signaling and cellular functional adaptation.

Building on these findings, the present review provides a comprehensive overview of recent advances in elucidating the molecular mechanisms through which protein S-palmitoylation regulates T cell-mediated antitumor immunity. By integrating diverse mechanistic and functional findings, the present review aims to establish a coherent post-translational regulatory framework in which S-palmitoylation orchestrates multiple dimensions of immune regulation, encompassing the initiation of T cell receptor (TCR) signaling, integration of co-stimulatory and co-inhibitory pathways and dynamic modulation of immune checkpoint signaling networks. Furthermore, the present review explores emerging therapeutic strategies aimed at pharmacologically or genetically targeting the S-palmitoylation cycle to restore T cell effector functionality and reshape immunosuppressive TMEs toward a more immunogenic state. Collectively, these advances provide a conceptual foundation for future precision immunotherapy approaches pending further preclinical and clinical validation.

Several recent reviews have addressed protein S-palmitoylation in tumor immunity, the TME and cancer therapy (21-23); however, the present review offers distinct contributions by adopting a T-cell-centered, cell-type-resolved framework, providing an evidence-grade matrix for ZDHHC-substrate relationships (Table SI), analyzing the bidirectional immune effects of S-palmitoylation, integrating recent (2024-2026) immune-checkpoint studies and outlining a translational roadmap emphasizing cell-, enzyme- and substrate-selective intervention. A narrative search was performed in PubMed (https://pubmed.ncbi.nlm.nih.gov/) using terms including 'S-palmitoylation', 'protein palmitoylation', 'ZDHHC', 'T cell', 'antitumor immunity', 'immune checkpoint', 'tumor microenvironment' and 'cancer immunotherapy', with the final search on August 31, 2026; priority was given to mechanistic studies published within the last 6 years (2020-2026), particularly those providing endogenous loss-of-function evidence, catalytic-dead rescue or *in vivo* immune validation.

2. Fundamentals and methodological considerations in protein S-palmitoylation

Protein S-palmitoylation is a reversible post-translational lipid modification in which long-chain fatty acids, predominantly palmitate (C16:0), are covalently attached to the cysteine residues of substrate proteins via labile thioester bonds (24). This modification affects ~25% of the human proteome and plays a critical role in regulating protein trafficking, protein-protein interactions and protein stability (25). Unlike other lipid modifications such as N-myristoylation and S-prenylation, protein S-palmitoylation is fully reversible, a property that enables cells to dynamically adjust protein membrane affinity, subcellular distribution and functional activity in response to changing physiological demands (25).

S-palmitoylation-depalmitoylation cycle. The forward reaction of S-palmitoylation is catalyzed by a family of ZDHHC-containing palmitoyl acyltransferases, commonly referred to as ZDHHC enzymes, which transfer palmitate from palmitoyl-CoA to the thiol group of cysteine residues (24,26). The reverse reaction (removal of the palmitate moiety) is mediated by APTs, palmitoyl protein thioesterases (PPTs) and α/β hydrolase domain (ABHD)-containing proteins of the ABHD17 family (27). This dynamic cycle operates on timescales ranging from seconds to hours, enabling proteins to rapidly traffic between specialized intracellular membrane compartments (24). The reversible nature of S-palmitoylation distinguishes it from other lipid modifications and renders it particularly suited to the regulation of rapid cellular signaling events (19).

ZDHHC family of palmitoyl acyltransferases. The ZDHHC family comprises 23 mammalian members, each containing a conserved DHHC motif within a cysteine-rich domain that is essential for catalytic activity. ZDHHC enzymes are multi-pass transmembrane proteins that are primarily localized in the Golgi apparatus, endoplasmic reticulum (ER) and plasma membrane (28,29). The Golgi apparatus serves as the primary site where most palmitoylated substrates are first modified before being transported to other subcellular compartments (26,30).

Structural and mechanistic studies have provided important insights into the mechanisms by which ZDHHC enzymes recognize and modify their substrates. ZDHHC proteins form an autoacylation intermediate that attaches a fatty acid to a cysteine residue in the target protein (31). Substrate recruitment by ZDHHCs may involve co-localization

through protein interactions, membrane-associated domains or prior lipid post-translational modifications (32). The ZDHHC13/ZDHHC17 subfamily, for example, participates in various pathological and physiological processes, including S-palmitoylation, Mg^{2+} transport and calcium binding and coiledcoil domain containing 1-mediated Golgiphagy (24).

Depalmitoylating enzymes. Depalmitoylation is mediated by several members of the thioesterase family, each displaying distinct subcellular distributions and substrate preferences. APT1 and APT2 are cytosolic depalmitoylases that share ~60% sequence identity. APT1 mainly localizes to the cytosol, but has also been reported in the plasma membrane, Golgi, ER, mitochondria and nuclear membrane (27). Both APT1 and APT2 are palmitoylated at Cys2, and APT1 can depalmitoylate itself and APT2, dynamically regulating both enzymes (27). Emerging evidence suggests that APTs display substrate selectivity: APT1, but not APT2, reverses agonist-induced S-palmitoylation of β_2-adrenergic receptors (33), whereas APT2 rather than APT1 mediates depalmitoylation of GAP-43 and ZDHHC6 (34,35).

In addition to cytosolic APTs, PPT1 and PPT2 localize in lysosomes and participate in protein depalmitoylation (36). PPT1 targets lysosomes via the mannose 6-phosphate receptor-mediated pathway and facilitates the degradation of palmitoylated proteins (27). The ABHD17 family (ABHD17A/B/C) represents another class of depalmitoylating enzymes that promote the turnover of palmitic acid on substrates such as postsynaptic density protein 95 and N-Ras (27).

Methodological approaches for studying protein S-palmitoylation. The study of protein S-palmitoylation has advanced significantly with the development of complementary biochemical and chemical approaches. The most widely used methods for detecting and characterizing palmitoylated proteins include acyl-biotin exchange (ABE), acyl resin-assisted capture (acyl-RAC), acyl-polyethylene glycol (PEG) exchange (APE) and metabolic labeling with fatty acid analogs.

ABE is a cysteine-centric approach in which free thiols are first blocked with a thiol-reactive reagent, followed by hydroxylamine-mediated cleavage of the thioester bond to expose palmitoylated cysteine residues. The newly exposed thiols are then labeled with a biotinylated reagent for subsequent detection or enrichment. ABE enables the identification of S-acylated proteins or peptides through the enrichment of previously S-acylated cysteines (37,38).

Acyl-RAC directly captures palmitoylated proteins onto a thiol-reactive resin following hydroxylamine-mediated cleavage, providing a straightforward method for enrichment and subsequent mass spectrometry-based identification. Both ABE and acyl-RAC are cysteine-centric approaches that do not require metabolic labeling of cells (39).

The APE assay is a complementary approach for detecting and quantifying protein S-palmitoylation. Based on the same principle as ABE, free cysteine thiols are first blocked with N-ethylmaleimide, after which hydroxylamine cleaves the thioester bonds of palmitoylated cysteines. The newly exposed thiols then react with thiol-reactive methoxy-PEG maleimide of defined molecular mass (40). This covalent attachment of a PEG moiety produces a discrete mass shift that can be readily detected by western blotting or gel electrophoresis, permitting visualization and semiquantitative assessment of the palmitoylation status of specific proteins (41). Unlike ABE and acyl-RAC, which rely on biotin-based enrichment, APE does not require affinity purification and is particularly useful for analyzing the palmitoylation of low-abundance proteins or for the rapid screening of candidate substrates (40). The APE assay can also be adapted for quantitative determination of palmitoylation stoichiometry.

Metabolic labeling with ω-alkynyl fatty acid analogs (such as 17-octadecynoic acid) enables the identification of palmitoylated proteins in living cells. The alkyne moiety serves as a bio-orthogonal handle for subsequent conjugation to the detection tags via copper-catalyzed azide-alkyne cycloaddition (click chemistry), which supports fluorescence visualization, affinity purification and mass spectrometry-based identification (42,43). This palmitate-centric approach has been widely used for proteome-scale profiling of palmitoylated proteins (44).

Recent advances in mass spectrometry-based strategies have substantially expanded the toolbox for studying protein S-palmitoylation introducing improved workflows that enable sensitive, site-specific and quantitative analyses. These include both direct and indirect mass spectrometry-based strategies such as ABE, lipid metabolic labeling and novel enrichment and fragmentation methods.

3. T cell-intrinsic S-palmitoylation during TCR signaling, activation, differentiation, exhaustion and apoptosis

S-palmitoylation initiates TCR signaling in the activation of naive T cells. The transition of naïve T cells into functionally specialized effector populations relies on the precise coordination of antigen receptor signaling and co-stimulatory inputs. This process is initiated by antigen recognition and executed through a highly organized intracellular signaling network commonly known as TCR signaling. According to the classical two-signal paradigm, productive T cell activation requires the coordinated integration of two distinct but complementary signaling events: The first signal is initiated by engagement of the TCR-CD3 complex with peptide-major histocompatibility complex (pMHC), whereas the second signal is provided through co-stimulatory receptors, particularly CD28. The integration of these signaling pathways establishes the molecular basis for T cell activation, clonal expansion, metabolic reprogramming and the acquisition of effector functions (43).

The TCR-CD3 complex constitutes the central signaling apparatus of adaptive immunity (45); it comprises a clonotypic TCRαβ heterodimer non-covalently associated with the invariant CD3 subunits (CD3γ, CD3δ, CD3ε and CD3ζ) (46,47). Whereas the TCRαβ heterodimer, through its variable and constant domains, mediates specific recognition of pMHC complexes, the CD3 subunits serve as indispensable signaling modules that couple extracellular antigen recognition to intracellular signal transduction (47-49). The signaling competence of the CD3 complex arises from its structural organization, including transmembrane domains that ensure stable receptor assembly and relatively long cytoplasmic tails containing immunoreceptor tyrosine-based activation motifs

