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Review

Lysine methylation as a bidirectional switch

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SUMMARY

Lysine methylation is classically linked to chromatin, yet an expanding literature shows that methylation on non-histone proteins can directly program protein lifetime through the Ub-proteasome system (UPS). We define a lysine methylation bidirectional switch in which methyl marks can be wired to opposite outcomes, degradation (methyl-degrons) or stabilization (methyl-stabilizers) depending on interpreter availability, competitive occupancy, and post-translational modification (PTM) neighborhood context. We organize the field into two symmetric frameworks and, within each, distinguish direct mechanisms from reader-mediated mechanisms. Across curated examples, both Kme1 and Kme2 are bidirectional, enabling either fate depending on the wiring. However, Kme1 dominates the degron pathways, while Kme3 only supports stabilization. We highlight recurring modular architectures and extract hypothesis-generating features that bias methyl sites toward degron versus stabilizer functions. Finally, we outline chemical biology opportunities to read and program this bidirectional switch, including antibody-independent chemoproteomics, proximity approaches for targeted methyl-editing for degradation and/or stabilization.

INTRODUCTION: THE DUAL LOGIC OF THE BIDIRECTIONAL SWITCH

Lysine methylation has long been associated with chromatin, but non-histone lysine methylation has emerged as a parallel layer of proteome regulation that can directly control protein lifetime through the ubiquitin-proteasome system (UPS) (Figure 1).[1–4]

Rather than acting as a static label, lysine methylation functions as interpretable molecular information whose consequence depends on context. A substrate's fate reflects not only its methylation state, but also the availability of effectors that can read or erase that state, the surrounding post-translational modification (PTM) environment, and subcellular localization.[5] This framework explains why the same methylation site can correlate with opposite outcomes in different settings.[6,7]

Lysine methylation is chemically well suited to encode stability decisions because it changes sterics, hydration, and local electrostatics without removing lysine's cationic character (Figure 1A).[8,9] These modest changes can create or disrupt docking surfaces that are coupled to ubiquitination or protection through writer-reader-eraser networks.[10,11]

We therefore frame lysine methylation as a bidirectional switch with two outputs, degradation (methyl-degrons) and stabilization (methyl-stabilizers) implemented through two recurring architectures each (Figures 1B and 1C). In direct pathways, methylation alters ubiquitin susceptibility, ligase docking, localization, or complex stability without a dedicated methyl-reader. In indirect pathways, methylation recruits a Kme-binding effector that couples the mark to an E3 ligase or to protective machinery, often including DUB activity (Figures 1B and 1C).

Across curated examples, Kme1 and Kme2 are both bidirectional, but Kme1 is the dominant mark among known methyl-degrons, whereas Kme3 appears only in stabilizer contexts (Figure 1D). Kme1 frequently serves as a docking surface for degradation-coupled readers or substrate receptors (Figure 1D).[12–30] Kme2 can amplify either degradation or protection by further reshaping binding geometry (Figure 1D).[15,31–38] By contrast, Kme3 is associated with protective occupancy, steric shielding from ubiquitination, or reinforcement of stable active conformations (Figure 1D).[36–39] Although methyl state biases the outcome without strictly dictating it, the ultimate fate emerges from competition between degradation- and stabilization-linked interpreters at a given site.

This logic is reversible. Demethylases can suppress degron potency by erasing destabilizing methyl states, rescuing proteins from premature turnover, and enabling rapid adaptation to cellular cues.[40–44] More broadly, lysine methylation can be understood as a stability language written by KMTs, erased by KDMs, and interpreted by effectors that couple methyl-recognition to either ubiquitination or deubiquitination. This framework also has translational implications: methyl-readers that bridge to E3 complexes suggest opportunities for targeted degradation, whereas methyl-dependent protectors and DUB-recruiting modules suggest routes to pharmacologic stabilization.

Despite the growing relevance of this stability switch to disease, progress has been limited by low-throughput, antibody-dependent detection methods.[6,45,46] State-selective chemical proteomic tools such as the selective triazenation reaction (STaR), secondary amine selective petasis (SASP) and tertiary amine coupling by oxidation (TACO), now offer routes to map Kme1 and Kme2 without antibody bias, while proximity-based strategies raise the possibility of rewriting methyl states to reprogram substrate stability.[47–53] In this review, we synthesize the architectural principles underlying methyl-dependent degrons

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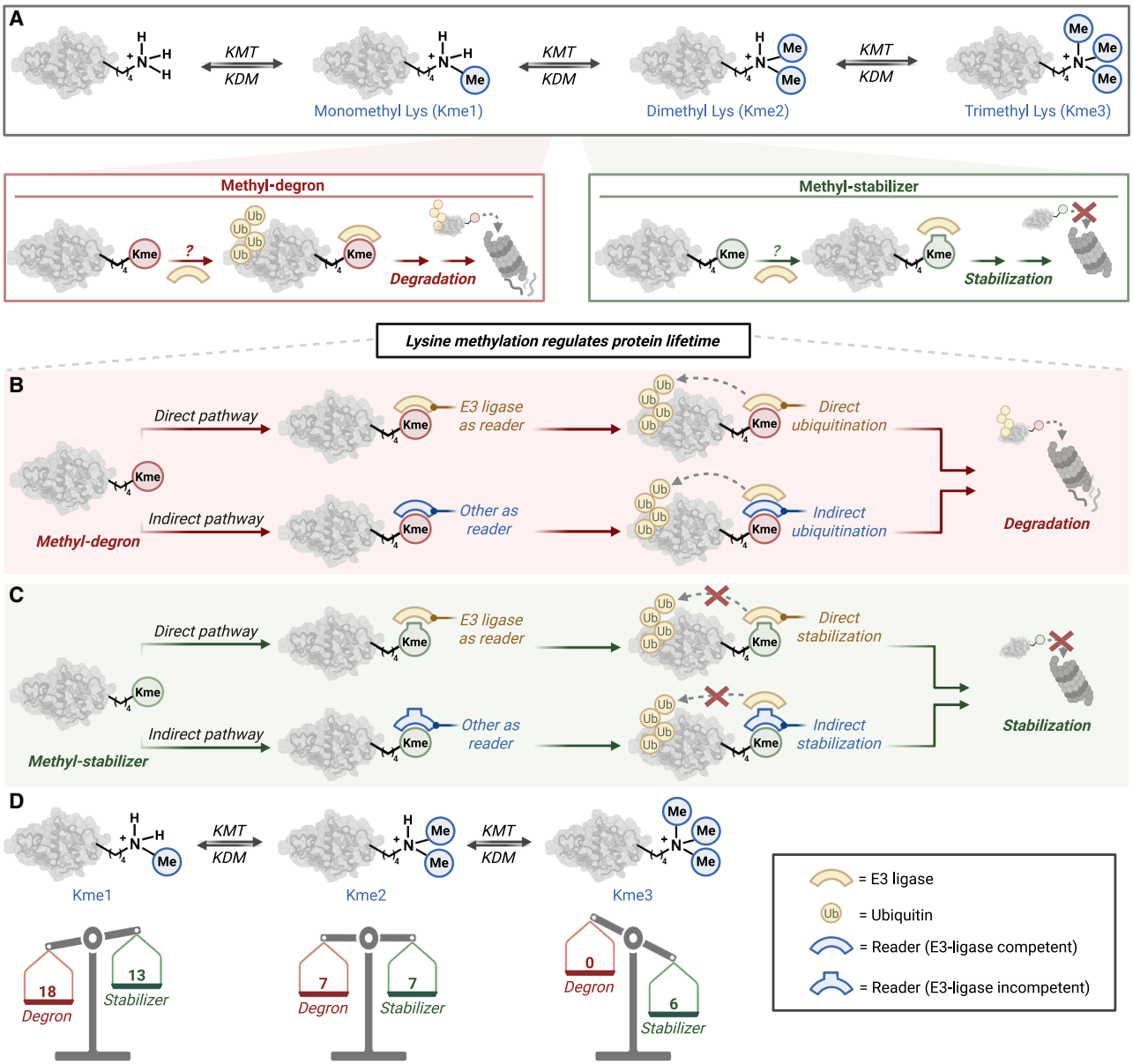

Figure 1. The dual logic of lysine methylation in protein stability control

(A) Lysine can exist in mono- (Kme1), di- (Kme2), or trimethylated (Kme3) states installed by KMTs and reversed by KDMs.

(B) Methyl-degron pathways: Kme can promote degradation through direct effects on ubiquitination or through indirect approach recruitment of E3 ligases.

(C) Methyl-stabilizer pathways: methylation can extend protein half-life either directly (blocking ubiquitination) or indirectly through recruitment of protective factors such as DUBs.

