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Review

Precision Photocatalytic Chemistry for Subcellular Proximity Labeling

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Abstract: Subcellular compartmentalization is essential for coordinating biochemical complexity in eukaryotes. The dynamic intracellular trafficking of biomacromolecules is vital for organelle functional integrity and cellular homeostasis. Photocatalytic proximity labeling (PPL) has emerged as a versatile strategy for probing these processes and subcellular omics, enabling in situ covalent tagging of biomolecules via light-triggered, short-lived reactive species. This review summarizes recent developments in precision photocatalytic chemistry for subcellular proximity labeling, as well as the targeting mechanisms that provide PPL with excellent spatial resolution. Furthermore, we highlight its applications in subcellular proteomics, spatial RNA/DNA profiling, and protein-protein/protein-RNA interaction mapping. We further discuss ongoing challenges and emerging innovations aimed at improving precision and broadening the scope of biological applications. Together, these light-controlled approaches provide high spatiotemporal resolution while maintaining biocompatibility with physiological environments, addressing key limitations of conventional methods, positioning PPL as a powerful framework for elucidating molecular mechanisms in living systems.

Keywords: photocatalysis; proximity labeling; subcellular omics

1. Introduction

Eukaryotic cells achieve functional complexity through precise compartmentalization, utilizing membrane-bound organelles and membraneless condensates to partition specific biomolecules.[1–3] These specialized microenvironments possess unique molecular signatures that dictate their physiological roles. Central to this organization is the spatiotemporal distribution of biomolecules. As primary effectors, proteins dynamically orchestrate essential processes including metabolism, signal transduction, and proteostasis within defined spatial domains and according to ordered temporal sequences.[4,5] This spatial dependency extends to DNA and RNA, whose functional integrity is similarly contingent upon their precise arrangement and dynamic interplays.[6,7] Disruption of this coordinated spatiotemporal organization has been implicated in the pathogenesis of diverse diseases.[8–11] This multilayered architecture underscores the urgent need for analytical methods that can resolve biomolecular localization and activity with high spatiotemporal reliability.

Traditional methodologies such as density gradient centrifugation and immunofluorescence laid the essential groundwork for mapping subcellular architecture.[12,13] However, their utility is constrained by organelle cross-contamination, loss of native biomolecular contexts, and reliance on predefined antibodies. These limitations are particularly acute when probing dynamic or membraneless compartments. To transcend these boundaries, enzyme-based proximity labeling strategies (such as BioID[14] and APEX[15,16]) revolutionized spatial biology by enabling in situ, proximity-dependent tagging with high spatiotemporal resolution in living cells.[17–19] While these approaches have transformed the study of organelle proteomes and transient interactomes, their performance differs in labeling speed, spatial resolution, genetic requirements, and biological compatibility. BioID typically requires hour-scale

labeling but operates under highly biocompatible conditions, whereas APEX enables minute-scale labeling with improved temporal control but requires H_2O_2 for activation. Both approaches generally rely on genetic fusion, while their spatial resolution depends on the lifetime and diffusion of the reactive labeling species.

Recently, photocatalytic proximity labeling has emerged as a powerful chemical strategy that exploits light-activated catalysts to generate transient reactive species for in situ, on-demand biomolecular tagging in living systems.[20–22] By employing photosensitive small molecules or genetically encoded proteins to drive bioconjugation between chemical probes and neighboring macromolecules, PPL achieves spatial resolution ranging from nanoscale to sub-micrometer dimensions.[17] Precise catalyst localization is accomplished through two complementary approaches: non-genetic strategies that rely on the intrinsic chemical affinity or organelle-targeting capabilities of small-molecule catalysts, and genetic strategies that employ recombinant fusion of catalytic modules with defined protein markers. Together, these approaches expand the applicability of PPL across diverse subcellular landscapes, including traditionally inaccessible or hard-to-transfect systems, and enable rapid, selective profiling of endogenous proteins and nucleic acids. By uniting spatiotemporal control with broad chemical compatibility, PPL establishes a broadly applicable framework for interrogating complex biological processes with rapid kinetics, high efficiency and versatility.