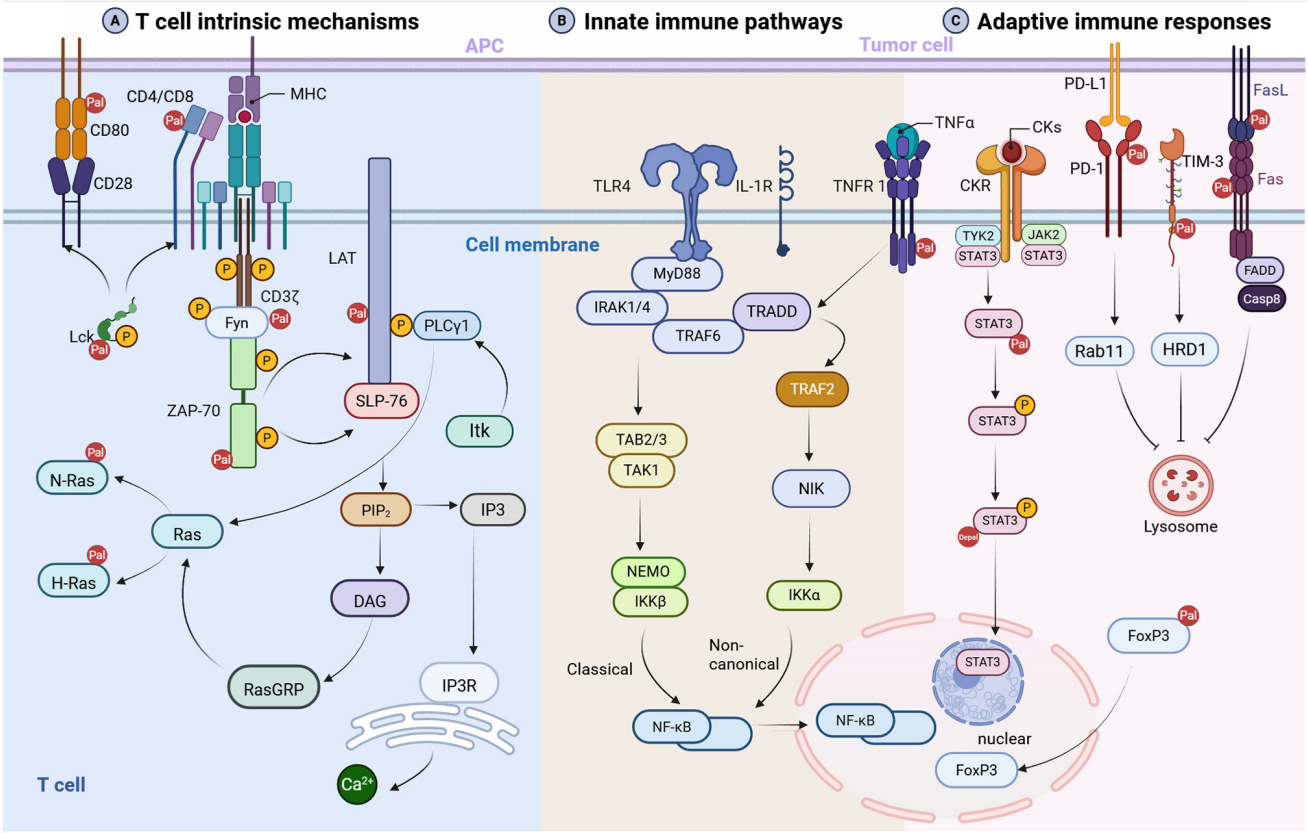


Figure 1. S-palmitoylation orchestrates T cell signaling activation, proliferation, differentiation, exhaustion and apoptosis. (A) T cell-intrinsic mechanisms. S-palmitoylation promotes the membrane localization and lipid raft partitioning of key T cell receptor-associated signaling molecules, including Lck, Fyn, LAT and CD4/CD8, facilitating ZAP-70 recruitment and LAT signalosome assembly. These membrane-proximal events activate downstream pathways, including PLCγ1, Ras-MAPK and calcium-dependent signaling cascades, which ultimately drive T cell activation, proliferation and effector differentiation. Palmitoylated Ras isoforms (N-Ras and H-Ras) are depicted. (B) Innate immune pathways. S-palmitoylation dynamically regulates the localization, trafficking, stability and signaling activity of innate immune regulatory proteins. TLR4/IL-1R signaling through MyD88-IRAK1/4-TRAF6 converges on the classical (TAK1/NEMO/IKKβ) NF-κB activation pathway, whereas TNFR1 signaling through TRADD/TRAF2 converges on the non-canonical (NIK/IKKα) NF-κB activation pathway. (C) Adaptive immune responses. S-palmitoylation of immune checkpoint molecules, including PD-1 and TIM-3, enhances receptor stability by promoting receptor recycling (such as Rab11) or preventing lysosomal degradation (such as HRD1), thereby sustaining inhibitory signaling and contributing to T cell exhaustion and tumor immune evasion. S-palmitoylation also regulates TNFR1 and CKR/JAK2/STAT3 signaling (CKs include TGF-β, IL-6 and IL-23; CKR denotes the corresponding receptors), as well as Fas/FasL membrane organization, to modulate apoptotic signaling and immune homeostasis. FoxP3 S-palmitoylation facilitates its nuclear accumulation and maintains regulatory T cell suppressive function. Figure created with BioRender.com. ZAP-70, ζ-chain-associated protein kinase 70; LAT, linker for activation of T cells; PLCγ1, phospholipase C γ1; NF-κB, nuclear factor κB; STAT3, signal transducer and activator of transcription 3; FoxP3, forkhead box P3; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TIM-3, T cell immunoglobulin and mucin-domain containing-3; TNFR1, tumor necrosis factor receptor 1; CKs, cytokines; CKR, cytokine receptor; JAK2, Janus kinase 2; Fas, Fas cell surface death receptor; FasL, Fas ligand; Pal, S-palmitoylation; Depal, depalmitoylation.

(ITAMs), which function as the principal signaling platforms of the receptor complex (45,50).

Following the engagement of the TCR with the cognate pMHC, conformational rearrangements expose ITAMs, permitting their phosphorylation by lipid raft-associated Src-family kinases, principally Lck and Fyn (47). Fully phosphorylated (biphosphorylated) ITAMs subsequently recruit ζ-chain-associated protein kinase 70 (ZAP-70) through its tandem Src homology 2 (SH2) domains (51). ZAP-70 is then activated by Lck-dependent phosphorylation, enabling it to function as a central amplifier of proximal TCR signaling (52). Activated ZAP-70 phosphorylates multiple adaptor proteins, most notably the linker for the activation of T cells (LAT) and SH2 domain-containing leukocyte protein of 76 kDa (SLP-76), which together nucleate the assembly of a multicomponent signaling complex, commonly referred to as the LAT signalosome (53). This signaling platform coordinates and amplifies proximal TCR signaling through multiple downstream pathways, including the phospholipase Cγ1 (PLCγ1), Ras/mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/AKT and nuclear factor-κB (NF-κB) cascades, culminating in extensive transcriptional and functional reprogramming that supports T cell activation, proliferation, survival and effector differentiation (Fig. 1) (46,54,55). Taken together, these membrane-proximal signaling events form a highly integrated signaling network that ensures efficient signal initiation, propagation and amplification, ultimately enabling functional maturation of antigen-responsive naïve T cells.

S-palmitoylation and membrane localization of Src kinases. The earliest events of T cell activation are orchestrated by a network of membrane-proximal signaling molecules associated with the TCR complex. Among these, the Src-family kinases Lck and Fyn function as key initiators of proximal TCR signaling and play complementary roles in thymocyte development, antigen recognition and mature

T cell activation (56-59). A defining feature of Lck and Fyn is their regulated association with the cytoplasmic leaflet of the plasma membrane, which is mediated by sequential N-myristoylation and reversible S-palmitoylation. Although N-myristoylation provides an initial membrane-targeting signal, S-palmitoylation enhances membrane affinity and directs these kinases into specialized lipid raft microdomains, a process essential for their optimal participation in proximal TCR signaling (60-63).

The role of S-palmitoylation in membrane targeting has been well characterized for Fyn. Fyn undergoes S-palmitoylation at two N-terminal cysteine residues, Cys3 and Cys6. A site-directed mutagenesis study has demonstrated that modification of Cys3 represents the predominant and functionally indispensable S-palmitoylation event required for its stable localization within lipid rafts and cholesterol- and sphingolipid-enriched membrane microdomains that function as signaling platforms (64). This modification is mediated by the palmitoyl acyltransferase DHHC21 (65). Covalent attachment of the palmitate moiety increases its hydrophobicity, facilitating stable retention of Fyn within lipid rafts and enabling efficient engagement with proximal signaling components, particularly the TCR ζ-chain, where it phosphorylates ITAM tyrosines and cooperates with Lck to initiate early TCR signaling (Fig. 1A) (57,66).

Similarly, the lymphocyte-specific kinase Lck, a master regulator of proximal TCR signaling, is subject to stringent regulation by reversible S-palmitoylation. Lck is also palmitoylated at Cys3 and Cys5 (57,67,68). Using acyl-RAC to profile protein lipidation, Fan *et al* (65) demonstrated that DHHC21 is indispensable for Lck S-palmitoylation and for the propagation of Lck-dependent apoptotic signaling in T cells, identifying DHHC21 as a common regulatory node controlling multiple Src-family kinases. Following antigen-induced TCR engagement, palmitoylated Lck is constitutively enriched within the TCR-CD3 complex, where it performs its canonical signaling function by phosphorylating paired tyrosine residues within the ITAMs of CD3 subunits. Phosphorylated ITAMs subsequently recruit the Syk family kinase ZAP-70, which is further activated by Lck-mediated phosphorylation (64,69). Activated ZAP-70 propagates proximal TCR signaling by phosphorylating downstream adaptor proteins and signaling effectors, leading to robust amplification of the TCR signaling cascade (Fig. 1A) (53).

The phosphorylation cascade initiated by Lck and Fyn constitutes the molecular foundation of proximal TCR signal transduction. Nevertheless, efficient propagation of these signaling events depends not only on the catalytic activities of these Src-family kinases but also on precise membrane localization, dynamic assembly and coordinated regulation of downstream signaling complexes that relay and amplify activation signals throughout the T cell signaling network.

ZAP-70: A core kinase for signal amplification and its regulation by S-palmitoylation. ZAP-70 serves as a central tyrosine kinase that coordinates T cell immune responses. Dysregulated expression or functional impairment of ZAP-70 has been implicated in diverse human diseases, including immunodeficiencies, autoimmune disorders and leukemia (70). Within the TCR signaling cascade, antigen engagement activates the Src-family kinase Lck, which subsequently mediates dual phosphorylation of ITAMs within the TCR-associated CD3ζ chain (71). These phosphorylated ITAMs function as high-affinity docking platforms for the SH2 domains of ZAP-70, thereby promoting their recruitment to the TCR-CD3 signaling complex. ITAM binding induces conformational rearrangements in ZAP-70 that enhances its accessibility to Lck-mediated phosphorylation, ultimately resulting in autophosphorylation-dependent full activation (70). Once activated, ZAP-70 drives the assembly of proximal signaling complexes by phosphorylating key adaptor proteins, including LAT and SLP-76, which subsequently initiate PLCγ1 activation and downstream signaling cascades. This signaling axis plays an essential role in T cell development, activation and effector differentiation (55,72). In ZAP-70-deficient T cells, defective phosphorylation of LAT and SLP-76 disrupts the formation of the LAT signalosome and impairs downstream signal propagation, further underscoring the central role of ZAP-70 in TCR signal transduction (53,73,74).

Emerging evidence has indicated that ZAP-70 activity is regulated by S-palmitoylation. Using the ABE assay, Cys564 was identified as the principal S-palmitoylation site and this modification was dependent on TCR stimulation. S-palmitoylation mediates the stimulus-dependent translocation of ZAP-70 to discrete plasma membrane microdomains, facilitating its interaction with downstream effector molecules (Fig. 1A) (75). Therefore, these findings demonstrate that S-palmitoylation of ZAP-70 is essential for its function in the proximal TCR signaling pathway. Notably, downregulation of DHHC21 concurrently suppresses the S-acylation of Lck, Fyn and LAT, suggesting that this acyltransferase may serve as a shared regulatory hub in the proximal TCR signaling network (65,67). However, whether DHHC21 directly catalyzes ZAP-70 S-palmitoylation, and the molecular determinants underlying its substrate selectivity, remain unclear.

LAT: Signal integration and downstream conduction. LAT, a transmembrane adaptor protein modified by dual palmitoylation, is indispensable for T cell development and activation (76). Within the juxtamembrane cytoplasmic region, dual cysteine residues (Cys26 and Cys29) undergo S-palmitoylation, directing LAT to the plasma membrane to ensure proper TCR signal transduction (67,77). Although both residues are modified, evidence from a LAT-deficient Jurkat cell system indicates that S-palmitoylation at Cys26 is both necessary and sufficient for plasma membrane localization and TCR signaling, whereas the lipid raft partitioning reported in microdomain studies is dispensable for its function (76,78).

A study by Hundt *et al* (76) demonstrated that anergic T cells exhibit selective defects in LAT S-palmitoylation, underscoring the fact that intact S-palmitoylation is required not only for T cell development but also for productive TCR-driven activation. The loss of LAT S-palmitoylation promotes its dissociation from the plasma membrane and impairs its recruitment to immunological synapses. This mis-localization prevents LAT from efficiently engaging downstream signaling partners, resulting in attenuated signal propagation and the consequent suppression of T cell activation (69,79). However, the precise mechanism through which S-palmitoylation supports LAT function remains unclear. While S-palmitoylation is required for efficient plasma membrane delivery and spatial organization of LAT, the extent to which its function depends on its

partitioning into biochemically defined lipid rafts rather than broader membrane sub-compartmentalization remains controversial. Hundt *et al* (76) reported that although LAT S-palmitoylation is essential for plasma membrane transport, LAT-dependent signaling proceeds independently of lipid raft integrity, indicating that its functional role may extend beyond classical raft targeting. These results highlight the distinction between the well-established requirement for S-palmitoylation for membrane localization and the more nuanced assay-dependent evidence concerning lipid raft partitioning. Further studies are warranted to reconcile these observations and define the precise molecular mechanisms through which LAT S-palmitoylation coordinates TCR signal initiation and propagation.

Following TCR stimulation, multiple cytoplasmic tyrosine residues within LAT are phosphorylated primarily by Syk-family kinases, enabling LAT to serve as a central scaffold for the recruitment of key signaling effectors, including PLCγ1 and Grb2 (71,80). These adaptor proteins are subsequently activated via ZAP-70-dependent signaling cascades. Activated PLCγ1 hydrolyzes phosphatidylinositol 4,5-bisphosphate into inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG), initiating two major signaling branches: IP_3 triggers calcium release from the ER via its receptor, whereas DAG activates downstream NF-κB and Ras/MAPK pathways (Fig. 1A). As signal transduction progresses, S-palmitoylation-dependent spatial organization continues to modulate downstream signaling modules, including MAPK and NF-κB cascades, ultimately driving T cell activation, proliferation and cytokine production (67,71). Thus, these findings establish LAT S-palmitoylation as a critical molecular determinant of both the initiation and propagation of TCR signaling. Aberrant regulation of this lipid modification represents a key mechanism underlying T cell hypo-responsiveness

S-palmitoylation and T cell signal transduction

CD4/CD8 co-receptors. CD4 and CD8 function as essential co-receptors in T cell activation, selectively binding to MHC class II and class I molecules, respectively, through their extracellular domains. This interaction stabilizes the physical interface between T cells and antigen-presenting cells, enhancing TCR engagement with peptide-loaded MHC complexes and facilitating the efficient initiation of antigen recognition (45,81). In addition to their roles in peripheral T cell activation, both co-receptors are critically involved in thymic selection, assisting the TCR complex in discriminating between MHC class II and class I molecules, ultimately directing lineage commitment toward the $CD4^+$ or $CD8^+$ T cell fate (82,83). The functional competence of these co-receptors is tightly linked to their precise plasma membrane localization and stability, processes centrally regulated by S-palmitoylation.

CD4 undergoes site-specific S-palmitoylation at two membrane-proximal cysteine residues (Cys396 and Cys399) in its cytoplasmic tail (84-86). Although this lipid modification is dispensable for CD4 trafficking and surface expression, it significantly enhances CD4 partitioning into lipid raft microdomains. This spatial organization positions CD4 in close proximity to the TCR complex, enabling rapid co-receptor engagement following antigen stimulation and promoting efficient propagation of downstream signaling events (56,84). Furthermore, S-palmitoylation enhances CD4 enrichment within lipid raft microdomains and promotes its association with Lck, facilitating the assembly of signaling-competent co-receptor complexes and sustaining efficient TCR signal propagation (Fig. 1A) (67,84).