(D) Methyl state biases outcome: Kme1 and Kme2 are frequently associated with degron and stabilizer behavior, and Kme3 is commonly linked to stabilization. Created in BioRender. Villalobos, A. (2026) https://BioRender.com/s4rkuxh.

and stabilizers and outline chemical biology strategies to read and program this stability switch.

LYSINE METHYLATION AS A DEGRON FOR PROTEIN DEGRADATION

Lysine methylation serves as a powerful degron, acting as a molecular tag that signals specific proteins for rapid destruction by the cellular machinery. By transforming unmodified lysines into distinct recognition motifs, this PTM recruits E3 Ub ligases directly, through specialized reader proteins, or via spatial relocalization (Table 1; Figure 2). Ultimately, these targeted degradation networks orchestrate vital cellular processes, though their dysregulation is frequently exploited to drive cancer progression.

Direct methyl-degron pathways: E3 ligase complexes as intrinsic methyl-readers

In direct methyl-degron pathways, the E3 ligase complex itself contains the methyl-recognition function (Figure 2B). A

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Table 1. Summary of lysine methyl-degrons

Pathways	Methylated protein	Methyltransferase	E3 Ligase	Methylated sites	Reference
Direct	RORα	EZH2	DCAF1/DDB1/CUL4	K38me1	Lee[12]
	DLC1	EZH2	DCAF1/CUL4A/DDB1/FBXW5	K678me1	Tripathi[13]
	RelA	SETD7	–	K314me1 K315me1	Yang[29]
	RelA	SETD7	$ECS^{WSB1/2}$	K314me1 K315me1	Zhang[14]
	p53	–	SCF^{Fbxo22}	K370me2	Johmura[31]
	FOXO1	EHMT2	SKP2	K273me1 K273me2	Chae[15]
	KRAS	SETD7	RABGEF1	K182me1 K184	Chiang[16]
	SOX2	SETD7	WWP2	K119me1	Fang[17]
	Smad7	SETD7	Arkadia	K70me1	Elkouris[18]
	PLZF	EZH2	CUL3	K430	Vasanthakumar[19]
Indirect	DNMT1	SETD7	–	K142me1	Estève[20]
	DNMT1	–	$CRL4^{DCAF5}$	K142me1	Leng[21]
	E2F1	–	$CRL4^{DCAF5}$	K185me1	Leng[21]
	SOX2	SETD7	$CRL4^{DCAF5}$	K42me1 K117me1	Zhang[22]
	EZH2	–	$CRL4^{DCAF5}$	K20me1	Guo[23]
	E2F1	SETD7	–	K185me1	Kontaki[30]
	IκBα	SUV39H1	SCF	K38me1	Li[24]
	PGC-1α	SMYD5	–	K223me1 (mouse) K224me1 (human)	Hou[25]
Other	Numb	SETD8	MDM2	K158me2 K163me2	Dhami[32]
	Yap	SETD7	–	K494me1	Oudhoff[26]
	LC3B	SETD7	BIRC6	K51me1 K51me2	Zhang[27]
	TRβ	EZH2	–	K40	Park[28]
PTM crosstalk	RelA	SETD7	–	K314me1 K315me1	Yang[29]
	p53	SETD7	MDM2	K372me1	Ivanov[54]
	E2F1	SETD7	–	K185me1	Kontaki[30]
	E2F1	SETD7	–	K185me1	Xie[55]
	DNMT1	SETD7	–	K142me1	Estève[56]
	AURKA	MMSET (for p53)	MDM2	K14me1 K117	Park[57]
Reverse switch	DNMT1	SETD7	–	K1096 (mouse) K1094 (human)	Wang[42]
	E2F1	SETD7	–	K185me1	Kontaki[30]
	SOX2	SETD7	–	K42me1 K117me1 (human) K119me1 (mouse)	Zhang[40]
	HIF-1α	Set9	–	K32me1	Kim[41]
	HIF-1α	Set9	VHL	K391me2	Lee[43]
	RACK1	–	Elongin C-containing E3 ligase	K271me2	Yang[44]

This table outlines characterized lysine methyl-degrons, detailing the target proteins, the specific lysine methyltransferases that catalyze the modification, and the corresponding E3 ubiquitin ligases that recognize the methylated sites to mediate degradation. Lysine residues are listed alongside their specific methylation states (e.g., Kme1 or Kme2). Where the methylation state is omitted, this information was not specified in the original reference.

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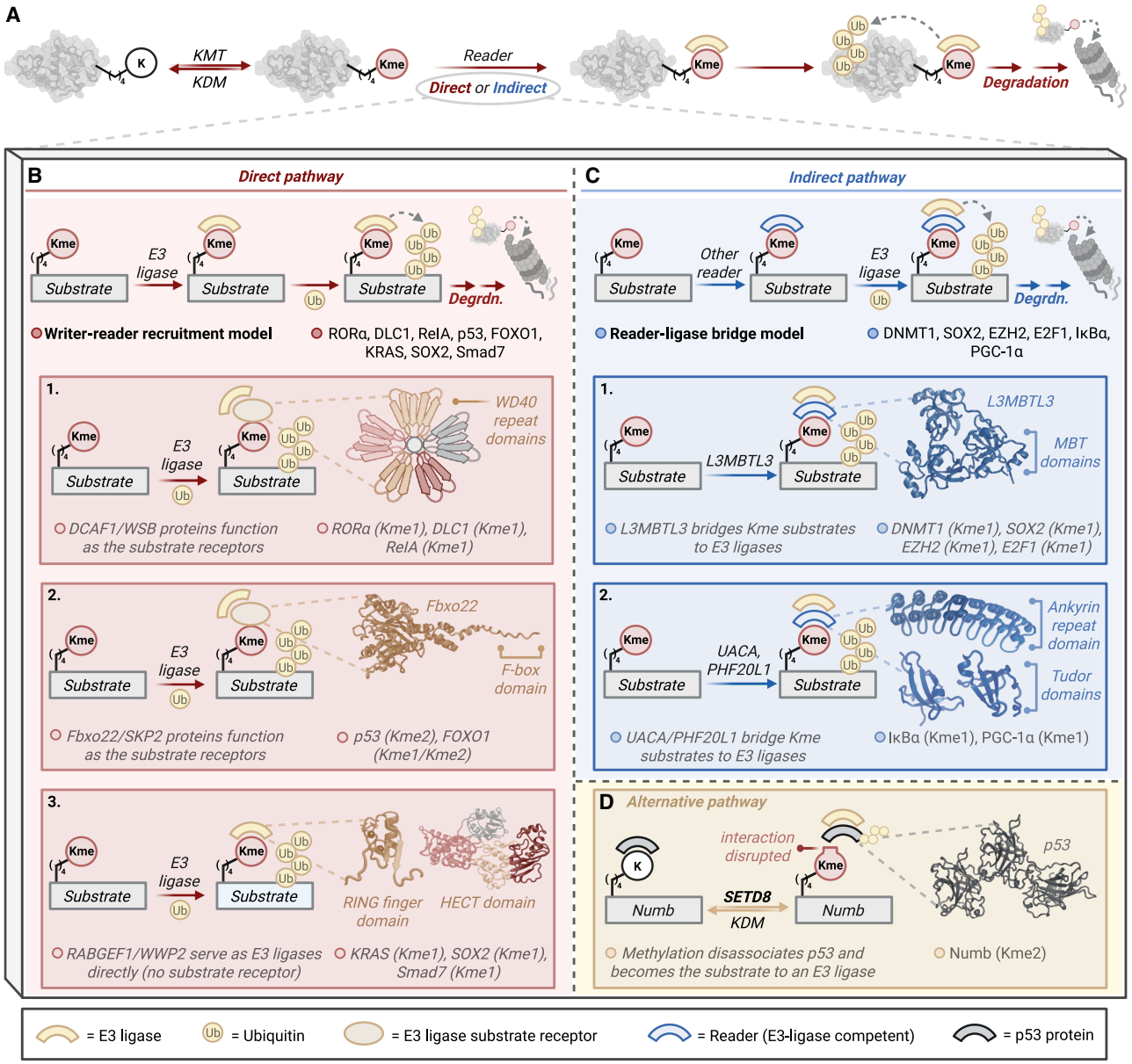

Figure 2. Architectural logic of methyl-degron pathways

(A) Lysine methylation converts unmodified lysine into a degradation signal that directly or indirectly promotes ubiquitination and proteasomal turnover.
(B1-3) Direct pathways: Kme is recognized intrinsically by E3 ligase components, including WD40-repeat proteins, F box receptors within SCF complexes, or RING/HECT ligases, enabling direct substrate capture and ubiquitination.
(C1-2) Indirect pathways: specialized Kme readers bridge methylated substrates to E3 ligase complexes. Examples include MBT-domain reader L3MBTL3 and Ankyrin- or Tudor-containing adaptors, and related modules such as Numb that couple methyl recognition disruption to Ub transfer.
(D) Alternative pathway: methylation disrupts the Numb-p53 interaction, redirecting the unshielded partner (p53) toward E3 ligase-mediated ubiquitination. Created in BioRender. Villalobos, A. (2026) https://BioRender.com/mqhulgp.

constitutive substrate receptor or catalytic domain binds the Kme mark and couples recognition directly to ubiquitin transfer, eliminating the need for an external bridging reader. The subsections below show how distinct ligase families have convergently evolved this intrinsic Kme-reading capacity.