Beyond its analytical capabilities, PPL aligns closely with key concepts of green chemistry and sustainable biotechnology. Unlike stoichiometric labeling systems or enzyme-based methods requiring continuous cofactor consumption and toxic oxidants (such as millimolar H_2O_2 in APEX workflows), PPL harnesses light as a traceless, non-invasive trigger to drive efficient catalytic turnovers under ambient, near-physiological aqueous conditions. The high catalytic efficiency of localized photosensitizers substantially decreases required probe and catalyst concentrations to micromolar or nanomolar levels, minimizing chemical waste. Furthermore, non-genetic targeting strategies enable direct profiling of native primary specimens, biopsies, and hard-to-transfect cell lineages, significantly streamlining experimental pipelines and reducing reliance on engineered models or animal-intensive exploratory procedures.

Driven by the expanding interest in this domain, this review provides a comprehensive overview of precision photocatalytic chemistry for subcellular proximity labeling (Figure 1). We systematically outline the key targeting mechanisms governing current PPL platforms and survey major advances in subcellular proteomics, spatial RNA/DNA profiling, and interactome mapping. Finally, we discuss existing challenges and prospective innovations designed to elevate spatiotemporal precision and broaden the applicability of PPL across complex biological systems.

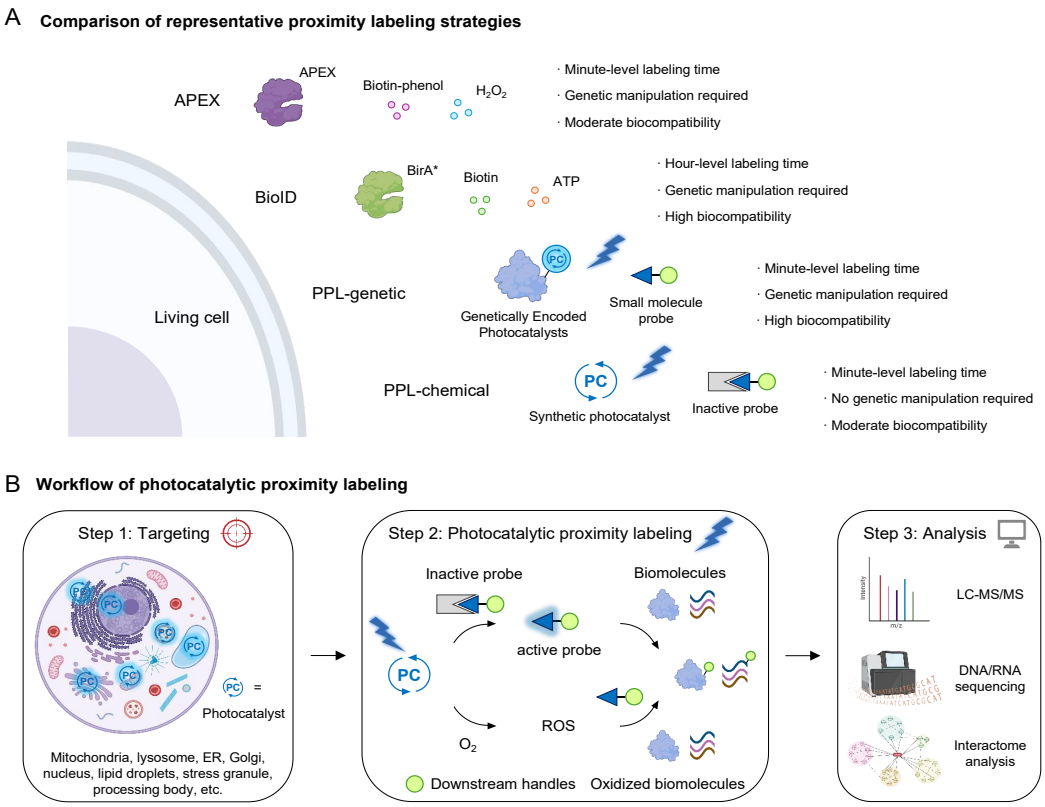

Figure 1. Overview of proximity labeling strategies and the workflow of photocatalytic proximity labeling. (**a**) Comparison of representative proximity labeling strategies. APEX utilizes an engineered peroxidase to oxidize biotin-phenol in the presence