CD8 predominantly exists as a disulfide-linked CD8αβ heterodimer in conventional $CD8^+$ T cells. S-acylation of the CD8β cytoplasmic tail promotes its partitioning into lipid raft microdomains, a process essential for optimal co-receptor function (87,88). CD8 S-palmitoylation exhibits marked species-specific divergence. In human T cells, both CD8α and CD8β chains undergo S-palmitoylation, whereas in murine T cells, S-palmitoylation is restricted primarily to CD8β, which is essential for lipid raft targeting and optimal CD8 co-receptor function (69,89). Functional studies have revealed species-dependent mechanisms underlying CD8 S-palmitoylation. In murine T cells, CD8β S-palmitoylation promotes CD8αβ partitioning into lipid raft microdomains, facilitating its association with raft-resident Lck and enhancing downstream TCR signaling. By contrast, although both CD8α and CD8β undergo S-palmitoylation in human T cells, this modification appears dispensable for raft targeting; instead, CD8 localization is primarily dictated by CD8β-mediated structural organization, whereas S-palmitoylation may contribute to the assembly and stabilization of signaling-competent CD8-TCR/CD3 complexes (Fig. 1A) (67,69,87,88).

These findings establish S-palmitoylation as a critical mechanistic node within the regulatory network governing T cell immune responses. By dynamically controlling membrane microdomain partitioning, protein stability and Lck coupling of CD4 and CD8, S-palmitoylation fine tunes antigen sensitivity and the efficiency of T cell signaling, ultimately shaping the magnitude and quality of adaptive immune responses.

Co-stimulatory signaling. Optimal T cell activation requires the integration of dual-signal inputs; recognition of pMHC complexes by the TCR delivers the primary activation signal, whereas co-stimulatory molecules provide the essential secondary signal required for full T cell activation (90). Among these, CD28 is a central co-stimulatory receptor constitutively expressed on the T cell surface. The engagement of CD28 with its ligands B7.1 (CD80) or B7.2 (CD86) on antigen-presenting cells is indispensable for initiating productive immune responses in naïve T cells (91,92). Although CD28 possesses a canonical extracellular immunoglobulin-like domain, its signaling competence is largely dictated by its spatial organization within specialized plasma membrane microdomains. The recruitment of CD28 to lipid rafts and immunological synapse-associated signaling compartments facilitates the assembly of proximal signaling complexes and amplifies downstream co-stimulatory responses (93,94).

In parallel, the CD28 ligand CD80 is subject to stringent regulation by S-palmitoylation. CD80 is a B7 family transmembrane glycoprotein that critically modulates T cell responses through interactions with CD28 and CTLA-4 (95,96). Using a metabolic labeling strategy in 293T cells, Lu *et al* (97) demonstrated that CD80 undergoes S-palmitoylation at multiple cysteine residues within its transmembrane and intracellular regions, specifically at Cys261, Cys262, Cys266 and Cys271 (Fig. 1A). This study, employing proximity-dependent biotin identification and co-immunoprecipitation in 293T cells

identified ZDHHC20 as the principal palmitoyltransferase that catalyzes this modification. In the same study, mechanistic experiments using cycloheximide chase and lysosomal/proteasomal inhibition assays in a 293T stable cell line overexpressing wild-type CD80-Flag or the palmitoylation-deficient CD80-4CS-Flag mutant demonstrated that S-palmitoylation protects CD80 from ubiquitination-mediated degradation, tightly controlling its protein stability and ensuring accurate trafficking and retention at the plasma membrane (97). By contrast, S-palmitoylation-deficient CD80 mutants in CHO-K1 cells, as well as endogenous CD80 in human Raji B-lymphoma cells treated with the palmitoylation inhibitor tunicamycin, exhibit disrupted plasma membrane localization, reduced protein stability and impaired co-stimulatory capacity (97). These findings from co-culture assays of CHO-K1 cells expressing membrane-bound OKT3 single-chain variable fragment (anti-CD3 monoclonal antibody) and CD80 with human Jurkat T cells collectively demonstrate that S-palmitoylation functions as a key regulatory mechanism controlling CD80 function, ultimately optimizing co-stimulatory signal transmission and reinforcing effective T cell activation.

Nevertheless, whether CD28 itself undergoes direct S-palmitoylation remains unknown, as the available evidence is primarily derived from studies on CD80. Although CD28 partitions into lipid rafts and its membrane organization is critical for signaling, its direct S-palmitoylation, along with the responsible residues and acyltransferases, remains unknown. Thus, while the role of CD80 S-palmitoylation in co-stimulation is established, whether CD28 undergoes direct S-palmitoylation remains unresolved and warrants further investigation.

Taken together, S-palmitoylation has emerged as a critical regulatory node in the molecular circuitry underlying T cell immune responses. By dynamically coordinating membrane microdomain partitioning, protein stability, and the co-receptor organization of CD4 and CD8, this lipid modification fine-tunes antigen recognition sensitivity and enhances the efficiency of T cell signaling.

Ras signaling. Ras proteins are canonical small GTPases that function as molecular switches, transitioning between an active GTP-bound conformation and an inactive GDP-bound state to control downstream signaling (98-101). TCR-mediated Ras activation is essential for T cell development, proliferation and functional differentiation by activating the Ras/RAF/MEK/ERK signaling cascade (102-104). The Ras superfamily comprises three major isoforms, H-Ras, N-Ras and K-Ras, with K-Ras existing as two splice variants, K-Ras4A and K-Ras4B. All Ras isoforms share a highly conserved G-domain, whereas sequence divergence is primarily localized within the hypervariable region. These structural differences, together with distinct lipid modifications, confer isoform-specific membrane targeting and subcellular distribution, ultimately shaping divergent downstream signaling outputs (105-107).

Reversible S-palmitoylation is the central mechanism that controls the subcellular localization of H- and N-Ras (108). Following S-palmitoylation by Golgi-resident palmitoyl acyltransferases, H- and N-Ras are trafficked through the secretory pathway to the plasma membrane (109). This cycle precisely regulates Ras membrane residence and spatial redistribution between the plasma membrane and Golgi compartments, as demonstrated in 293T cells using fluorescence resonance energy transfer and live cell imaging (108). Beyond determining gross subcellular localization, lipid modifications also control lateral partitioning within membrane microdomains, ensuring spatially restricted and efficient signal propagation (67,105). In particular, palmitoylated N-Ras preferentially associates with raft/non-raft boundary regions across the plasma membrane, which is consistent with its distinct signaling behavior and functional specificity (Fig. 1A) (105). Collectively, the isoform-specific structural features, reversible S-palmitoylation dynamics and compartmentalized trafficking behavior of Ras proteins confer functional diversification within the Ras family, positioning Ras as a key fate-determining signaling hub that orchestrates T cell biology and directs cellular differentiation programs.

Proliferation and differentiation of T cells. Precise regulation of T cell proliferation and differentiation constitutes a prerequisite for the acquisition and execution of effector functions. Throughout these dynamic developmental processes, S-palmitoylation has emerged as an important post-translational regulatory mechanism that orchestrates protein subcellular distribution and signaling activity. Maintaining an appropriate balance of S-palmitoylation is crucial for preserving the physiological proliferative potential and directing lineage-specific differentiation programs, ultimately supporting effective T cell-mediated immune responses and sustaining immune homeostasis.

NF-κB signaling in T cell proliferation: ZDHHC11/TRAF6 axis. NF-κB signaling is essential for T cell proliferation, survival and effector differentiation (110,111). TRAF6, a member of the TNF receptor-associated factor family, functions as a key adaptor linking IL-1β and Toll-like receptor (TLR) signaling to downstream NF-κB activation (112). A study has identified ZDHHC11 as a positive modulator of NF-κB signaling in response to IL-1β, lipopolysaccharide (LPS) and DNA virus infection. Mechanistically, ZDHHC11 interacts with TRAF6 through its C-terminal region (amino acids 198-412) in a domain-dependent manner. In 293T cells overexpressing these proteins, this association promotes TRAF6 oligomerization, enhances E3 ubiquitin ligase activity and facilitates TGF-β-activated kinase 1 (TAK1) activation. Functionally, in in 293 C6 cells (a 293-derived cell line ectopically expressing IL-1R; not PER.C6 cells) ectopically expressing IL-1R, ZDHHC11 overexpression increased TRAF6-dependent IL-8 mRNA expression, whereas TRAF6 knockdown attenuated ZDHHC11-induced NF-κB activation (113). In mouse embryonic fibroblasts and bone marrow-derived macrophages from Zdhhc11-knockout ($Zdhhc11^{-/-}$) mice, ZDHC11 deficiency reduced IL-1β- and LPS-stimulated phosphorylation of TAK1, IKKα/β and p65, as well as IL-6 and TNFα production. *In vivo*, $Zdhhc11^{-/-}$ mice treated with LPS/D-galactosamine or infected with herpes simplex virus 1 showed significantly lower serum IL-6 levels than wild-type controls, confirming the physiological relevance of this axis in acute inflammation and antiviral responses (113). Collectively, this regulatory axis provides a mechanistic link between S-palmitoylation and NF-κB-driven

transcriptional programs that support T cell expansion and functional differentiation (Fig. 1B) (113). However, whether ZDHHC11 directly palmitoylates TRAF6 to drive this regulation or if direct TRAF6 palmitoylation underlies this regulation remains unclear.

STAT3 S-palmitoylation-depalmitoylation cycle drives Th17 differentiation. TH17 cells are a pro-inflammatory $CD4^+$ T cell subset characterized by the production of IL-17A, IL-17F and other inflammatory mediators. Dysregulated expansion and differentiation of TH17 cells, driven primarily by IL-6, TGF-β and IL-23 signaling, contribute substantially to intestinal inflammation and the pathogenesis of inflammatory bowel disease (IBD) (114,115). Consistent with this, TH17 cell abundance correlates positively with disease severity in both experimental models of IBD and in patients (116-120). STAT3 is a master transcription factor that integrates cytokine signals to regulate inflammatory and malignant processes. In naïve $CD4^+$ T cells, cytokine stimulation activates Janus kinase (JAK) -dependent STAT3 phosphorylation, resulting in its nuclear translocation and the transcriptional activation of Th17-associated genes, including RORC and IL17A, thereby promoting Th17-cell differentiation (116,121-123).

Membrane recruitment of STAT3 is a prerequisite for its efficient phosphorylation. A study has identified DHHC7 as the principal palmitoyl acyltransferase that catalyzes S-palmitoylation of STAT3 at Cys108 in both 293T cells and primary mouse splenocytes. As a membrane-targeting lipid modification, S-palmitoylation promotes the translocation of STAT3 to the plasma membrane, facilitating its interaction with JAK2 and subsequent phosphorylation. Functional analyses demonstrated that the S-palmitoylation-deficient C108S mutant exhibited markedly reduced phosphorylation compared with wild-type STAT3 in 293T cells and mouse splenocytes under TH17-polarizing conditions. Conversely, the phosphorylation-deficient STAT3 Y705F mutant retained normal S-palmitoylation, indicating that DHHC7-mediated S-palmitoylation promotes STAT3 activation, whereas STAT3 phosphorylation does not reciprocally regulate its S-palmitoylation status (Fig. 1C) (116).

Following cytokine-induced activation, phosphorylated STAT3 is selectively depalmitoylated by acyl protein thioesterase 2 (APT2/LYPLA2) in 293T cells and mouse splenocytes, facilitating its release from the plasma membrane and subsequent nuclear translocation (116). Thus, STAT3 activity is controlled by a reversible S-palmitoylation-depalmitoylation cycle coordinated by DHHC7 and APT2. DHHC7-mediated S-palmitoylation promotes membrane recruitment and JAK-dependent phosphorylation, whereas APT2-mediated depalmitoylation enables nuclear accumulation of activated STAT3 (116). This lipidation cycle is essential for optimal STAT3 signaling and TH17-cell differentiation in mouse splenocytes cultured under TH17-inducing conditions, as the disruption of either modification step significantly impairs TH17 lineage development, as assessed by flow cytometry and qPCR (116). In a dextran sulfate sodium (DSS)-induced mouse model of colitis (C57BL/6J mice), pharmacological inhibition of APT2 using ML349 or genetic knockout of Zdhhc7 alleviated colitis symptoms and reduced TH17 cell frequencies in splenocytes (116). Moreover, in human peripheral blood mononuclear cells from patients with IBD, including those with Crohn's disease and ulcerative colitis, ZDHHC7 and LYPLA2 mRNA levels were upregulated and correlated with STAT3 target gene expression and p-STAT3 levels, supporting the pathophysiological relevance of this cycle in human IBD (116). Overall, these findings establish that the STAT3 S-palmitoylation-depalmitoylation cycle is a critical regulatory mechanism controlling TH17-cell differentiation and highlight its important contribution to the pathogenesis of IBD in both murine models and human patients.

Loss of FoxP3 S-palmitoylation attenuates the immunosuppressive function of regulatory T cells (Tregs). Tregs are a specialized $CD4^+$ T cell subset that maintain immune homeostasis and prevent excessive immune activation. The transcription factor FoxP3 functions as a lineage-defining regulator of Tregs and is essential for their development, stable identity and suppressive function (124-126). Accumulating evidence indicates that FoxP3 activity is extensively regulated by diverse post-translational modifications, including S-palmitoylation, phosphorylation, ubiquitination, glycosylation and acetylation (127,128).