Recognition by WD40-repeat domains

WD40-repeat proteins provide a versatile platform for direct recognition of monomethylated substrates (Figure 2B-1). In nuclear receptor signaling, the histone methyltransferase, EZH2 methylates RORα at K38me1, creating a methyl-degron read by DCAF1, the substrate receptor of the DDB1-CUL4 ligase complex.[12] Structural analysis supports recognition of K38me1 through a chromo-like aromatic cage within DCAF1, linking EZH2-dependent methylation to turnover of this tumor suppressor. Notably, this intrinsic Kme-reading function is not universal across CRL4 receptors; DCAF5, for example, requires the external reader L3MBTL3, discussed in Section indirect methyl-degron pathways: reader-mediated coupling of

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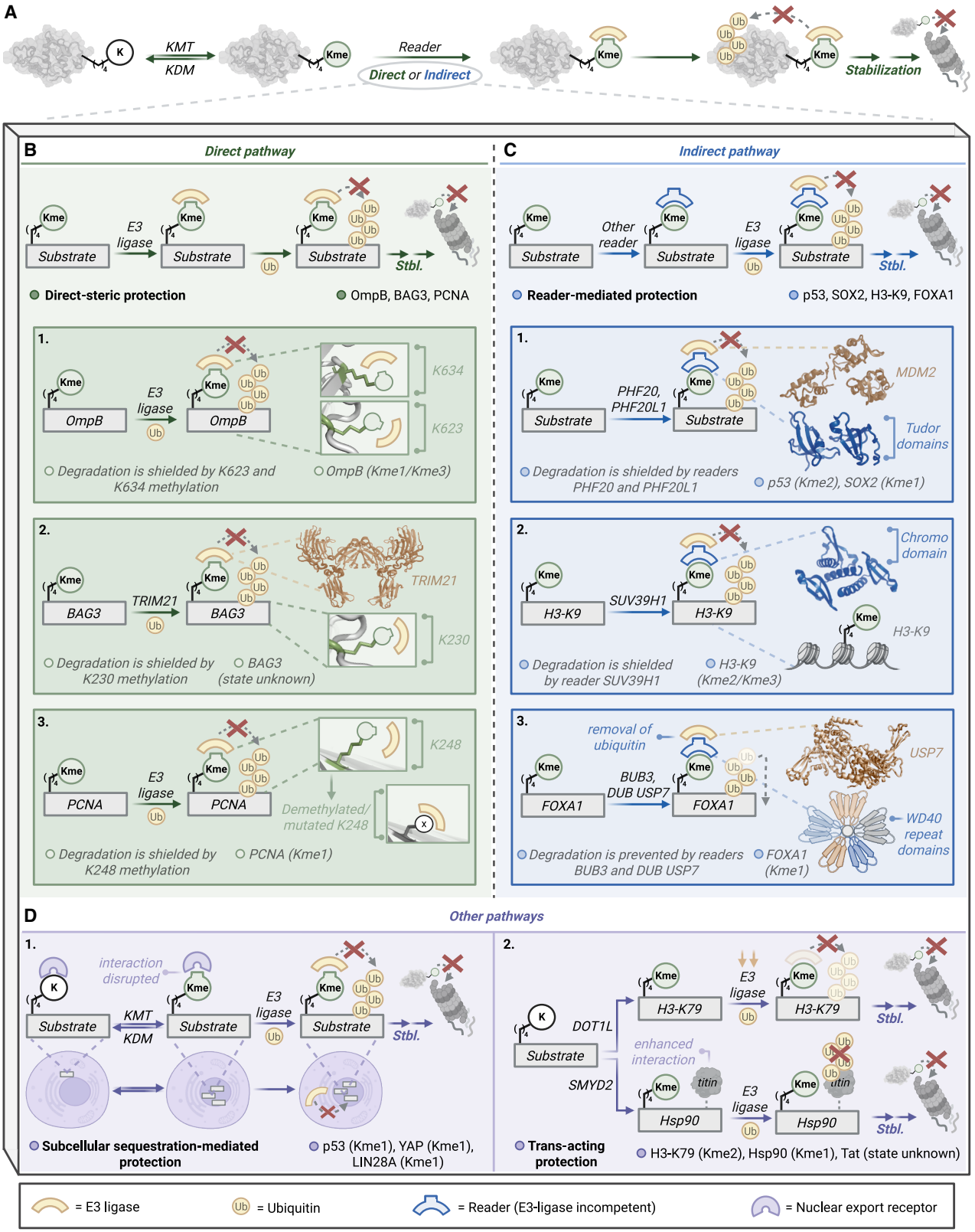

Figure 3. Architectural logic of methyl-stabilizer pathways

(A) Lysine methylation can directly or indirectly protect substrates from Ub-mediated degradation, extending protein half-life.

(B1-3) Direct pathways: methylation sterically blocks Ub attachment or disrupts E3 ligase docking at the substrate interface.

(legend continued on next page)

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methylation to ubiquitination. A closely related mechanism operates in the cytoplasm, where EZH2 monomethylates DLC1 at K678me1 (Figure 2B-1).[13] DCAF1 again functions as the methyl reader and recruits the CUL4A-DDB1 complex, promoting rapid proteasomal degradation of this Rho-GAP tumor suppressor.

The same architectural logic also terminates NF-κB signaling (Figure 2B-1). Following TNF-α stimulation, SETD7 methylates RelA at K314me1/K315me1,[29] and these marks are recognized by the WD40 domains of WSB1/2.[14]

Unlike DCAF1, WSB proteins use a SOCS box to engage an Elongin-Cullin 5 ligase complex, leading to degradation of chromatin-bound RelA and shutdown of pro-inflammatory transcription. Together, these cases show that WD40-repeat proteins can act as direct methyl readers across distinct compartments and signaling contexts.

Recognition by F box proteins in SCF complexes

Within the SCF (Skp1-Cul1-F-box) ligase family, specific F box proteins act as direct methyl-readers, often with strict methylation state specificity. Fbxo22, a non-canonical F box protein, targets p53 for degradation during senescence by binding the p53 C-terminal domain when it is methylated at K370 (Figure 2B-2).[31] Notably, Fbxo22 preferentially recognizes the dimethylated state (K370me2), allowing discrimination among methylation states and precise control of p53 levels in senescent cells.

More broadly, methyl-degrons can function as high-fidelity timers for cell-cycle progression, but cancer cells frequently exploit them to eliminate tumor suppressors. In the SCF pathway, the methyltransferase G9a (EHMT2) mono- and dimethylates FOXO1 at K273, promoting its interaction with SKP2, the F box substrate receptor (Figure 2B-2).[15] SKP2 binding to methylated FOXO1 facilitates ubiquitination and proteasomal degradation.

Direct capture by HECT and RING ligases

Direct methyl-degron recognition is not limited to multi-subunit Cullin-RING complexes. Single-chain RING ligases and HECT domain ligases can also bind Kme directly and dysregulation of these methylation events can drive pathological stabilization of potent oncogenes (Figures 2B–3). One such example is KRAS, methyltransferase SETD7 methylates K182me1 and K184 within the C-terminal polybasic domain of KRAS, creating a high-affinity binding interface for RABGEF1, a RING-finger E3 ligase.[16] Biochemical analyses show that RABGEF1 preferentially binds to methylated KRAS, with substantially reduced interaction when these methylation sites are disrupted, indicating that the Kme itself stabilizes the E3-substrate complex.

This direct capture principle also applies to HECT ligases, as seen in regulation of the stem cell factor SOX2 (Figures 2B–3). SETD7-mediated methylation of SOX2 at K119me1 promotes recruitment of WWP2, a HECT-domain E3 ligase.[17] Notably, the HECT domain itself, usually the catalytic unit, functions as a reader module required for recognizing the K119me1 substrate.