Sustain. Sci. Innov. **2026**, *1*, 103389
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of H_2O_2; BioID uses BirA-derived biotin ligases to label proximal proteins in an ATP-dependent manner; genetically encoded photocatalytic proteins (e.g., miniSOG) are activated by light to generate reactive species; synthetic small-molecule photocatalysts similarly use light to produce reactive intermediates for covalent labeling. Key features of these strategies, including labeling time, genetic requirement, and biocompatibility, are summarized alongside the corresponding schematic. (**b**) Schematic illustration of the general workflow of photocatalytic proximity labeling. Photocatalysts are localized to specific subcellular regions through diverse targeting strategies and activated by light irradiation to initiate spatially restricted labeling. Photocatalytic labeling can proceed by activating inert probes to generate reactive intermediates or by generating reactive oxygen species (ROS) that oxidize proximal biomolecules, enabling their subsequent covalent capture. The labeled proteins and nucleic acids can then be analyzed by LC-MS/MS, DNA/RNA sequencing, or interactome analysis to characterize subcellular molecular landscapes. Created in BioRender. Agreement numbers: SJ2A6PWFCI and IS2A6PGPK7.

2. Photocatalytic proximity labeling chemistry

PPL converts spatial information into covalent molecular signatures by utilizing localized photocatalysts to generate short-lived reactive chemical species under light irradiation. Mechanistically, PPL platforms can be classified into two fundamentally distinct chemical paradigms: (i) photo-oxidative tagging, in which an excited photocatalyst oxidizes electron-rich biomolecular residues to enable subsequent nucleophilic capture, and (ii) catalytic precursor activation, in which light triggers the in situ generation of transient electrophilic or diradical intermediates that directly modify neighboring macromolecules. The overall labeling outcome is governed by a sequence of photocatalyst excitation, intermediate generation, and localized biomolecular capture. Below, we discuss representative photochemical pathways illustrating these relationships, including triplet-triplet energy transfer (TTET) for singlet oxygen generation, single-electron transfer (SET) for radical generation, Dexter energy transfer (DET) for carbene generation, and bioorthogonal photocatalytic deprotection for quinone methide (QM) generation.

2.1. Singlet oxygen generation via triplet–triplet energy transfer

A representative class of PPL mechanisms exploits photosensitizers to generate singlet oxygen ($^1O_2$) through TTET. Photosensitizers utilizing this mechanism encompass a broad range of organic chromophores and metal complexes.[23,24] One of the most widely used genetically encoded platforms is miniSOG, a flavin-based photosensitizer derived from the LOV (light-oxygen-voltage) domain of Arabidopsis thaliana phototropin 2.[25] MiniSOG noncovalently binds flavin mononucleotide (FMN), which serves as the photosensitizing chromophore, while the protein scaffold provides genetically programmable subcellular localization. Upon blue-light irradiation, the flavin group of FMN is excited from its ground singlet state (S_0) to the excited singlet state (S_1), followed by intersystem crossing to the triplet excited state (T_1). The triplet-state flavin can then undergo TTET with ground-state triplet oxygen ($^3O_2$), generating the short-lived $^1O_2$ intermediate. $^1O_2$ subsequently oxidizes proximal biomolecules, primarily protein histidine residues and nucleic acid guanosine bases. The resulting oxidized products can be captured by nucleophilic probes, such as propargylamine or aniline derivatives, installing alkyne handles for subsequent click-chemistry-based analysis and enrichment (Figure 2a).[26–28] The effective spatial range of miniSOG labeling has traditionally been associated with the short lifetime and limited diffusion of $^1O_2$ in cells, with an often-cited action radius of approximately 70 nm.[29] However, recent dSTORM (direct stochastic optical reconstruction microscopy) measurements in mammalian cells showed an illumination-dependent labeling diameter of approximately 70–180 nm over 5–30 min irradiation, highlighting that the effective labeling range is strongly influenced by irradiation conditions and cellular microenvironment.[30]