To define the S-palmitoylation landscape of FoxP3, Zhou *et al* (129) generated FoxP3-Myc and FoxP3-Flag expression constructs, overexpressed and affinity-purified the corresponding proteins in 293T cells and subsequently performed mass spectrometric analysis. They identified five S-palmitoylation sites within FoxP3 (Cys204, Cys218, Cys280, Cys281 and Cys424), each of which produced a characteristic mass increase of 238 Da in the corresponding peptide fragment. Subsequent co-immunoprecipitation analyses demonstrated that ectopic expression of DHHC2, DHHC3 or DHHC7 markedly enhanced FoxP3 S-palmitoylation. Mechanistically, S-palmitoylation-mediated regulation of FoxP3 subcellular localization may promote its nuclear enrichment and transcriptional activity, contributing to the maintenance of Treg suppressive programs (Fig. 1C). Accordingly, ABE and acyl-RAC assays confirmed that FoxP3 is palmitoylated in primary Tregs isolated from the lymph nodes of C57BL/6 mice. In parallel, flow cytometric analyses revealed that genetic deletion of Dhhc2 in C57BL/6 mice, generated by CRISPR/Cas9 genome editing, significantly increased the frequencies of activated $CD4^+$ and $CD8^+$ T cells in the spleens. Moreover, in a YUMM3.3 melanoma syngeneic mouse model, T-cell-specific deletion of Dhhc2 ($Dhhc2^{Flox/Flox}$; Dhhc2-T cell KO) suppressed tumor growth, reduced intranuclear FoxP3 expression in tumor-infiltrating Tregs and enhanced IFN-γ secretion by tumor-infiltrating $CD8^+$ T cells (129). These observations suggest that FoxP3 S-palmitoylation is closely associated with the maintenance of Treg suppressive function and may consequently modulate antitumor T cell immunity.

Integrating these observations, deficiency of DHHC enzymes responsible for FoxP3 S-palmitoylation markedly reduced the nuclear accumulation of FoxP3 in both peripheral lymphoid tissues and tumor-infiltrating Treg cells, resulting in impaired immunosuppressive activity within the TME. These findings further support the concept that S-palmitoylation-dependent regulation of FoxP3 constitutes an important molecular mechanism controlling Treg stability and function, with potential implications for antitumor immune regulation.

S-palmitoylation in T cell exhaustion and apoptosis. Following T cell proliferation and differentiation, chronic antigen exposure progressively induces a state of T cell exhaustion, characterized by diminished effector capacity and persistent upregulation of inhibitory receptors. Negative co-stimulatory receptors, including programmed cell death protein 1 (PD-1) and T cell immunoglobulin and mucin-domain containing-3 (TIM-3), serve as essential regulators of T cell responses by constraining their magnitude and duration, thus preserving immune equilibrium and preventing uncontrolled immune activation (130-132). Accordingly, immune checkpoint pathways have emerged as key therapeutic targets for the treatment of malignancies, autoimmune diseases and other immune-related disorders.

Accumulating evidence indicates that S-palmitoylation is closely associated with tumor initiation, progression and therapeutic responsiveness (130,132,133). Given its multifaceted roles in tumor biology, elucidating how S-palmitoylation regulates immune checkpoint signaling in T cells is of considerable mechanistic and translational significance. A more comprehensive understanding of this regulatory axis is expected to provide a molecular framework for the development of next-generation immunotherapeutic strategies and further improve the efficacy of current immune checkpoint-based therapies.

Tumor-cell-intrinsic PD-1 S-palmitoylation: Established evidence and unresolved relevance to exhausted T cells. PD-1, a critical inhibitory receptor expressed on the surface of T cells, is progressively upregulated following effector T cell activation. Engagement of PD-1 by its ligands, particularly programmed cell death ligand-1 (PD-L1), triggers the recruitment of SHP-1/SHP-2 phosphatases to immunoreceptor tyrosine-based switch motif, thereby attenuating proximal TCR/CD28 signaling, cytokine production, proliferation and cytotoxic effector functions (130,131,133,134). Yao *et al* (135) identified Cys192, located at the junction between the transmembrane domain and cytoplasmic tail of PD-1, as a *bona fide* S-palmitoylation site, which was subsequently validated by metabolic labeling assays in human colorectal cancer (CRC) RKO and HCT116, melanoma A375 and hepatoblastoma-derived HepG2 cells. In addition to serving as a post-translational modification, S-palmitoylation also plays an essential role in maintaining PD-1 protein stability. Elevated PD-1 expression has been observed in certain tumors, where it contributes to tumor progression independent of adaptive immune surveillance. Mechanistically, S-palmitoylation promotes the interaction of PD-1 with Rab11, as demonstrated by co-immunoprecipitation assays in HCT116, RKO, and LoVo cells, facilitating PD-1 transport to recycling endosomes while limiting its lysosomal degradation (Fig. 1C) (135). This process results in sustained PD-1 expression and prolonged inhibitory signaling. Consistently, treatment with the palmitoylation inhibitor 2-bromopalmitate (2-BP) or a mutation of Cys192 to serine disrupted PD-1-Rab11 binding and accelerated PD-1 degradation, which was rescued by the lysosomal inhibitor chloroquine in RKO and A375 cells. Although PD-1 S-palmitoylation stabilizes PD-1 and enhances tumor-intrinsic mTOR signaling, as evidenced by the increased phosphorylation of S6 and eIF4E following DHHC9 overexpression or palmostatin-B treatment in HepG2, NB4 and LoVo cells (135), whether this lipid modification regulates PD-1 function and metabolic reprogramming in exhausted T cells remains unclear. Thus, these results identify PD-1 S-palmitoylation as an important regulatory mechanism controlling immune checkpoint signaling and highlight its pharmacological targeting as a promising therapeutic strategy in cancer immunotherapy.

DHHC9-mediated TIM-3 S-palmitoylation stabilizes immune checkpoint molecules and drives immune exhaustion. TIM-3 was initially identified as a cell-surface receptor preferentially expressed in Th1 cells, in which interaction with its ligand galectin-9 triggers inhibitory signals that drive Th1-cell apoptosis (136,137). TIM-3 has emerged as a broadly expressed immune checkpoint receptor in diverse immune cell subsets, and its interactions with multiple ligands orchestrate immune tolerance, inflammatory responses and immune homeostasis (132,138,139).

Zhang *et al* (132) demonstrated that human TIM-3 undergoes S-palmitoylation at Cys296, a modification catalyzed by the palmitoyl acyltransferase DHHC9. Mechanistically, S-palmitoylation inhibits the interaction between TIM-3 and the E3 ubiquitin ligase HRD1, preventing TIM-3 polyubiquitination and subsequent proteasomal degradation and ultimately stabilizing TIM-3 protein (Fig. 1C). Conversely, depletion of DHHC9 alleviates CAR-T cell exhaustion, whereas peptide-mediated inhibition of TIM-3 S-palmitoylation accelerates TIM-3 turnover and enhances the antitumor activity of both CAR-T and natural killer (NK) cells. In summary, these studies revealed that S-palmitoylation serves as a critical regulatory axis controlling TIM-3 stability and checkpoint function, which, in turn, shapes the balance between immune suppression and antitumor immunity. Targeting the DHHC9/TIM-3 S-palmitoylation pathway may provide a promising strategy for reprogramming exhausted immune cells and improving the efficacy of next-generation adoptive cell therapies.

S-palmitoylation-depalmitoylation of tumor necrosis factor receptor 1 (TNFR1): A binary switch steering prosurvival vs. apoptotic signaling. As a pleiotropic cytokine, TNF-α coordinates diverse biological processes, including inflammation, cellular proliferation, differentiation and multiple forms of programmed cell death (140-142). The biological activities of TNF-α are primarily mediated through two receptors, TNFR1 and TNFR2. Among these, TNFR1 contains a C-terminal death domain and belongs to the death receptor superfamily, mediating the majority of characterized TNF-induced cellular responses (142,143). Following ligand binding, TNFR1 undergoes oligomerization and serves as a signaling scaffold that recruits multiple adaptor proteins to form a membrane-associated signaling complex. This complex subsequently activates the NF-κB and MAPK pathways to promote cell survival or, alternatively, undergoes endocytosis to initiate apical caspase activation and apoptotic signaling (141,144). The balance between survival and apoptosis is determined by the selective assembly of distinct signaling complexes that are closely linked to the subcellular localization of TNFR1. TNFR1 retention at the plasma membrane preferentially supports pro-survival signaling, whereas receptor internalization redirects signaling toward apoptotic pathways (145-147). Consequently, the internalization and intracellular trafficking

of TNFR1 constitute essential steps in signal diversification, suggesting that S-palmitoylation participates in coordinating receptor trafficking to distinct signaling platforms.

S-palmitoylation of TNFR1 occurs during its trafficking from the ER and Golgi apparatus to the plasma membrane. In human monocytic U937 cells, although Cys248 is not the only S-palmitoylation site, it is indispensable for efficient receptor delivery to the plasma membrane and subsequent activation of NF-κB signaling (Fig. 1C), as demonstrated by reduced surface expression and impaired IκB degradation in TNF-R1-knockout U937 cells reconstituted with the C248S mutant (145). Activation of TNFR1 requires depalmitoylation mediated by APT2, which permits receptor redistribution into distinct lipid raft microdomains and facilitates the recruitment of membrane-associated signaling complex I, comprising TRADD, RIPK1 and TRAF2. In U937 cells, APT2 is transiently recruited to the TNFR1 signaling complex within 5-10 min of TNF stimulation, and its inhibition by the selective inhibitor ML349 or shRNA-mediated knockdown blocks TNF-induced IκB degradation (145). Conversely, APT2 inhibition prevents the redistribution of activated TNFR1 and retains the receptor within the plasma membrane caveolae, resulting in enhanced neutral sphingomyelinase (nSMase) activity, increased ceramide production and a subsequent shift toward apoptotic signaling (145). In U937 cells, APT2 inhibition also enhances TNF-induced ceramide generation and caspase-3 activation, effects that are reversed by the nSMase inhibitor GW4869. These findings indicate that the dynamic S-palmitoylation-depalmitoylation cycle of TNFR1 functions as a molecular switch that determines cellular fate and is indispensable for maintaining TNF-mediated signaling homeostasis.

Fas/FasL S-palmitoylation dynamically regulates apoptotic signaling and cellular homeostasis. Fas (also known as CD95; encoded by FAS, formerly TNFRSF6) is a prototypical death receptor within the TNFR superfamily. Following interaction with its cognate ligand FasL (formerly TNFSF6), Fas initiates a well-orchestrated cascade of signaling events. In primary cells, Fas transduces apoptotic signals through the assembly of the death-inducing signaling complex, which comprises the adaptor protein FADD, caspase regulator c-FLIP and initiator protease caspase-8 (148-150).

Accumulating evidence indicates that efficient propagation of Fas-mediated apoptotic signaling requires receptor clustering within defined plasma membrane subdomains. Fas is palmitoylated at an intracellular cysteine residue proximal to its transmembrane domain (Cys199 in humans), which is essential for inducing cell death (151,152). Mechanistic studies by Rossin *et al* (153), Chakrabandhu *et al* (151) and Hueber *et al* (154) demonstrated that the pro-apoptotic function of Fas S-palmitoylation depends on two interrelated processes: The formation of higher-order Fas supramolecular clusters and the partitioning of Fas into cholesterol- and sphingolipid-enriched membrane nanodomains. Both processes are required for the optimal activation of Fas-triggered apoptotic signaling. Loss of Fas S-palmitoylation leads to impaired receptor internalization and attenuated activation of downstream caspase cascades (151,154).

In human colorectal adenocarcinoma SW480 and SW620 cells, reduced Fas expression following the disruption of S-palmitoylation suggests that S-palmitoylation-deficient Fas is more susceptible to degradation. Indeed, compared with wild-type Fas, both the total and plasma membrane-associated pools of palmitoylation-deficient Fas C199V mutant exhibits markedly reduced stability, indicating that S-palmitoylation stabilizes Fas at the cell surface and prevents premature receptor turnover (153). Palmitoyl acyltransferase DHHC7 was identified as the principal enzyme catalyzing Fas S-palmitoylation, as demonstrated by siRNA-mediated knockdown and overexpression experiments coupled with ABE assays. DHHC7-mediated S-palmitoylation preserves Fas expression by limiting lysosomal degradation, as evidenced by the restoration of Fas protein levels following treatment with the lysosomal inhibitors chloroquine and bafilomycin A1, which in turn sustains Fas-dependent apoptotic signaling (Fig. 1C) (153).

FasL is a type II transmembrane protein belonging to the TNF superfamily. Upon binding to Fas, FasL induces apoptosis in Fas-expressing target cells (155). FasL is predominantly expressed in hematopoietic compartments *in vivo*, where it plays a critical role in activation-induced cell death of T lymphocytes and contributes to the cytotoxic effector functions of T and NK cells (156). Using human WSU B cells stably transfected with hFasL and co-cultured with Fas-expressing human JH6.2 Jurkat T cells, Guardiola-Serrano *et al* (156) demonstrated that human FasL undergoes S-palmitoylation at Cys82, located within the N-terminal region of its transmembrane domain (Fig. 1C). Using WSU cells expressing the palmitoylation-deficient hFasLC82S mutant, subsequent experiments revealed that ADAM10-mediated cleavage and processing of FasL require intact cholesterol- and sphingolipid-rich membrane nanodomains (lipid rafts) as well as Fas-FasL engagement. In WSU cells expressing the receptor-binding-deficient hFasLA247E mutant, which cannot interact with Fas, FasL processing by ADAM10 was markedly reduced, indicating that receptor binding is required for efficient cleavage. Proteolytic processing of FasL following receptor binding confines its cytotoxic activity to engaged target cells, thereby limiting bystander cell damage. S-palmitoylation of FasL modulates its partitioning into lipid rafts, as demonstrated by fluorescence correlation spectroscopy analysis of GFP-tagged hFasL, hFasLC82S and hFasLA247E expressed in COS-7 cells, representing a key regulatory mechanism that fine-tunes ADAM10-dependent FasL processing and the magnitude of FasL-mediated cytotoxicity (156).