Finally, when the substrate is a negative regulator, lysine methylation can amplify signaling via inhibitor clearance. In TGF-β signaling, the inhibitory Smad protein, Smad7 constrains pathway activity (Figures 2B–3). SETD7 methylates Smad7 at K70me1, promoting Arkadia-dependent ubiquitination and degradation of Smad7.[18] In the absence of this Kme, the interaction is reduced and Smad7 is stabilized.

Unresolved methyl-degron networks: The Cullin 3 hypothesis

While the preceding examples establish well-defined direct methyl-degron pathways, other degradation networks remain mechanistically unresolved and may ultimately belong to either the direct or indirect category. A prime example of this emerging complexity is found in the regulation of the transcription factor PLZF by the methyltransferase EZH2.

During natural killer T (NKT) cell development, EZH2 directly methylates PLZF at K430.[19] This modification functions as a methyl-degron, triggering rapid ubiquitination and proteasomal degradation of PLZF. The physiological consequence is significant.

While the exact methylation state and reader linking K430 to the Ub machinery remains uncharacterized, PLZF is known to associate with the E3 ligase Cullin 3 in NKT cells. Cullin 3-ligases typically use BTB-domain containing proteins as substrate adaptors. Given that PLZF itself is a BTB-domain transcription factor, this suggests a highly specialized, methylation-dependent degradation network. Whether the Kme mark is read directly by a constitutive Cullin 3 adaptor or requires an extrinsic reader remains to be determined.

Indirect methyl-degron pathways: Reader-mediated coupling of methylation to ubiquitination

Indirect methyl-degron pathways separate Kme recognition from ubiquitin transfer (Figure 2C). Here, a dedicated reader binds the methylated substrate and recruits a more generic E3 ligase complex, allowing the same catalytic machinery to be redirected by swapping reader modules. The best-defined examples use MBT, Ankyrin-repeat, or Tudor-containing adaptors.

L3MBTL3-CRL4-DCAF5: A conserved reader-ligase module for methyl-dependent turnover

The clearest example of this modular architecture is L3MBTL3 (Lethal(3)malignant brain tumor-like protein 3), an MBT-domain reader that bridges methylated substrates to the CRL4-DCAF5 E3 Ub ligase complex (Figure 2C-1). DNMT1 provided the first well-defined case: SETD7 installs K142me1,[20] and during late S/early G2 this mark is recognized by L3MBTL3, which recruits CRL4-DCAF5 to drive DNMT1 degradation.[21] The same reader-ligase module is reused in other settings. In stem cells, L3MBTL3 preferentially recognizes SOX2 K42me1, with weaker engagement at K117me1, to promote SOX2 turnover during differentiation (Figure 2C-1).[22] The module also targets EZH2 itself after SET7-dependent methylation at K20me1, linking methyl-dependent degradation to regulation of PRC2 (Figure 2C-1).[23]

(C1-3) Indirect pathways: Kme readers bind the modified substrate to shield degrons, prevent E3 access, or recruit DUBs that actively remove Ub chains.
(D1-2) Additional stabilizing architectures include methylation-dependent subcellular sequestration and *trans*-acting regulatory networks that indirectly preserve protein stability. Created in BioRender. Villalobos, A. (2026) https://BioRender.com/9wb550w.

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E2F1 illustrates how reader-mediated degrons are integrated with broader PTM crosstalk (Figure 2C-1). SETD7 methylates E2F1 at K185me1 within a modification-rich region[30]; this mark both antagonizes stabilizing inputs by blocking acetylation of nearby lysines and phosphorylation at distant S375 and recruits the same L3MBTL3-CRL4-DCAF5 machinery, shifting E2F1 toward ubiquitination and apoptosis. Thus, L3MBTL3-CRL4-DCAF5 emerges as a reusable reader-ligase module that converts diverse Kme signals into turnover.

Alternative reader domains: Ankyrin repeats and Tudor domains as methyl-degron adaptors

Beyond the MBT domain, cells use structurally distinct reader modules to couple lysine methylation to degradation, often to clear inhibitory proteins quickly and unlock signaling (Figure 2C-2). In the NF-κB pathway, the transcription factor dimer is sequestered in the cytoplasm by the inhibitor IκBα. Cytoplasmic SUV39H1 methylates this inhibitor at K38me1, adjacent to its degradation motif.[24] This methylation does not recruit an E3 ligase directly, instead it recruits UACA, an Ankyrin repeat-containing adaptor (Figure 2C-2). UACA promotes IκBα destabilization and Ub-mediated degradation, thereby liberating NF-κB for nuclear translocation.

Recent studies extend this modular concept to cellular metabolism. Mitochondrial homeostasis depends on the transcriptional co-activator PGC-1α, which is negatively regulated in the intestinal epithelium by SMYD5.[25] SMYD5-mediated methylation of PGC-1α at K223me1 recruits the reader protein PHF20L1, which then bridges the modified substrate to an E3 ligase for Ub-proteasome-dependent degradation (Figure 2C-2).

Beyond direct and indirect pathways: Alternative mechanisms of methylation-dependent degradation

Beyond canonical direct and reader-mediated pathways, methylation can also promote degradation through interactome remodeling, spatial sequestration, and other mechanistically unresolved routes. These examples broaden the methyl-degron framework while preserving lysine methylation as the initiating signal for turnover (Table 1).

Methylation-driven interactome remodeling: Indirect destabilization of unmodified partners

While degrons operated by direct or indirect pathways typically result in the destruction of the methylated protein itself, lysine methylation can also trigger degradation indirectly by remodeling multi-protein complexes. Because protein stability often relies on protective chaperones, methylation can disrupt these interactions and expose a partner to targeted turnover.

This mechanism is exemplified by the SETD8 methylation of Numb, which normally binds and protects the tumor suppressor p53 from degradation (Figures 2C–3).[32] Methylation of Numb at K158me2 and K163me2 disrupts the Numb-p53 interaction. Once dissociated, p53 loses this protection and becomes vulnerable to recognition and degradation by the MDM2 E3 ligase. In this model, the reader-ligase machinery targets the newly unshielded p53 partner rather than the methylated protein, Numb. This illustrates how lysine methylation can rewire protein interactomes and silence pathways by indirectly destabilizing key regulatory nodes.

Spatial regulation and cytoplasmic sequestration

Beyond direct ligase recruitment, lysine methylation can modulate protein stability by altering subcellular localization. Because both protein function and degradation machineries are compartmentalized, relocalization can substantially change protein half-life.

The concept is illustrated in Hippo signaling, where SETD7 methylates the transcriptional co-activator Yap at K494me1.[26] This methylation prevents Yap nuclear entry and promotes cytoplasmic retention. By trapping Yap in the cytoplasm, SETD7 uncouples it from nuclear targets, suppressing its proliferative activity while facilitating its degradation. This highlights a spatial degron mechanism in which relocalization acts as a functional off-switch and can precede destruction.

Emerging methyl-degrons in autophagy and metabolic control

Methylation-dependent degradation is also being uncovered in autophagy and metabolic signaling, including cases where the precise reader-ligase architecture remains undefined.

Autophagy can be directly modulated by lysine methylation. SETD7 methylates the core autophagosome protein LC3B at K51me1/K51me2, a modification that promotes its ubiquitination and subsequent proteasomal degradation.[27] Reduced LC3B compromises autophagosome formation and diminishes autophagic flux.

In hepatocellular carcinoma, EZH2 promotes degradation of the thyroid hormone receptor β (TRβ), a tumor suppressor.[28] Lysine methylation of TRβ at K40 triggers robust Ub-proteasome degradation and loss of TRβ enhances hepatocellular carcinoma growth. Together, these examples reinforce that methylation-dependent degradation can be co-opted in malignancy to silence key metabolic and stress-response nodes.

LYSINE METHYLATION AS A SHIELD AGAINST PROTEIN DEGRADATION

While lysine methylation marks proteins for destruction, it can also act as molecular shield that protects them from turnover (Table 2; Figure 3). By interfering with key steps in the UPS, methylation can extend a protein half-life and preserve critical structural scaffolds, oncogenic drivers, and signaling nodes.

Direct methyl-stabilizer pathways: Direct steric occlusion

One of the simplest modes of methylation-dependent stabilization is direct physical competition with ubiquitination. Methylation at specific lysines can block access to the UPS by occupying a lysine acceptor site needed for Ub attachment and/or by inducing structural or interaction changes that reduce E3 ligase access to nearby lysines. In effect, methylation masks the protein from degradative machinery and extends its half-life (Figure 3B).