2.2. Photoredox radical generation via single-electron transfer

An alternative class of PPL mechanisms relies on photoredox reactions in which an excited photocatalyst undergoes single-electron transfer (SET) with a probe or a redox partner, thereby generating reactive radical species that covalently label nearby biomolecules. LITag provides a representative example. Upon excitation, the flavin photosensitizer can undergo electron transfer with biotin-phenol or biotin-aniline probes, generating phenol/aniline-derived radical species that react with proximal biomolecules, with tyrosine residues serving as prominent labeling sites.[31]

Importantly, SET does not necessarily occur directly between the excited photocatalyst and the labeling probe. μMap-Red, for example, employs a red-light-absorbing Sn-chlorin photocatalyst whose excited state undergoes reductive quenching by NADH. The resulting reduced photocatalyst subsequently transfers an electron to aryl azide probes, generating labeling-active aminyl radicals that react with proximal biomolecules.[32]

Although PPL mechanisms could be broadly classified into energy transfer and electron transfer pathways, these are not mutually exclusive. For example, miniSOG may also produce ROS via SET with surrounding biomolecules,[17,22] and LITag can support both SET-mediated radical generation and TTET-mediated $^1O_2$ production when an aniline probe is used.[31]

Sustain. Sci. Innov. **2026**, *1*, 103389
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2.3. Carbene generation via dexter energy transfer

A distinct PPL strategy μMap (MicroMap) uses an Ir(III) photocatalyst to activate a nearby diazirine probe through DET (Figure 2b).[33] Photoexcitation of the Ir catalyst generates a long-lived triplet excited state, which transfers energy to the diazirine through the orbital-overlap-dependent Dexter mechanism. The excited diazirine then undergoes elimination of N_2 to generate a highly reactive carbene that can covalently insert into nearby C–H, N–H, O–H, or S–H bonds.[34] Thus, spatial restriction is imposed both by short-range Dexter energy transfer and by the ultrashort lifetime of the carbene intermediate. Subsequent single-catalyst calibration measured a maximum carbene-labeling distance of approximately 11 nm from the catalyst attachment site,[35] although the actual PPL resolution could be affected by the geometry of targeting moieties (e.g., ~54 nm when catalyst was localized by dual-antibody targeting).[36]