Therefore, the dynamic S-palmitoylation-depalmitoylation cycles of Fas and FasL critically regulate membrane compartmentalization, protein stability and signal output. This regulatory axis determines the balance between cell survival and apoptosis, functioning as a molecular rheostat that shapes immune homeostasis and contributes to cancer pathogenesis.

4. Tumor-cell-intrinsic S-palmitoylation regulating T cell immunity

S-palmitoylation serves as an important molecular interface that couples metabolic dysregulation with immune escape within the tumor immune microenvironment. Tumor cells exploit ZDHHC3- and ZDHHC9-mediated S-palmitoylation to enhance PD-L1 stability and attenuate $CD8^+$ T cell effector activity. In parallel,

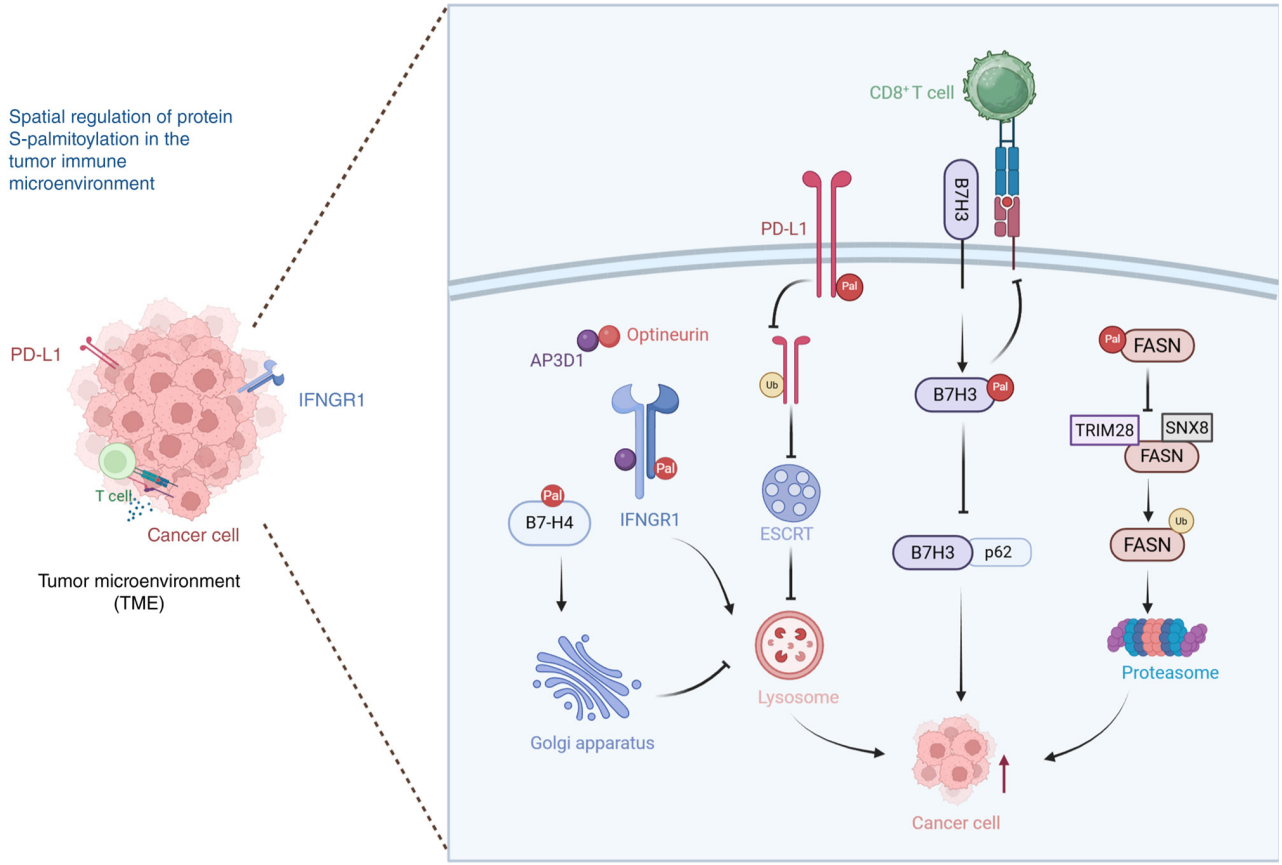


Figure 2. Spatial regulation of protein S-palmitoylation in the tumor immune microenvironment. Left panel: schematic overview of the TME, illustrating the interaction between cancer cells and CD8+ T cells. Right panel: magnified view of S-palmitoylation-mediated regulation of key immune-regulatory and metabolic proteins in tumor cells. B7-H4 is palmitoylated in the Golgi apparatus, which protects it from lysosomal degradation and sustains its immunosuppressive function. IFNGR1 S-palmitoylation, in coordination with optineurin, prevents AP3D1-mediated lysosomal sorting and degradation, preserving IFN-γ signaling integrity. S-palmitoylation of PD-L1 prevents its ubiquitination and subsequent ESCRT-mediated lysosomal degradation, thereby sustaining PD-L1 surface expression and attenuating CD8+ T cell-mediated antitumor immunity. S-palmitoylation of B7H3 disrupts its interaction with the autophagy receptor SQSTM1/p62, limiting autophagic degradation and enhancing B7H3 stability, which further suppresses CD8+ T cell activity. In addition, S-palmitoylation of FASN disrupts its interaction with the TRIM28-SNX8 E3 ubiquitin ligase complex, thereby preventing ubiquitin-proteasome-mediated degradation and promoting *de novo* fatty acid synthesis. Collectively, these spatially regulated S-palmitoylation events promote tumor immune evasion and metabolic adaptation. Figure created with BioRender.com. PD-L1, programmed death-ligand 1; B7H3, B7 homolog 3; B7-H4, B7 homolog 4; IFNGR1, interferon γ receptor 1; FASN, fatty acid synthase; ESCRT, endosomal sorting complex required for transport; Ub, ubiquitin; Pal, S-palmitoylation; TME, tumor microenvironment.

ZDHHC24-dependent S-palmitoylation of B7 homolog 3 (B7H3) protein prevents its autophagic turnover, consequently maintaining an immunosuppressive tumor milieu (157). Collectively, tumor-cell-intrinsic S-palmitoylation orchestrates a multifaceted immuno-evasive program by stabilizing immune checkpoint proteins at the post-translational level while simultaneously reinforcing metabolic adaptations that support tumor growth and immune evasion (22,158).

In addition to PD-L1 and B7H3, emerging evidence has extended the regulatory scope of tumor-cell-intrinsic S-palmitoylation to other immunomodulatory targets. B7-H4 S-palmitoylation at Cys130, catalyzed by ZDHHC3, protects this checkpoint molecule from lysosomal degradation, sustains its immunosuppressive activity and promotes tumor progression (159). Likewise, S-palmitoylation of IFN-γ receptor 1 (IFNGR1) at Cys122 governs receptor trafficking and turnover, with its disruption compromising IFN-γ signaling integrity and conferring intrinsic resistance to immune checkpoint blockade (ICB) in CRC (160). These findings collectively establish tumor-cell-intrinsic S-palmitoylation as a key regulatory hub that links post-translational lipid modifications to immune checkpoint stability, metabolic adaptation and therapeutic responsiveness, thereby offering multiple nodes for therapeutic intervention in cancer immunotherapy (Fig. 2).

PD-L1 S-palmitoylation: A lipidic rheostat tuning tumor immune evasion. PD-L1 is a type I transmembrane glycoprotein that is widely expressed across diverse tumor types (161). Under physiological conditions, activated antigen-specific cytotoxic T lymphocytes (CTLs) recognize and directly eliminate malignant cells. However, tumor cells with elevated PD-L1 expression effectively escape immune surveillance by interacting with PD-1 on infiltrating immune cells. The PD-1/PD-L1 interaction induces exhaustion of infiltrating CD8+ CTLs, compromises tumor-reactive CTL responses and suppresses the function of Tregs, which collectively attenuate immune activation and ultimately facilitate tumor progression into the surrounding tissues (162,163). Beyond its immunosuppressive activity, PD-L1 provides intrinsic protection against apoptosis in tumor cells, underscoring the PD-1/PD-L1 signaling axis as an attractive target for cancer immunotherapy (163,164).

Studies have shown that S-palmitoylation is a critical determinant of PD-L1 protein stability. Yang *et al* (165) demonstrated that in breast cancer cells, palmitoyl acyltransferase ZDHHC9 catalyzes PD-L1 S-palmitoylation at Cys272, thus enhancing PD-L1 stability. Similarly, Yao *et al* (166) reported that ZDHHC3 mediates PD-L1 S-palmitoylation at the same residue in CRC. This modification sustains elevated PD-L1 expression by suppressing ubiquitination and preventing its trafficking into multivesicular bodies via the endosomal sorting complex required for transport pathway, which reduces lysosomal degradation and sustains immune checkpoint activity (Fig. 2). In human CRC RKO and HCT116 cells, treatment with the marine natural product benzosceptrin C (BC) inhibited DHHC3, blocked PD-L1 palmitoylation at Cys272 and promoted PD-L1 degradation through the lysosomal pathway. Consistently, in MC38 tumor-bearing C57BL/6 mice, BC administration reduced tumoral PD-L1 expression, increased tumor-infiltrating $CD8^+$ T cells and suppressed tumor growth (163). Together, these findings demonstrate that S-palmitoylation represents a key post-translational regulatory mechanism controlling PD-L1 protein stability. Furthermore, it highlights the broader role of S-palmitoylation in shaping tumor immune escape and remodeling of the tumor immune microenvironment.

B7H3 S-palmitoylation: Maintenance of immunosuppression through the inhibition of autophagy-mediated degradation. B7H3 (also known as CD276) is a type I transmembrane protein that belongs to the B7 immunoglobulin superfamily (167). B7H3 is aberrantly upregulated across a broad spectrum of malignancies and its elevated expression is closely associated with unfavorable clinical outcomes and poor patient prognosis (168-170). Accumulating evidence indicates that therapeutic blockade of B7H3 enhances $CD8^+$ T cell infiltration, restores effector function and restrains tumor progression, highlighting B7H3 as a promising target for cancer immunotherapy (168,171,172).

Rao *et al* (157) demonstrated that palmitoyl acyltransferase ZDHHC24 catalyzes the S-palmitoylation of B7H3 at Cys496. In human (RKO and SW480) and murine (CT26 and MC38) CRC cell lines, this lipid modification disrupts the B7H3-SQSTM1/p62, interaction, limiting autophagic degradation and enhancing B7H3 protein stability, as demonstrated by acyl-biotin exchange, cycloheximide chase and co-immunoprecipitation assays. Increased B7H3 expression suppressed $CD8^+$ T cell-mediated antitumor immunity and promoted an immunosuppressive TME (Fig. 2). In a colitis-associated CRC mouse model using intestinal epithelial cell-specific Zdhhc24-deficient ($Zdhhc24^{\Delta IEC}$) mice on a C57BL/6J background, disruption of this regulatory axis significantly enhanced $CD8^+$ T cell-dependent antitumor responses. This effect was observed either through mutation of the C496 residue in CT26 and MC38 cells implanted subcutaneously in immunocompetent BALB/c and C57BL/6J mice, or through genetic deletion of ZDHHC24, and was evidenced by increased tumor-infiltrating $CD8^+$ T cells, elevated granzyme B and IFN-γ expression as well as reduced tumor growth (157). At the mechanistic level, Cys496 S-palmitoylation stabilizes B7H3 by preventing autophagic turnover, allowing B7H3 to maintain its immunosuppressive activity within the TME and facilitating tumor immune escape. Collectively, these findings establish B7H3 S-palmitoylation as a critical post-translational mechanism that regulates immune evasion by controlling protein stability and identify the ZDHHC24/B7H3 axis as a potential therapeutic target for restoring $CD8^+$ T cell-mediated antitumor responses.

B7-H4 S-palmitoylation: Evading lysosomal degradation and enhancing immune suppression. B7-H4 (also known as VTCN1, B7S1 or B7x) is a type-I transmembrane glycoprotein belonging to the B7 family. Through interactions with an unidentified receptor expressed on activated T cells, B7-H4 suppresses T cell proliferation and cytokine production (173-175). In addition to its immunomodulatory activity, B7-H4 exerts diverse pro-tumorigenic functions by promoting tumor cell proliferation, invasion, metastasis and resistance to apoptosis. Aberrant upregulation of B7-H4 has been documented across multiple human malignancies, including breast, ovarian and uterine cancer. In these settings, B7-H4 functions as an immune checkpoint molecule that reinforces the immunosuppressive TME (176,177).

Yan *et al* (159) demonstrated that the palmitoyl acyltransferase ZDHHC3 catalyzes S-palmitoylation of B7-H4 at Cys130 in human (MDAMB468 and T47D) and mouse (4H11 and Py230) breast cancer cell lines. Mechanistically, this lipid modification protected B7-H4 from lysosomal degradation, resulting in sustained protein stability and persistent immunosuppressive activity. As ZDHHC3 is predominantly localized in the Golgi apparatus, B7-H4 S-palmitoylation likely occurs during Golgi-associated protein trafficking. Consistent with these observations, genetic depletion of ZDHHC3 in 4H11 mouse breast cancer cells elicited robust antitumor immune responses and markedly suppressed tumor progression in subcutaneous syngeneic C57BL/6 mouse models.