Molecular shielding and camouflage of bacterial surface proteins (The PKMT-OmpB model)

In host-pathogen interactions, direct steric occlusion is observed in the intracellular bacterium *Rickettsia parkeri*, where lysine methylation shields outer membrane proteins (OMPs) from host-mediated ubiquitylation and autophagic clearance (Figure 3B–1). Two bacterial protein-lysine methyltransferases, PKMT1 and PKMT2 catalyze methylation of K623me1 and K634, respectively, on the abundant surface protein

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Table 2. Summary of lysine methyl-stabilizers

Pathways	Methylated protein	Methyltransferase	E3 Ligase	Methylated sites	Reference
Direct	OmpB	PKMT1/PKMT2	–	K623me1 K634	Engström[58]
	BAG3	METTL21A	TRIM21	K230	Zhan[59]
	PCNA	SETD8	RAD18	K248me1	Takawa[60]
Indirect	p53	SMYD2 SETD8	MDM2	K370me2 K382me2	Cui[33]
	SOX2	SETD7	–	K42me1 K117me1 (human) K119me1 (mouse)	Zhang[40]
	Histone H3	EHMT2	–	K9me2 K9me3	Sekar[36]
	FOXA1	EZH2	–	K295me1	Park[61]
Other	p53	SETD7	MDM2	K372me1	Chuikov[62]
	YAP	SET1A	–	K342me1	Fang[63]
	LIN28A	SETD7	–	K135me1	Kim[64]
	Histone H3	DOT1L	HECTD4 MYCBP2	K79me2	Vatapalli[34]
	Hsp90	SMYD2	–	K616me1	Donlin[65]
	Tat	SMYD5	–	–	Boehm[66]
	MYPT1	SETD7	SIAH2	K442me1	Twomey[67]
	EZH2	SMYD2	–	K307me2	Zeng[35]
	LSD1	SUV39H2	–	K322me3	Piao[39]
	Gli3	SETD7	$SCF^{Slimb/\beta-TrcP}$	K436me1 K595me1	Fu[68]
	Cyclin D1	SMYD3	–	K4me1 K12me3 K22me3 K26me2 K46me3	Asuthkar[37]
	NSD3	EHMT2	–	K477me1 K477me2 K477me3	Krishnamoorthy[38]
3.1.4	E2F1	SETD6	–	K117me1	Kublanovsky[69]

This table outlines characterized lysine methyl-stabilizers, detailing the target proteins, the specific lysine methyltransferases that catalyze the modification, and the corresponding E3 ubiquitin ligases that recognize the methylated sites. Lysine residues are listed alongside their specific methylation states (e.g., Kme1, Kme2, Kme3). Where the methylation state is omitted, this information was not specified in the original reference.

OmpB.[58] In their demethylated state, these sites serve as targets for host Ub ligases. In PKMT-deficient bacteria, OmpB and other OMPs become hyper-ubiquitylated (7–10,000-fold at K623 and K634), driving Ub-mediated surface loss, autophagic targeting, and diminished virulence in mice. Here methylation competes directly for the same lysine acceptor sites required for Ub conjugation, creating a steric barrier that limits E3 access, thereby stabilizing the bacterial envelope and promoting pathogenesis.

Steric hindrance at the E3 ligase-substrate binding interface (The METTL21A-BAG3 axis)

Methylation can also block degradation by disrupting the E3 ligase-substrate binding interface rather than only masking the target lysine. In hepatocellular carcinoma, METTL21A stabilizes BAG3 by methylating K230 (Figure 3B-2).[59] This modification creates steric hindrance that interferes with binding of TRIM21, the E3 Ub ligase responsible for BAG3 degradation. By physically obstructing docking at the interface, methylation extends BAG3 half-life without requiring a separate reader or helper protein.

Site-specific competition and the methyl-Ub switch (The SETD8-PCNA pathway)

The stabilization of essential nuclear proteins like PCNA further illustrates the inverse correlation between lysine methylation and ubiquitylation (Figure 3B-3). SETD8 methylates PCNA at K248me1, and this modification correlates with enhanced PCNA protein stability.[60] Experimentally, SETD8 depletion or substitution of K248 to alanine (K248A) accelerates PCNA ubiquitination and degradation, although whether methylation and ubiquitination compete at the same residue or whether K248 methylation indirectly suppresses ubiquitination elsewhere on the protein remains to be determined. Together, these cases show how steric mechanisms enable precise control of protein longevity, protecting critical scaffolds and surface proteins

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from degradative signals through the simple addition of a methyl group.

Indirect methyl-stabilizer pathways: Reader-mediated protection

Direct steric mechanisms rely on the methyl group to block degradation. A second major pathway uses a third player, a reader protein (Figure 3C). Here, the Kme becomes a high-affinity docking site for a Kme reader domain (Tudor, Chromo, MBT, or WD40). Once bound, the reader can stabilize the target either by blocking E3 ligase access, masking degrons, and/or recruiting DUBs to remove Ub chains. In this way, methylation functions as a platform for protective protein-protein interactions rather than acting solely through steric occlusion.

Shielding targets from E3 Ub ligases

A common mode of protection by indirect approach is physical exclusion of an E3 ligase (Figures 3C–1). For example, p53 is methylated at specific lysine residues, such as K370me2 or K382me2.[33] The effector protein PHF20 recognizes these Kme2 marks via its Tudor domain, and this interaction stabilizes p53 by limiting access of the E3 ligase MDM2, thereby reducing MDM2-mediated ubiquitylation and degradation.

Similarly, the pluripotency factor SOX2 is methylated at residues such as K42me1 and K117me1 by the SETD7, a modification that can promote Ub-dependent proteolysis (Figures 3C–1).[40] The reader protein PHF20L1 counteracts this by docking on these monomethylated sites via its MBT domain, protecting SOX2 from degradation and maintaining its cellular stability.

Conformational masking of degrons

Readers can also protect targets by masking degrons, so the proteasome cannot engage them. This principle has been engineered into synthetic sensors, in a fusion protein containing a Histone H3 methylation site (H3-K9) and a cODC degron (Figure 3C-2). Methylations by EHMT2 at K9me2 and K9me3 recruit the SUV39H1 chromodomain.[36] Reader binding imposes a conformational lock that blocks access to the degron, sparing the sensor from proteasomal destruction.

Active reversal via DUB recruitment

Beyond passive shielding, reader proteins can actively reverse degradation signals by recruiting DUBs. The transcription factor FOXA1 is methylated at K295me1 by EZH2 creating a docking site for the WD40 repeat protein BUB3 (Figure 3C-3).[61] BUB3 then recruits the DUB USP7, which removes Ub chains from FOXA1 and increases its stability.

Methylation-mediated protection through subcellular sequestration

Protein stability is often determined by subcellular localization rather than intrinsic biochemical resistance. Because components of the UPS are unevenly distributed, many E3 ligases act primarily in the cytoplasm. Lysine methylation can therefore act as a spatial regulator of half-life by modulating trafficking. By masking nuclear export signals or strengthening nuclear localization signals, methylation can sequester proteins within the nucleus or nucleolus, compartments that can reduce exposure to cytoplasmic degradative machinery (Figure 3D-1). A foundational example occurs in the p53 network, where SETD7-mediated methylation at K372me1 is required for nuclear retention and accumulation of p53.[62] By confining p53 to the nucleus, this methylation shields it from cytosolic degradation pathways (Figure 3D-1).

A similar sequestration-based mechanism stabilizes the Hippo effector YAP (Figure 3D-1). SET1A-mediated methylation at K342me1 impairs its interaction with the nuclear export receptor CRM1 effectively locking YAP in the nucleus.[63] By retaining YAP in the nucleus, this confinement enhances its stability: major E3 ligases, including β-TRCP, reside predominantly in the cytoplasm, and limiting export reduces YAP engagement with the polyubiquitination machinery. Similarly, the pluripotency factor LIN28A uses methylation-driven sequestration to evade proteasomal destruction (Figure 3D-1). SETD7 methylates LIN28A at K135me1, triggering a conformational or interactome change that promotes nucleolar retention in human embryonic stem cells.[64] This sequestration both positions LIN28A to inhibit *let-7* microRNA and protects it from the cytoplasmic proteasome.

Trans-acting stabilization and regulatory networks

Methyl-dependent stability can extend beyond the modified substrate and act as a network-level switch that preserves distal proteins (Figure 3D-2). In this *trans*-acting model, lysine methylation coordinates the stability of multi-protein complexes or regulates expression/activity of the degradation machinery itself, allowing single methylation events to synchronize the lifespan of multiple functional partners.

A clear example involves high-turnover oncogenic drivers such as AR and MYC. The histone methyltransferase DOT1L stabilizes histone H3 (H3-79) indirectly through transcriptional control, by maintaining K79me2 methylation at specific enhancers, DOT1L represses expression of the E3 Ub ligases, HECTD4, and MYCBP2.[34] This repression dampens the degradation program and helps sustain AR and MYC. When DOT1L is inhibited, loss of K79me2 methylation upregulates these ligases, triggering rapid proteasomal destruction of both AR and MYC (Figure 3D-2).