In addition, the FDA-approved cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, abemaciclib, reduced B7-H4 protein abundance independent of CDK4/6 inhibition or cell cycle arrest, leading to enhanced antitumor immunity and reduced tumor growth (159). Given that ZDHHC3-mediated S-palmitoylation stabilizes B7-H4 by preventing lysosomal degradation, the selective inhibition of ZDHHC3 or pharmacological manipulation of the lysosomal degradation pathway may destabilize B7-H4 and accelerate its turnover, ultimately enhancing antitumor immune responses (Fig. 2) (159). Thus, these findings identify B7-H4 S-palmitoylation as an important post-translational mechanism that supports tumor immune evasion. They further highlight therapeutic targeting of the ZDHHC3/B7-H4 axis, together with repurposing of abemaciclib, as a promising strategy for the treatment of B7-H4-positive malignancies.

IFNGR1 S-palmitoylation: Maintaining signal integrity to counteract immunotherapy resistance. Although ICB has achieved durable clinical responses in multiple malignancies, its efficacy in CRC remains largely limited to molecularly-defined subsets of patients. For instance, ~15% of CRCs exhibit microsatellite instability-high or deficient mismatch repair phenotypes, which are characterized by elevated neoantigen burden and enhanced responsiveness to PD-1/PD-L1 blockade. However, the

majority of microsatellite-stable CRCs remain refractory to current immunotherapeutic approaches (178-180).

IFNγ signaling represents a central axis of antitumor immunity; it enhances tumor immunogenicity, promotes antigen presentation and coordinates immune cell recruitment. IFNγ induces the expression of MHC class I and class II molecules, stimulates IL-12 production by antigen-presenting cells, reinforces Th1 differentiation through the STAT1/T-bet pathway and drives CXCL9/CXCL10-mediated recruitment of CTLs and NK cells into the TME, thereby facilitating effective immune-mediated tumor control (181,182).

IFNGR1 undergoes S-palmitoylation at Cys122. Under physiological conditions, the adaptor protein AP3D1 recognizes palmitoylated IFNGR1 and directs the receptor for lysosomal degradation. Conversely, optineurin, an immune regulatory adaptor protein, interacts with AP3D1 and prevents lysosomal trafficking of palmitoylated IFNGR1, preserving receptor stability and maintaining the integrity of IFNγ signaling as well as MHC class I antigen-presentation pathways (Fig. 2) (160). In human (LS174T and DLD1) and murine (MC38 and CT26) colon cancer cell lines, optineurin deficiency (via shRNA knockdown or CRISPR/Cas9 knockout) compromises these processes, promotes immune evasion and confers intrinsic resistance to ICB. By contrast, loss of IFNGR1 S-palmitoylation via the C122A mutation abolishes the IFNGR1-AP3D1 interaction, stabilizes IFNGR1 and enhances IFNγ/MHC-I signaling (160). In syngeneic mouse models (C57BL/6 MC38 and BALB/c CT26 tumor-bearing mice) and an azoxymethane/DSS-induced colitis-associated CRC model with intestinal epithelial cell-specific optineurin deletion (optineurin$^{\Delta IEC}$ mice), optineurin deficiency accelerated tumor growth, impaired $CD8^+$ T cell effector function and reduced the efficacy of anti-PD-L1 therapy (160). Based on these results, Du *et al* (160) proposed in a proof-of-concept study that therapeutic strategies aimed at stabilizing IFNGR1 via modulation of its S-palmitoylation status, may overcome intrinsic immunotherapy resistance in CRC. In preclinical models, pharmacological inhibition of IFNGR1 S-palmitoylation using the palmitoylation inhibitor cerulenin enhanced antitumor immune responses and sensitized previously resistant tumors to ICB. Together, these findings establish dynamic regulation of IFNGR1 S-palmitoylation as a critical determinant of IFNγ signaling integrity and responsiveness to immune checkpoint therapy in CRC. In addition, they highlight the IFNGR1-optineurin signaling axis as an attractive therapeutic target for overcoming intrinsic resistance to cancer immunotherapy.

5. S-palmitoylation in dendritic cells (DCs) and other antigen-presenting or myeloid cells

DCs are the most potent professional antigen-presenting cells and serve as central orchestrators of adaptive immune responses while maintaining critical functions in innate immune surveillance (183,184). Therefore, a comprehensive understanding of post-translational modifications that regulate DC biology is crucial for elucidating the complex molecular mechanisms underlying immune regulation. Utilizing click chemistry-based proteomic profiling combined with high-resolution mass spectrometry, researchers have identified >550 palmitoylated proteins in resting bone marrow-derived DCs, including key components of TLR signaling pathways (TLR2 and TLR9), co-stimulatory molecules (CD80 and CD86), transcriptional regulators (NF-κB1 and NEMO) and metabolic enzymes (185,186). Among these substrates, the S-palmitoylation of TLR2 at Cys609 is essential for proper membrane localization and functional responsiveness to microbial ligands (69).

Notably, a 2024 study by Ni *et al* (187) revealed a distinct cyclical mechanism of TLR9 regulation. In this model ZDHHC3 mediates S-palmitoylation of TLR9 in the Golgi apparatus, whereas PPT1 catalyzes its depalmitoylation in lysosomes. In murine RAW264.7 macrophages and 293T cells overexpressing TLR9, as well as in mouse Flt3L-derived plasmacytoid DCs (pDCs) and bone marrow-derived macrophages, this dynamic cycle precisely controls TLR9 trafficking, its release from the chaperone UNC93B1 and subsequent ligand responsiveness, thereby providing a direct regulatory layer for TLR9 function at the level of the receptor itself (187). The physiological significance of this regulatory axis was further validated in a B6.Sle1yaa mouse model of systemic lupus erythematosus (SLE), in which genetic deficiency of PPT1 or pharmacological inhibition with HDSF reduced antinuclear antibody levels and attenuated nephritis. Furthermore, *in vitro* treatment with HDSF suppressed IFNα production by pDCs in both patients with SLE and healthy donors, confirming the translational relevance of this mechanism in human immune cells (187). Notably, this mechanism differs from TLR9-driven palmitoylome remodeling in DCs, which results from broad alterations in the cellular S-palmitoylation landscape rather than the direct modification of TLR9.

Activation of TLR9 induces extensive remodeling of the DC S-palmitoylation landscape. This remodeling results in increased modification of 185 proteins, which are significantly enriched in pathways associated with NF-κB signaling, the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway and mitochondrial respiratory chain function (183). These findings indicate that S-palmitoylation contributes to metabolic reprogramming associated with DC activation. Notably, the palmitoyl transferase ZDHHC9 displays substrate-selective activity in DCs; its deficiency selectively reduces TLR9-induced S-palmitoylation of NF-κB1, NEMO, interferon-induced transmembrane protein 3 and several metabolic enzymes, including NADH dehydrogenase ubiquinone flavoprotein 1 and ubiquinol-cytochrome c reductase iron-sulfur protein 1. However, depletion of ZDHHC9 does not affect DC differentiation, maturation or their capacity to activate T cells, suggesting functional compensation among members of the ZDHHC enzyme family (185,186).

In addition to functioning as an endogenous post-translational modification, S-palmitoylation can also be exploited exogenously as a chemical tool to modulate antigen presentation. Exogenously palmitoylated antigenic peptides provide an innovative approach to enhance DC-mediated cross-presentation by virtue of their intrinsic membrane-integrating properties. The covalent attachment of a single palmitic acid moiety (C16:0) to the N-terminus of antigenic peptides enables efficient receptor-independent incorporation into the DC lipid bilayer, facilitating rapid cellular uptake. Following internalization, these peptides undergo processing through both

cytosolic proteasome-dependent degradation and vacuolar processing pathways, substantially enhancing MHC class I peptide loading and subsequent $CD8^+$ T cell activation (188). Notably, in Batf3-deficient mice, palmitoylated antigenic peptides are efficiently cross-presented by DCs, demonstrating that this process does not strictly depend on conventional cross-presenting DC subsets. Moreover, this strategy can be directly applied to tumor cells or tumor-derived apoptotic vesicles, increasing the abundance of MHC-I/peptide complexes on tumor cell surfaces and enhancing CTL-mediated recognition and elimination. These modifications ultimately confer robust tumor-suppressive effects *in vivo* (188).

This exogenous application is mechanistically distinct from the endogenous cysteine S-acylation catalyzed by ZDHHC palmitoyltransferases. Although both involve covalent palmitate attachment, the exogenous conjugation of palmitic acid to the N-terminus of antigenic peptides does not rely on enzymatic catalysis or target endogenous cysteine residues. Instead, it exploits the physicochemical properties of the lipid moiety to facilitate membrane integration and antigen uptake. Although both strategies rely on palmitate modification, their mechanisms, downstream effects and applications differ fundamentally.

Collectively, endogenous S-palmitoylation represents an important regulatory mechanism controlling DC signaling and functional activation, whereas exogenous palmitoylated antigenic peptides provide an effective strategy for enhancing antigen presentation. Together, these findings establish S-palmitoylation as a fundamental regulatory axis in DC-mediated immune regulation and highlight its potential for therapeutic manipulation of antitumor immunity.

6. Metabolism-S-palmitoylation crosstalk in the TME

Aberrant fatty acid metabolism within the TME is characterized by enhanced *de novo* lipogenesis and increased uptake of extracellular fatty acids, resulting in substantial local accumulation of palmitate (189,190). Metabolic reprogramming reshapes cellular lipid availability and palmitoyl-CoA metabolism by modulating global protein S-palmitoylation profiles. Conversely, S-palmitoylation dynamically regulates the localization, stability and functional activity of metabolic enzymes and transporters, revealing an interconnected regulatory network linking lipid metabolism with post-translational modification (11,191-193). A well-characterized example of this regulatory interplay was provided by Hao *et al* (194), who elucidated the critical role of dynamic CD36 S-palmitoylation in controlling fatty acid uptake in murine 3T3-L1 adipocytes and primary adipocytes derived from stromal vascular fractions of wild-type and Cd36-knockout mice, as well as in high-fat-diet-induced obesity models. Under basal conditions, S-palmitoylation maintains CD36 enrichment within the plasma membrane lipid rafts, ensuring its functional availability for fatty acid sensing and transport. Following binding to long-chain fatty acids, CD36 activates the downstream kinase, LYN, which subsequently phosphorylates and inhibits DHHC5, a palmitoyl acyltransferase responsible for CD36 modification. This inhibition triggers APT1-mediated CD36 depalmitoylation. The depalmitoylated CD36 then recruits SYK kinase and initiates VAV- and JNK-dependent caveolae-mediated endocytosis, ultimately promoting fatty acid internalization (194). This reversible S-palmitoylation-depalmitoylation cycle enables CD36 to dynamically adapt to fluctuations in extracellular fatty acid availability and precisely adjust fatty acid uptake efficiency. However, it should be noted that this model was primarily established in adipocytes and validated in the context of highfatdietinduced metabolic stress. Its direct applicability to tumor or immune cells within the TME remains to be experimentally verified.

S-palmitoylation of fatty acid synthase (FASN) is another important regulatory mechanism involved in metabolic reprogramming. Mo *et al* (195) demonstrated that, in human hepatocellular carcinoma (HCC) cell lines (Huh7, HCCLM3 and Hep3B) and the hepatoblastoma-derived HepG2 cell line, as well as in diethylnitrosamine (DEN) and DEN/carbon tetrachloride-induced HCC mouse models, the palmitoyl transferase ZDHHC20 catalyzed FASN S-palmitoylation at cysteine residues 1471 and 1881. This modification prevented ubiquitin-proteasome-mediated degradation of FASN by disrupting its interaction with the E3 ubiquitin ligase complex SNX8-TRIM28, consequently stabilizing FASN protein abundance and sustaining *de novo* fatty acid synthesis (Fig. 2). Genetic deletion of ZDHHC20 or mutation of FASN S-palmitoylation sites accelerated FASN turnover and markedly suppressed chemically-induced hepatocarcinogenesis. Overall, these findings demonstrated that the palmitate-driven equilibrium between S-palmitoylation and depalmitoylation coordinates two fundamental aspects of fatty acid metabolism: Transport mediated by CD36 and synthesis mediated by FASN. This reciprocal regulatory network integrates metabolic adaptation with lipid modification, linking tumor metabolic reprogramming to S-palmitoylation-dependent signaling regulation; it further identifies this axis as a potential therapeutic vulnerability for targeting tumor metabolism.

7. Therapeutic strategies, supporting evidence and translational barriers

Therapeutic strategies targeting S-palmitoylation in cancer immunotherapy primarily involve two complementary approaches: Broad-spectrum inhibition of S-palmitoylation and selective targeting of individual ZDHHC palmitoyltransferases. Although the pan-S-palmitoylation inhibitor, 2-BP, exhibits potent antitumor activity by suppressing tumor cell proliferation, inducing apoptosis and displaying synergistic effects in combination with chemo- or immunotherapy, its clinical application remains limited owing to poor target specificity, substantial off-target effects, and unfavorable pharmacokinetic properties (196-201). Consequently, the development of subtype-selective ZDHHC inhibitors has become a major research focus. Several ZDHHC enzymes, including ZDHHC3, ZDHHC12 and ZDHHC15, have been identified as potential therapeutic targets; however, selective small-molecule inhibitors of these enzymes remain largely confined to preclinical investigations (197,198).

Targeting S-palmitoylation also provides opportunities for synergistic integration with the established anticancer therapies. In combination with an ICB, transmembrane peptides designed to disrupt B7H3 S-palmitoylation accelerate B7H3 degradation and enhance the efficacy of anti-PD-1 monoclonal

antibodies by restoring $CD8^+$ T cell effector activity. In the context of metabolic intervention, enhanced carnitine palmitoyltransferase 1A (CPT1A) expression promotes mitochondrial antiviral signaling protein (MAVS) S-palmitoylation and type I interferon signaling, whereas pharmacological inhibition of ZDHHC8 by PF-670462 induces glutathione peroxidase 4 (GPX4) degradation and triggers ferroptotic cell death, both of which improve tumor responsiveness to PD-1-based immunotherapy (202,203). Furthermore, combining S-palmitoylation-targeted approaches with chemotherapy or molecular targeted therapies may overcome treatment resistance. For example, siRNA-mediated inhibition of ZDHHC12 increases cisplatin sensitivity through reactive oxygen species (ROS) accumulation and targeting ZDHHC2 reverses enzalutamide resistance (204,205). In addition, pharmacological inhibition of FASN with orlistat reduces PD-L1 S-palmitoylation and membrane stability, consequently enhancing antitumor immune responses (206). Thus, these combination strategies exploit the multifaceted functions of S-palmitoylation in regulating immune checkpoint stability, metabolic adaptation and tumor cell survival. By promoting immunogenic cell death (ICD), reshaping the tumor immune microenvironment and restoring metabolic homeostasis, therapeutic modulation of the S-palmitoylation machinery represents a promising avenue for overcoming acquired resistance and expanding the efficacy of current cancer treatment modalities.

Monotherapy targeting S-palmitoylation. 2-BP is the most widely used broad-spectrum inhibitor of protein S palmitoylation. As a palmitate analog, 2-BP inhibits the DHHC family of palmitoyl acyltransferases by covalently modifying the catalytic cysteine within the DHHC motif, thereby blocking auto-S-palmitoylation and subsequent substrate acylation. However, its broad reactivity toward multiple cellular targets should be considered when interpreting the experimental results (196,207). Several studies have demonstrated the antitumor activity of 2-BP in multiple cancer types. For instance, in Burkitt's lymphoma cells, 2-BP reduced cell viability in a dose-dependent manner by triggering a marked increase in apoptosis, with similar outcomes observed in other B-cell lymphoma subtypes (196,197). In glioma models, 2-BP inhibited GL261 cell growth in a time- and dose-dependent manner, promoted apoptotic cell death and attenuated autophagic activity (198). Furthermore, 2-BP reduced PD-L1 abundance in tumor cells and tumor-derived exosomes, alleviated immunosuppressive signaling and enhanced the antitumor efficacy of cisplatin-based therapy (199). In HCC, 2-BP suppressed GSDME S-palmitoylation, thereby limiting lenvatinib-induced pyroptotic responses (200).

Despite its broad experimental utility, the clinical translation of 2-BP remains severely restricted by intrinsic limitations, notably its lack of target selectivity. Proteomic profiling of 2-BP-treated Burkitt's lymphoma cells revealed 1,089 differentially expressed proteins, with only a proportion directly attributable to known S-palmitoylation-dependent pathways, highlighting extensive downstream perturbations and potential off-target effects associated with global S-palmitoylation inhibition (197,201). Significant cytotoxicity has also been reported; for example, treatment with 200 μM 2-BP induced extensive cell death in B-cell lymphoma, resulting in the exclusion of the highest concentration from subsequent analyses (197). Moreover, certain tumor models exhibit limited responsiveness to 2-BP, as demonstrated by the minimal sensitivity of glioma C6 cells, which may be attributed to insufficient drug uptake or elevated expression of S100 proteins (198). Thus, these limitations have confined 2-BP primarily to use as a preclinical research tool with limited potential for clinical applications. As a broad-spectrum inhibitor, 2-BP has been used primarily as a mechanistic tool, with antitumor effects demonstrated *in vitro* and in animal models. However, it has not yet been evaluated in humanized models, pharmacokinetic/pharmacodynamic studies or clinical trials.

Given these challenges, the development of selective inhibitors that target individual ZDHHC isoforms has become an important direction in this field. In B-cell lymphoma, Liu *et al* (197) evaluated cyano-myracrylamide (CMA), another broad-spectrum S-palmitoylation inhibitor, and found that it induced apoptosis at relatively low concentrations while displaying reduced inhibitory activity toward ZDHHC3 and ZDHHC12. Although CMA exhibits partial subtype preference, it lacks sufficient selectivity for therapeutic applications. Thus, CMA also remains a broad mechanistic tool with limited subtype selectivity and has not advanced beyond *in vitro* pharmacological validation. Tang *et al* (198) identified ZDHHC12, ZDHHC15, ZDHHC22 and ZDHHC23 as important palmitoyltransferases involved in glioma biology. Elevated expression of ZDHHC12 and ZDHHC15 was correlated with poor prognosis and activation of the PI3K/AKT signaling pathway, suggesting their potential value as druggable targets. However, selective small-molecule inhibitors against these ZDHHC subtypes have not yet been developed and current functional investigations remain largely dependent on genetic approaches, including gene knockdown and overexpression strategies. These results constitute genetic proof-of-concept. However, no selective small-molecule inhibitors are currently available, and *in vivo* validation in immunocompetent models remains lacking.

Synergistic strategies combining S-palmitoylation modification with antitumor therapy. Targeting S-palmitoylation has emerged as a promising therapeutic strategy for enhancing the antitumor efficacy of conventional chemotherapeutic agents, metabolic interventions and ICB, exhibiting substantial synergistic potential across diverse cancer models (Fig. 3).

Platinum-based chemotherapeutic agents exert cytotoxic effects, primarily by inducing DNA damage. A recent studies has demonstrated that the palmitoyl transferase ZDHHC12 facilitates ovarian cancer progression by modulating mitochondrial function and maintaining ROS homeostasis. Consistently, its expression is markedly elevated in ovarian malignancies. In the human high-grade serous ovarian cancer cell lines SNU119 and OVSAHO, genetic depletion of ZDHHC12 or pharmacological inhibition of S-palmitoylation using the broad-spectrum inhibitor 2-BP increased intracellular ROS accumulation, which enhanced cisplatin-induced cytotoxicity (Fig. 3A) in a ROS-dependent manner across two-dimensional cultures, three-dimensional Matrigel spheroid models and SNU119 xenograft tumors in immunodeficient mice (204). This approach has been validated at

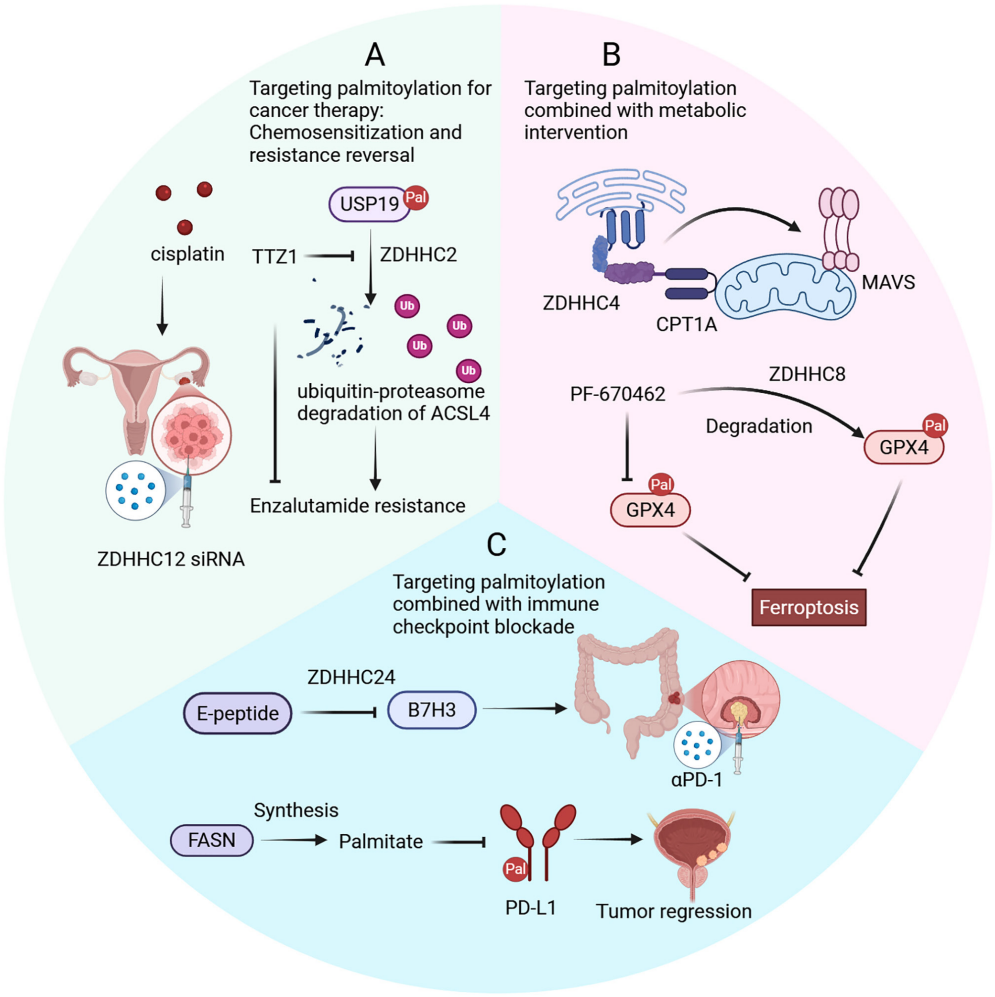


Figure 3. Therapeutic strategies targeting S-palmitoylation to enhance antitumor responses. S-palmitoylation is a promising target that can be combined with chemotherapy, metabolic intervention and immune checkpoint blockade to improve cancer treatment efficacy. (A) Chemosensitization and resistance reversal. siRNA-mediated inhibition of ZDHHC12 increases cisplatin sensitivity in ovarian cancer. Targeting ZDHHC2 with TTZ1 reduces USP19 S-palmitoylation, thereby preventing ubiquitin-proteasome degradation of ACSL4, promoting ferroptosis and reversing enzalutamide resistance in prostate cancer. (B) Metabolic intervention. The CPT1A/ZDHHC4/MAVS axis promotes MAVS S-palmitoylation and type I interferon signaling. PF-670462 promotes ZDHHC8 degradation, thereby reducing GPX4 S-palmitoylation, leading to GPX4 degradation and enhanced ferroptosis. (C) Immune checkpoint blockade. The E-peptide disrupts ZDHHC24-mediated B7H3 S-palmitoylation, promoting B7H3 degradation and improving anti-PD-1 responses. Inhibition of FASN reduces palmitate synthesis, thereby decreasing PD-L1 S-palmitoylation and restoring sensitivity to immune checkpoint blockade. Figure created with BioRender.com. ICB, immune checkpoint blockade; ZDHHC, zinc finger DHHC-type palmitoyltransferase; CPT1A, carnitine palmitoyltransferase 1A; MAVS, mitochondrial antiviral signaling protein; GPX4, glutathione peroxidase 4; FASN, fatty acid synthase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; B7H3, B7 homolog 3; ACSL4, acyl-CoA synthetase long-chain family member 4.

both the genetic (knockdown) and pharmacological (2-BP) levels in cell-based assays, 3D cultures and immunodeficient xenograft models; it currently resides at the stage of genetic proof-of-concept and *in vitro* pharmacological validation, with early *in vivo* efficacy demonstrated in immunodeficient xenograft models. Furthermore, emerging platinum-based compounds have been reported to induce ICD by activating ER stress pathways and eliciting sustained antitumor immune responses. Given that S-palmitoylation critically regulates cellular stress responses, mitochondrial metabolism and immune-related signaling pathways, pharmacological modulation of S-palmitoylation represents a potential strategy to enhance platinum-based therapies. However, whether such approaches directly potentiate platinum-induced ICD requires further investigation (208-210).

In prostate cancer, ZDHHC2 mediates S-palmitoylation of the deubiquitinase USP19 at Cys152, which in turn weakens the USP19-ACSL4 interaction and promotes ubiquitin-proteasome degradation of ACSL4, consequently suppressing lipid peroxidation and ferroptosis. ZDHHC2 is transcriptionally upregulated by a FOXA1/CXXC5/TET2 complex and is implicated in enzalutamide resistance in castration-resistant prostate cancer (CRPC) (Fig. 3A) (205). In human CRPC cell lines (C4-2, 22Rv1 and LNCaP) and enzalutamide-resistant patient-derived xenograft (PDX) models, treatment with the ZDHHC2-selective inhibitor TTZ1 (as well as the broad-spectrum inhibitor 2-BP) substantially restored drug sensitivity, whereas proteomic analyses revealed that differentially palmitoylated proteins were significantly enriched in ferroptosis-related and lipid metabolic pathways, highlighting the importance of metabolic-epigenetic interactions in the development of therapeutic resistance (205). In a ZDHHC2-knockout mouse model of spontaneous prostate cancer (CRISPR/Cas9, immunocompetent), ZDHHC2

depletion significantly limited tumor growth and enhanced enzalutamide sensitivity. Similar to the ovarian cancer strategy, this CRPC-directed intervention has been demonstrated in cell lines and PDX models, placing it at the stages of genetic proof-of-concept (ZDHHC2 knockout in immunocompetent mice) and *in vitro* pharmacological validation (TTZ1 in cell lines), with early *in vivo* pharmacological proof-of-concept in immunodeficient PDX models. However, it has not yet advanced to humanized animal validation, pharmacokinetic/pharmacodynamic development or clinical evaluation (Fig. 3A). Overall, these observations establish a mechanistic connection between chemoresistance and lipid metabolic abnormalities, providing a potential framework for the development of S-palmitoylation-targeted combination therapies.