Trans-acting stabilization also occurs through chaperone networks. SMYD2 methylates the cytoplasmic chaperone Hsp90 at K209me1 and K616me1, a modification required for Hsp90 to maintain the structural integrity and stability of client proteins such as titin.[65] Here, methylation of the chaperone does not protect Hsp90 from degradation. Instead, it enhances Hsp90's capacity to shield clients from misfolding and subsequent proteolysis (Figure 3D-2).

A related network-level logic appears in viral transcription, where methyltransferases intersect with deubiquitination machinery (Figure 3D-2). SMYD5 participates in a stability-linked loop with HIV-1 Tat and the DUB USP11.[66] Tat and USP11 stabilize SMYD5 by preventing its degradation, and SMYD5 is in turn required to amplify transcription from the viral genome. This suggests a system in which maintaining methyltransferase stability is itself necessary for sustained activity of the broader transcriptional complex.

Mechanistic ambiguity and the E3 ligase knowledge gap

While the direct steric occlusion and indirect protection by readers provide clear frameworks for methylation-dependent stabilization, much of the literature remains mechanistically unresolved. Many studies show that lysine methylation suppresses polyubiquitination and extends protein half-life, yet stop short of

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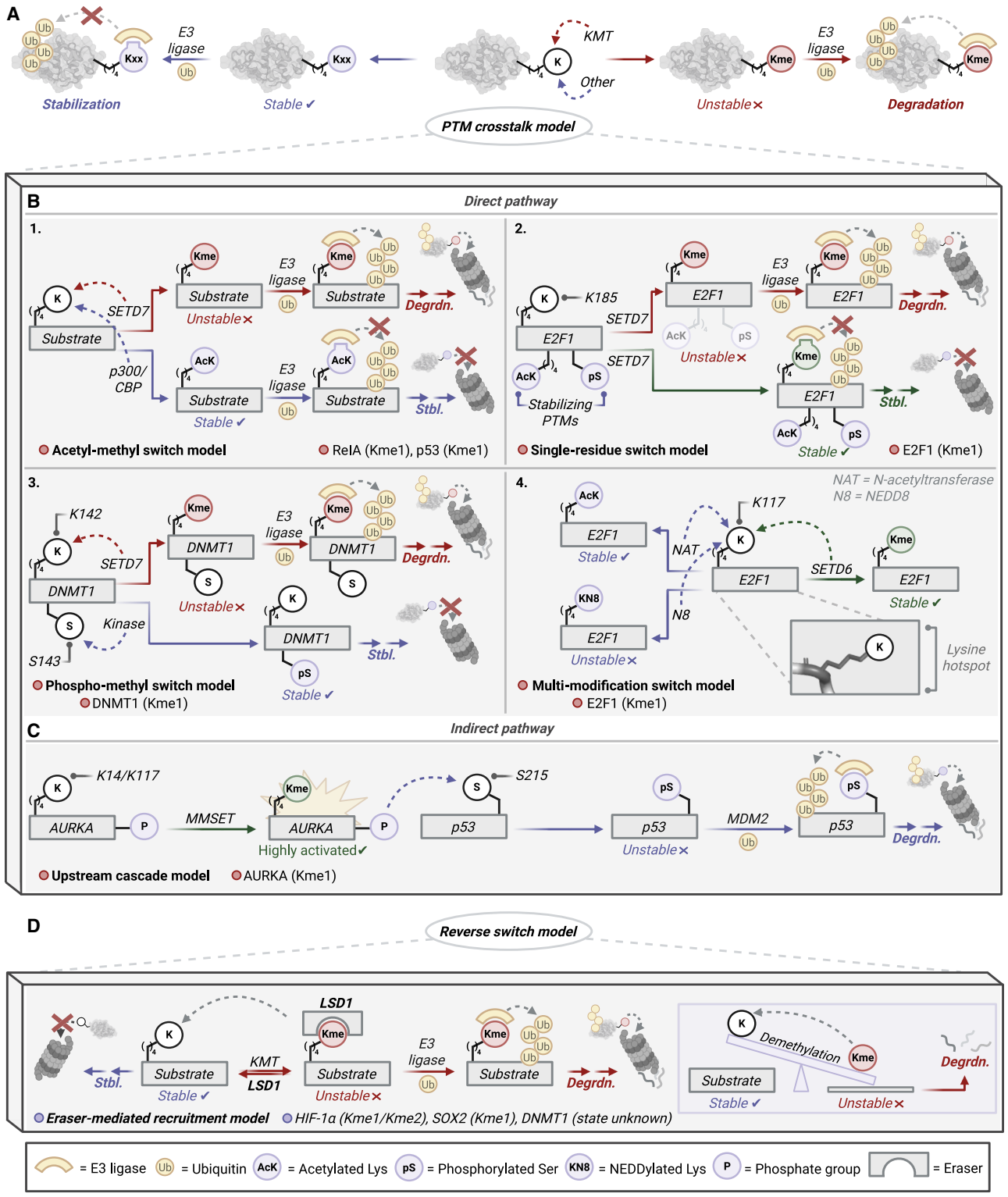

Figure 4. Lysine methylation within PTM crosstalk and reverse-switch control

(A) PTM crosstalk model: lysine methylation functions within a competitive and cooperative network of modifications to determine substrate stability. (B1-4) Direct pathway: methylation competes with acetylation, phosphorylation, ubiquitination, or NEDDylation at the same or adjacent residues, generating binary or multi-modification switches that toggle proteins between stable and degradable states.

(legend continued on next page)

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defining how, at the molecular level, ubiquitination is being blocked. This gap is particularly evident in recent work on several methyltransferases and their targets (Table 2).

A recurring theme is an interconnected network of epigenetic regulators whose stability is controlled by methylation. SETD7-mediated methylation of MYPT1 at K442me1 increases its half-life by reducing polyubiquitination, an effect reversed by the demethylase LSD1.[70] Similarly, SMYD2 methylation of EZH2 at K307me2 stabilizes EZH2 and is rapidly reversed by LSD1.[35] Strikingly, LSD1 itself is stabilized by SUV39H2-catalyzed methylation at K322me3, which suppresses polyubiquitination and protects LSD1 from proteasomal degradation.[39]

Comparable stabilization dynamics also appear in developmental and signaling pathways: in Hedgehog signaling, SETD7 methylation of full-length Gli3 at K436me1 and K595me1 increases stability and half-life.[68] More broadly, studies of SMYD3 and EHMT2 likewise report methylation-dependent protection of substrates through reduced Ub-chain accumulation and evasion of the UPS.[37,38]

Across these examples, a striking commonality emerges: although methylation consistently shows an inverse relationship with polyubiquitination, the E3 Ub ligases responsible for targeting the demethylated substrates are often unidentified. Instead, many studies rely on proteasome inhibitors (MG132) and pan-Ub readouts to infer stabilization, which establishes the phenotype but not the bypassed ligase machinery.

Defining these E3-substrate interfaces will be essential to fully map the landscape of non-histone protein stabilization by lysine methylation.

WRITING PROTEIN FATE: LYSINE METHYLATION IN PTM CROSSTALK

The regulation of protein fate is rarely dictated by a solitary chemical mark. Rather, it is governed by a highly integrated network of PTMs. This dynamic interplay, known as PTM crosstalk, allows cells to process diverse environmental and metabolic cues into precise, coordinated responses. Whether competing for the same amino acid, sterically shielding adjacent sites, or sequentially priming downstream modifications, overlapping PTMs form a regulatory language (Tables 1 and 2; Figure 4). Decoding this language, including the central and context-dependent role of lysine methylation, is essential for understanding how proteins are stabilized, activated, or targeted for destruction.

Direct antagonism: Binary switches

At the most fundamental level of PTM crosstalk, individual lysine residues act as hotspots for competing modifications, including methylation, acetylation, ubiquitination, SUMOylation, and NEDDylation (Figure 4B). Because the ε-amine can accommodate only one covalent modification at a time, these marks are chemical mutually exclusive. Even when modifications occur on neighboring residues, steric effects can impose functional exclusivity.

As a result, lysine methylation often functions as a binary switch that toggles proteins between stable and degradable states. By blocking deposition of destabilizing marks, methylation integrates diverse signals into decisive outcomes for protein half-life.

The acetyl-methyl switch: Antagonistic and cooperative control

The most common direct crosstalk involves the interplay between acetylation (often stabilizing) versus methylation (often destabilizing). Because acetylation neutralizes lysine's positive charge while methylation preserves it, these marks recruit distinct readers and can drive opposing outcomes (Figure 4B-1).

RelA (p65) provides a definitive model. RelA stability reflects competition between acetyltransferase p300/CBP and SETD7. Acetylation at K310 supports transcriptional activity and stability whereas SETD7-mediated methylation at K314me1 and K315me1 promotes ubiquitination and proteasome-dependent turnover of chromatin-associated RelA.[29] Critically, acetylation at K310 blocks SETD7 access to K314/K315, making SIRT1-mediated deacetylation a prerequisite for methylation. In this system, acetylation protects RelA by preventing installation of a methyl-dependent degron (Figure 4B-1).

In contrast, acetylation and methylation can cooperate. In the DNA damage response, SETD7-mediated methylation of p53 at K372me1 does not directly block ubiquitination (Figure 4B-1).[54] Instead, it primes p53 for efficient p300/CBP-dependent acetylation of C-terminal lysines and this acetylation then blocks MDM2-mediated ubiquitination to stabilize p53. This sequential model highlights methylation as an initiating signal that enables a broader protective PTM program.

The E2F1 paradox: Conflicting outcomes at a single residue

Although acetyl-methyl crosstalk often yields a clear binary outcome, lysine methylation can produce divergent readouts across studies, as illustrated by E2F1 (Figure 4B-2). Two separate studies investigating the exact same modification, monomethylation at K185 by the enzyme SETD7, report diametrically opposed biological mechanisms. One model proposes that SETD7 methylates E2F1 at K185me1, a linker region residue surrounded by stabilizing acetylated (Ac) and phosphorylated (p) sites.[30] In this view, methylation at K185me1 blocks nearby acetylation and phosphorylation at S364 residue, shifting E2F1 toward ubiquitination and cell death.

Conversely, other work reports that SETD7 methylation at the same site, K185me1, stabilizes E2F1 by inhibiting ubiquitination.[55] In this context, E2F1 drives DNA damage-induced apoptosis by inducing pro-apoptotic targets such as TP73 and Bim. The authors of the latter study explicitly acknowledge this contradiction. They hypothesize that the discrepancy between the two models might arise from experimental variations, specifically pointing to the use of different cell types, distinct

(C) Indirect pathway: methylation of upstream regulators (kinases) alters downstream substrate fate, coupling stabilizing and destabilizing signals across signaling networks.
(D) Reverse switch model: demethylases erase methyl-degrons to restore stability, dynamically rescuing substrates from Ub-mediated degradation. Created in BioRender. Villalobos, A. (2026) https://BioRender.com/ojfbcu1.

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DNA-damaging agents, or differing methods of analyzing cell death. However, rather than attributing the paradox to dynamic biological rewiring, they defend their findings by arguing that their model, where SETD7 stabilizes E2F1 to promote apoptosis, is more consistent with the broadly recognized pro-apoptotic biological function of SETD7 reported in prior studies.

The phospho-methyl switch: Steric hindrance

Methylation also competes directly with phosphorylation. DNA methyltransferase DNMT1 exemplifies a phospho-methyl switch (Figure 4B-3). SETD7 methylation at K142me1 promotes degradation whereas AKT1 phosphorylation at S143 blocks K142 methylation.[56] Structural and biochemical analyses support that S143 phosphorylation prevents formation of the methyl-dependent degron, stabilizing DNMT1 in response to growth signaling by protecting it from SETD7-driven turnover.

The multi-modification hotspot: Complex convergence

Direct antagonism reaches peak complexity when a single residue integrates three or more PTMs (Figure 4B-4). E2F1's K117me1 is one such hub, serving as an acceptor for acetylation, methylation, and NEDDylation.[69] NEDD8 conjugation at K117 site destabilizes E2F1, whereas SETD6-mediated methylation occupies the site, preventing NEDDylation and maintaining E2F1 stability and transcriptional output. This positions Kme as active integration nodes that process competing inputs to determine protein fate.

Indirect regulation: Upstream control of substrate fate

Crosstalk can also be indirect, where methylation occurs on an upstream regulator rather than substrate itself (Figure 4C). In cancer signaling, MMSET methylates Aurora kinase A (AURKA) at K14 and K117, enhancing its kinase activity.[57] This stabilizing activation event upstream ultimately destabilizes p53. Activated AURKA phosphorylates p53, promoting recruitment of MDM2 and accelerating p53 ubiquitination and proteasomal degradation. This cascade illustrates how methylation can stabilize an upstream kinase while simultaneously promoting the selective degradation of a downstream regulatory effector.

THE REVERSE SWITCH: DYNAMIC STABILIZATION BY DEMETHYLASES

When lysine methylation functions as a degron, the dominant stabilizing force is often not the KMT (writer) but the KDM (eraser). In this reverse switch, protein half-life is maintained by continuous removal of a methyl-degron (Table 1; Figure 4D). Erasing the mark returns the substrate to a stable state and rescues it from Ub-proteasome-dependent turnover.

Preserving epigenetic and cell cycle machinery

The reverse switch operates in basal processes such as epigenetic maintenance. DNA methyltransferase DNMT1 stability is compromised by SETD7-mediated methylation at K1096 (in mouse DNMT1)/K1094 (in human DNMT1), which serves as a degradation signal (Figure 4D).[42] To sustain DNMT1 levels and preserve DNA methylation patterns during replication, the demethylase LSD1 must continuously erase this mark. Failure of this reverse switch results in accelerated DNMT1 turnover and global DNA hypomethylation.

A similar binary logic is proposed for cell cycle regulator E2F1. Under basal conditions, SETD7 methylates E2F1 at K185me1.[30] This modification is reported to favor turnover by ubiquitination while antagonizing stabilizing acetylation at the same site, keeping E2F1 suppressed to avoid inappropriate apoptosis. Upon DNA damage, LSD1 removes this methyl mark, enabling rapid E2F1 accumulation and activation of cell-death programs.

Safeguarding stem cell pluripotency (SOX2)

Beyond maintenance, the reverse switch governs developmental state transitions, such as pluripotency. The transcription factor SOX2 is subject to methylation-dependent proteolysis (Figure 4D). While previous research identified SETD7 methylation of mouse SOX2 at K119me1 (equivalent to K117 in humans) in Ub-dependent degradation, human SOX2 is regulated by methylation at two distinct sites: K42me1 and K117me1. Pluripotency is preserved through two parallel stabilization strategies.[40] First, LSD1 selectively removes methylation at both K42me1 and K117me1. LSD1 loss or inhibition leads to accumulation of methylated SOX2, rapid degradation, and impaired stem cell growth. Second, SOX2 can be stabilized by shielding. PHF20L1 binds to the monomethylated K42me1 and K117me1 residues, protecting SOX2 from ubiquitination and proteolysis.

The hypoxia network: A multi-tiered stabilization strategy

This layered logic is especially clear in hypoxia signaling, where demethylation protects hypoxia-inducible factor 1α (HIF-1α) (Figure 4D). In addition to oxygen-dependent hydroxylation pathways, SETD7 creates an oxygen-independent destruction route by methylating HIF-1α at K32me1, generating a degron that triggers ubiquitination in both normoxia and hypoxia.[41] LSD1 stabilizes HIF-1α by erasing K32me1 methylation, thereby preventing proteasomal turnover and promoting tumor angiogenesis.

A second SETD7-site at K391me2 reveals more elaborate crosstalk.[43] Methylation at K391me2 facilitates recruitment of PHD2, which hydroxylates HIF-1α and commits it to destruction. LSD1 counteracts this feedforward pathway by removing the K391me2 mark, interrupting the sequence upstream of hydroxylation.

Strikingly, the reverse switch can also act indirectly by disarming degradation machinery. LSD1 targets RACK1, a scaffold required for HIF-1α turnover. RACK1 methylation at K271me2 enables RACK1 to bind HIF-1α and recruit an Elongin C-containing E3 Ub ligase complex.[44] Demethylation of RACK1 at K271me2, erases this docking signal, preventing assembly of degradation complex and providing an additional layer of HIF-1α stabilization. Loss of RACK1 demethylation restores the degradation pathway, enabling downregulation of HIF-1α during later, chronic stages of hypoxia.