Given the extensive interplay between S-palmitoylation and lipid metabolic regulation, the targeting of metabolic pathways has emerged as a promising strategy for improving therapeutic responses. Zhang *et al* (202) demonstrated that mitochondrial CPT1A recruits ER-associated ZDHHC4 to mediate MAVS S-palmitoylation at Cys79, resulting in MAVS stabilization and amplification of IFN-I signaling. Pharmacological activation of CPT1A enhanced the efficacy of combined epigenetic therapy and PD-1 blockade in refractory tumor models, highlighting the therapeutic potential of manipulating metabolism-S-palmitoylation crosstalk in cancer immunotherapy (Fig. 3B). This pharmacological activation strategy has been evaluated in immunocompetent tumor models (with anti-PD-1), thus achieving immune-competent animal validation.

Within the ferroptosis regulatory network, ZDHHC8-mediated GPX4 S-palmitoylation is a critical mechanism that preserves tumor cell resistance to ferroptotic stress. Zhou *et al* (203) identified PF-670462 as a ZDHHC8-targeting compound that promotes ZDHHC8 degradation, reduces GPX4 S-palmitoylation and enhances susceptibility to ferroptosis. Notably, PF-670462 synergized with anti-PD-1 therapy to prolong the survival of tumor-bearing mice without apparent toxicity, highlighting the therapeutic potential of targeting S-palmitoylation-dependent metabolic vulnerabilities to enhance cancer immunotherapy. PF-670462 has been tested in combination with anti-PD-1 in tumor-bearing mice, reaching the stage of immune-competent animal validation with preliminary pharmacodynamic assessment (Fig. 3B). Together, these strategies integrate the regulation of lipid metabolism, susceptibility to ferroptosis and protein S-palmitoylation, thereby enabling coordinated metabolic remodeling and immune activation.

Advances highlighting the interplay between metabolic regulation and immune surveillance have stimulated growing interest in combining S-palmitoylation-targeted approaches with PD-1/PD-L1 ICB. B7H3 (CD276) is highly expressed in multiple solid tumors and promotes malignant progression by suppressing T cell-mediated antitumor immunity and inducing tumor-associated macrophage polarization toward an immunosuppressive M2 phenotype (211,212). In microsatellite-stable CRC, ZDHHC24-mediated S-palmitoylation of B7H3 at Cys496 prevents its interaction with the autophagy receptor SQSTM1/p62, consequently limiting selective autophagic degradation and resulting in B7H3 accumulation, which ultimately impairs $CD8^+$ T cell-mediated antitumor immunity. A cell-penetrating peptide (E-peptide) targeting the ZDHHC24-B7H3 interaction interface disrupts B7H3 S-palmitoylation and promotes its degradation, which, in combination with anti-PD-1 antibodies, effectively restores $CD8^+$ T cell-dependent antitumor responses *in vivo* (Fig. 3C) (157). This peptide-based intervention has been validated in immune-competent mouse models, placing it at the immune-competent animal validation stage.

Moreover, in bladder cancer, FASN inhibition disrupts PD-L1 S-palmitoylation and reduces PD-L1 protein stability, revealing a metabolic mechanism linking lipid synthesis to immune checkpoint regulation and providing a rationale for the combined therapeutic targeting of FASN and PD-L1 (Fig. 3C) (206,213). Currently, this FASN/PD-L1 axis is supported by *in vitro* and biochemical evidence, thus placing it at the *in vitro* pharmacological validation stage. Therefore, therapeutic interventions targeting immune checkpoint S-palmitoylation, particularly when integrated with PD-1/PD-L1 blockade, represent a promising avenue for advancing next-generation cancer immunotherapy.

Collectively, S-palmitoylation modulation, either alone or in combination with chemotherapy, metabolic agents or ICIs, has progressed from genetic proof-of-concept to validation in immune-competent animal models. However, it remains confined to the preclinical stage. Although these strategies show promise in overcoming resistance and sustaining antitumor immunity, they require pharmacokinetic/pharmacodynamic optimization and humanized model testing before their transformative potential can be confirmed in clinical translation.

Challenges for clinical translation. Targeting S-palmitoylation has emerged as a promising therapeutic strategy for cancer immunotherapy; however, its clinical translation remains constrained by the limited availability of selective inhibitors, an incomplete understanding of ZDHHC substrate specificity and a lack of validated predictive biomarkers for patient stratification (21,214,215). From the perspective of biomarker development, accumulating evidence indicates that the expression patterns of ZDHHC family members may serve as potential predictors of immunotherapeutic responsiveness. In pancreatic cancer, elevated ZDHHC9 expression is associated with an immunosuppressive TME, whereas the genetic or pharmacological inhibition of ZDHHC9 remodels immune suppression and enhances tumor responsiveness to anti-PD-L1 therapy (216-218). Similarly, ZDHHC3 is markedly upregulated in pancreatic cancer and has emerged as a potential immunotherapeutic target; its disruption substantially improves the efficacy of anti-PD-1/PD-L1 blockade (219). In breast cancer, increased ZDHHC9 expression is associated with an unfavorable prognosis and diminished responsiveness to immunotherapy, whereas reduced ZDHHC9 abundance is correlated with improved therapeutic outcomes (220). In lung adenocarcinoma, high ZDHHC18 expression is linked to impaired immune cell activation and enhanced malignant progression, whereas ZDHHC18 depletion effectively strengthens antitumor immune responses (221). Collectively, these findings indicate that aberrant activation of ZDHHC-mediated S-palmitoylation networks, particularly in pancreatic cancer, is strongly associated with reduced $CD8^+$

T cell infiltration and the establishment of an immunosuppressive TME. Furthermore, emerging prognostic models based on S-palmitoylation-associated gene signatures have demonstrated potential utility for the molecular stratification of patients and the prediction of immunotherapy responsiveness across multiple cancer types (222-225). Thus, the expression profiles of specific ZDHHC enzymes and their corresponding S-palmitoylation landscapes may serve as informative biomarkers for optimizing the selection of individualized cancer immunotherapy strategies.

Although 2-BP remains the most widely used pharmacological inhibitor for suppressing global protein S-palmitoylation, its broad reactivity toward multiple DHHC palmitoyltransferases, depalmitoylating enzymes and un-related metabolic pathways markedly limits its therapeutic applicability (21,196,201,215,226). In addition, owing to its structural similarity to endogenous fatty acids, 2-BP exhibits broad metabolic activity beyond inhibition of protein S-palmitoylation, perturbing lipid metabolic pathways and generating substantial off-target effects that limit its translational potential (29,60,201,226). Accordingly, the development of ZDHHC isoform-selective inhibitors has become an important direction in this field, with several encouraging advances reported to date. Zhou *et al* (203) identified the ZDHHC8-selective inhibitor, PF-670462, using small-molecule screening approaches. This compound facilitated ZDHHC8 degradation, decreased GPX4 S-palmitoylation and increased the susceptibility of tumor cells to ferroptosis. In preclinical animal models, combined treatment with PF-670462 and anti-PD-1 antibodies markedly suppressed tumor growth without causing apparent systemic toxicity. Nevertheless, the development of selective ZDHHC inhibitors remains challenging, as the 23-member ZDHHC family shares a highly conserved catalytic DHHC domain. This conservation complicates the achievement of isoform-specific inhibition while maintaining favorable pharmacological properties (215). Future investigations should integrate complementary approaches, including high-throughput compound screening, structure-based drug optimization and targeted protein degradation technologies, to accelerate the development of S-palmitoylation-modulating therapeutics. However, successful clinical translation critically depends on addressing several key challenges, namely, achieving tumor cell-selective delivery to avoid off-target effects on T cells, establishing broad substrate selectivity to preserve essential physiological palmitoylation events, such as TCR signaling components, rigorously demonstrating target engagement and favorable pharmacokinetic properties *in vivo* and identifying predictive biomarkers to stratify responsive patient populations. In particular, inhibiting checkpoint palmitoylation in tumor cells may inadvertently suppress physiological TCR signaling. This, makes careful evaluation of T cell toxicity and immune synapse integrity essential.

8. Conclusions and perspectives

The regulation of T cell-mediated antitumor immunity is a fundamental biological principle that underpins the development and optimization of modern cancer immunotherapies. S-palmitoylation, a dynamic and reversible lipid-based post-translational modification, has emerged as an important regulatory mechanism that integrates multiple dimensions of T cell function, ranging from proximal signaling events to metabolic adaptation and immune effector responses. The present review systematically summarized the diverse functions of S-palmitoylation in shaping T cell-mediated antitumor immunity and highlighted its emerging therapeutic potential in cancer immunotherapy.

During T cell activation, S-palmitoylation facilitates precise membrane compartmentalization of essential signaling molecules, including Lck, Fyn, ZAP-70 and LAT, within lipid raft microdomains, ensuring efficient initiation and amplification of TCR signaling. S-palmitoylation fine-tunes the antigen responsiveness and activation threshold of T cells by regulating the plasma membrane localization and protein stability of CD4/CD8 co-receptors and the co-stimulatory receptor CD28. In addition, this modification modulates the activity, intracellular distribution and nuclear accumulation of critical transcriptional regulators, including STAT3, NF-κB and Foxp3, consequently shaping the differentiation equilibrium of effector T cell subsets, such as Th17 cells and Tregs. Simultaneously, S-palmitoylation participates in the regulation of T cell exhaustion and apoptosis through the stabilization of immune checkpoint molecules, including PD-1 and TIM-3, as well as the modulation of Fas/FasL-mediated death receptor signaling.

Within the tumor immune microenvironment, malignant cells exploit S-palmitoylation-dependent mechanisms to enhance the stability and functional persistence of immune checkpoint proteins, such as PD-L1 and B7H3, ultimately impairing $CD8^+$ T cell activity and facilitating immune escape. Metabolic abnormalities in the TME, characterized by increased local accumulation of palmitic acid, establish a reciprocal regulatory relationship with protein S-palmitoylation. Mechanistically, the reversible S-palmitoylation cycle of CD36 controls fatty acid uptake, whereas FASN S-palmitoylation stabilizes the metabolic enzyme and promotes *de novo* lipid biosynthesis. Furthermore, endogenous S-palmitoylation events in DCs, including modifications of TLR2 and TLR9, contribute to the regulation of DC activation and metabolic remodeling. Conversely, exogenous palmitoylated antigenic peptides enhance the DC cross-presentation efficiency, providing an additional strategy for potentiating antitumor immune responses.

From a therapeutic perspective, pharmacological interventions targeting S-palmitoylation have demonstrated the potential to remodel immunosuppressive TMEs and promote ICD, consequently improving the efficacy of chemo- and immunotherapy in multiple cancer models, including ovarian, prostate and bladder cancer. Despite these advances, several obstacles have impeded clinical translation. The highly conserved catalytic domains among ZDHHC family members present substantial challenges for the development of isoform-selective inhibitors. In addition, the currently available broad-spectrum inhibitors are limited by insufficient specificity, off-target effects and disruption of physiological lipid metabolic processes. Furthermore, the regulatory landscape of S-palmitoylation exhibits considerable tissue specificity, cell type dependence and tumor heterogeneity, and clinically validated biomarkers for patient selection are lacking.

Several key research directions are required to address these challenges. The integration of high-throughput screening

platforms, structure-guided drug discovery and targeted protein-degradation technologies may accelerate the development of highly selective and low-toxicity ZDHHC subtype-specific inhibitors, thereby overcoming the limitations associated with non-specific inhibition. In parallel, comprehensive characterization of S-palmitoylation profiles across distinct tumor types and cellular populations using multi-omics approaches will facilitate the discovery of robust prognostic and predictive biomarkers, enabling more precise patient stratification and therapeutic decision-making. Furthermore, exploring rational combination strategies that integrate S-palmitoylation-targeted interventions with emerging immunotherapeutic approaches, including CAR-T cells, bispecific antibodies and oncolytic viruses, may broaden the therapeutic potential of this strategy. As the molecular mechanisms underlying S-palmitoylation-mediated immune regulation continue to be elucidated, current strategies remain in preclinical stages, ranging from broad mechanistic tools and genetic proof-of-concept to *in vitro* pharmacological validation and immunocompetent animal validation. Therapies targeting S-palmitoylation may eventually contribute to cancer immunotherapy. However, further pharmacokinetic/pharmacodynamic optimization, humanized model testing and clinical evaluations are required.

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Authors' contributions

SW and XW conceived and designed the review. SW performed the literature search, collected, screened and categorized relevant studies and drafted the manuscript. RX and SJ contributed to literature collection, evidence synthesis and manuscript preparation. TY contributed to literature organization, figure preparation and writing and editing the manuscript. MQ participated in manuscript revision. LX and XW critically revised the manuscript and provided guidance throughout the preparation process. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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