FUTURE DIRECTIONS: PROGRAMMING THE BIDIRECTIONAL SWITCH

The emerging view of lysine methylation as a bidirectional switch creates a timely opportunity to move beyond isolated examples toward a programmable framework. The major advances now

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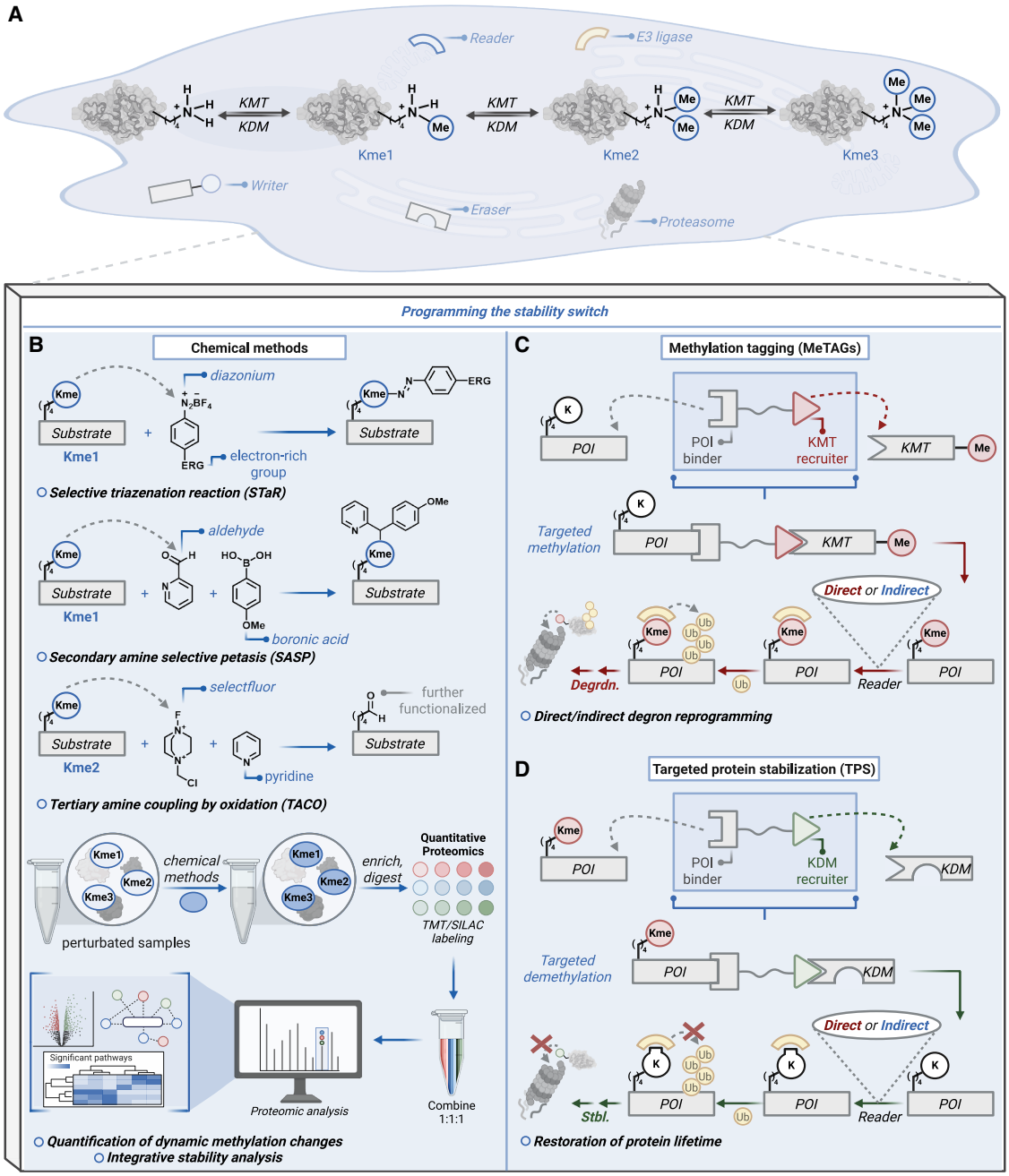

Figure 5. Programming the lysine methylation stability switch

(A) Lysine methylation states (Kme1-3) are dynamically written by KMTs and erased by KDMs, interpreted by readers, and coupled to Ub-mediated degradation or stabilization.

(B) Chemical proteomic strategies (STaR, SASP, TACO) enable state-selective enrichment of Kme1 and Kme2 to quantify dynamic methylation changes and integrative stability analysis.

(C) Methylation tagging (MeTAGs) uses proximity recruitment of KMTs to install neo-methyl marks on proteins of interest, enabling programmable direct or indirect degron formation.

(D) TPS recruits KDMs or protective factors to erase methyl-degrons or reinforce stabilizing pathways, restoring protein lifetime. Created in BioRender. Villalobos, A. (2026) https://BioRender.com/7kdmzt9.

required are clear: (1) read methyl states without discovery bias, (2) link methyl states to stability outputs at scale, and (3) develop tools to write and erase methyl states on demand to test causality and enable intervention (Figure 5).

Beyond antibodies: Chemical proteomics to read the stability switch at scale

Progress is still constrained by detection. Antibody-based workflows remain important for validating known sites, but discovery

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will require MS-first, proteome-wide mapping supported by state-selective chemical enrichment. STaR and SASP provide routes to enrich Kme1,[47–50] whereas TACO converts Kme2 into a chemically addressable handle for downstream tagging (Figure 5B).[51–53]

These tools become especially powerful when integrated with quantitative proteomics. Coupling methyl-state enrichment to SILAC or TMT under writer/eraser perturbation could identify responsive sites, and those data could be paired with orthogonal stability measurements such as cycloheximide chase, proteasome-inhibitor rescue, and site-directed mutagenesis.[71–74] Although no study has yet integrated these layers at proteome scale, the required components already exist. The next step is to move from cataloging individual methyl-degrons and methyl-stabilizers to building predictive frameworks that classify newly identified Kme sites by their likely stability output and mechanism.

From methyl marks to methyl-degrons: MeTAGs as programmable neo-degron writers

The degron branch of our framework reveals a powerful opportunity: methylation could serve as a programmable degradation tag if installed precisely where and when needed. Proximity-inducing chimeras have already been deployed to induce phosphorylation and arginine methylation with spatial precision,[75–77] and the clinical success of targeted protein degradation platforms demonstrates the therapeutic power of engineering local lysine modifications.[78–82] Extending this proximity logic to lysine methylation is a logical next step.[83,84]

We therefore propose MeTAGs (Methylation Tagging): proximity-inducing chimeras that recruit methyltransferases to a chosen target to install neo-degrons on demand (Figure 5C). Rather than globally inhibiting writers or erasers, MeTAGs would impose a local methyl state at a specific protein, allowing causal tests of stability wiring and enabling targeted proteome editing. From our taxonomy, two programming modes emerge: direct degron programming, where the E3 machinery itself recognizes the methyl-dependent surface, and indirect degron programming, where success depends on the availability of the appropriate reader-ligase module (Figure 5C).

Targeted protein stabilization: Rescuing proteins by enforcing protective wiring

The stabilizer side of the switch is not simply the inverse of degradation but a distinct wiring diagram involving steric protection, protective readers, or DUB-mediated rescue. This opens an underdeveloped therapeutic modality: Targeted protein stabilization (TPS), in which proximity strategies recruit erasers or protective factors to suppress latent methyl-degrons, thereby restoring protein abundance and function. For example, recruiting LSD1 or other KDMs to locally remodel methyl states on vulnerable substrates could be particularly attractive for tumor suppressor loss, where restoring protein lifetime may be more tractable than pharmacologically activating function (Figure 5D). From our framework, TPS can succeed by erasing methyl-dependent E3 docking surfaces, removing marks that enable degrader occupancy to favor protective partners, or reinforcing direct stabilizer behavior by shifting local interface chemistry. TPS may be particularly impactful for proteins where restoration of abundance is the primary barrier to function.

Challenges and outlook

A key challenge for both MeTAGs and TPS is achieving sufficient site-specificity, as recruited methyltransferases may modify multiple accessible lysines on the target surface. We envision that engineered SET-domain variants with constrained substrate preferences could help narrow the modification window. However, even modest site-selectivity may suffice, because the downstream outcome depends not only on which site is methylated but also on whether the cellular context contains the matching E3 or reader to execute the program. By controlling methyl state and occupancy, MeTAGs could dial degradation propensity, installing marks that favor degron execution while avoiding protective reader recruitment, creating methyl-directed degraders that complement PROTAC logic through PTM state editing rather than direct E3 tethering.

Taken together, these directions define the next phase of the field: (1) read the stability switch through chemical proteomics, (2) write it through MeTAG-installed neo-degrons, and (3) rescue via TPS through stabilizer wiring. Achieving these goals will convert lysine methylation from a descriptive PTM into an engineerable platform for controlling protein lifetime.

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AUTHOR CONTRIBUTIONS

The concept and content of the review were devised by M.R., B.Q.G.L., and A.V.G. B.Q.G.L. and M.R. contributed to the writing of the article. Tables were prepared by B.Q.G.L. and figures were prepared by A.V.G. The article was edited by M.R., B.Q.G.L., and A.V.G.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with language refinement and editorial polishing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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