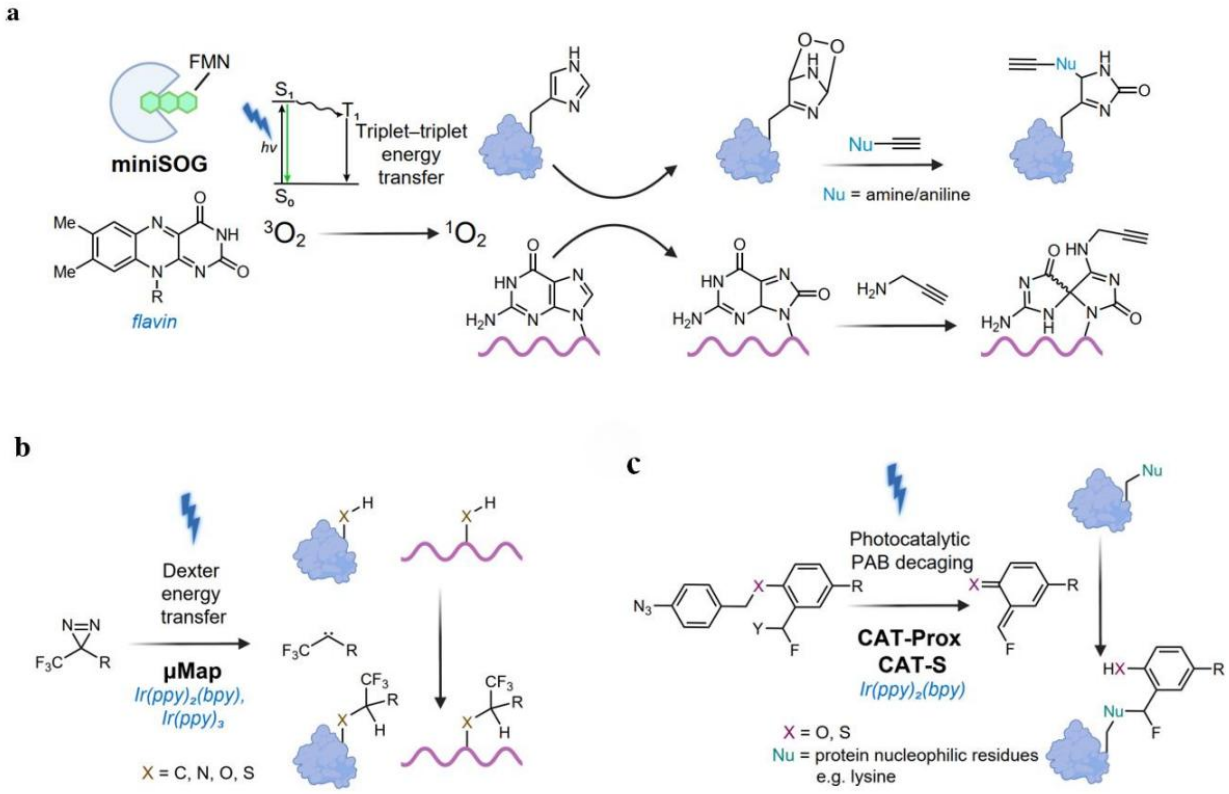

Figure 2. Representative photochemical mechanisms underlying PPL. (**a**) Singlet oxygen ($^1O_2$)-mediated PPL by miniSOG. miniSOG noncovalently binds flavin mononucleotide (FMN), whose flavin group serves as the photocatalytic center. Upon photoexcitation, the excited flavin generates $^1O_2$ through triplet–triplet energy transfer from molecular oxygen. The resulting $^1O_2$ oxidizes proximal biomolecules, including histidine residues and guanosine, which are subsequently captured by amine/aniline probes bearing an alkyne handle. The alternative pathway in which the flavin photocatalyst generates probe-derived radicals via single-electron transfer (SET), as exemplified by LITag, is not illustrated. (**b**) μMap employs Ir photocatalysts to activate diazirine probes through Dexter energy transfer, generating highly reactive carbenes that covalently insert into nearby X–H bonds (X = C, N, O, S). (**c**) CAT platforms, represented by CAT-Prox and CAT-S, use Ir photocatalysts to trigger photocatalytic deprotection of PAB-protected probes, generating electrophilic quinone methide (QM) or thioquinone methide (thioQM) intermediates that react with nucleophilic residues on proximal proteins.

2.4. Photocatalytic activation of quinone methide derivatives

CAT-Prox (bioorthogonal and photocatalytic deprotection-enabled proximity labeling) represents a different strategy in which an Ir photocatalyst enables deprotection of para-azidobenzyl (PAB)–protected QM probes. Upon visible-light irradiation, NADH reductively quenches the excited Ir photocatalyst, whose reduced state subsequently reduces the aryl azide group of the PAB-protected probe, triggering PAB deprotection and release of the electrophilic QM intermediate for subsequent biomolecular labeling (Figure 2c).[37] An advantage of the system is that the intermediate reactivity and diffusion properties can be tuned by modification of the employed QM probes. The CAT-S strategy builds upon this tunability and employs thioQM, enhancing reactivity for application in primary samples.[38] In PPL strategies employing QM intermediates,

Sustain. Sci. Innov. **2026**, *1*, 103389
https://doi.org/10.54963/ssi.103389

effective spatial range is determined not only by photocatalyst localization but also by photocatalytic deprotection kinetics, the lifetime and diffusion of the released QM/thioQM, and the rate of nucleophilic capture. Accordingly, the spatial precision of CAT should be interpreted as a combined property of catalyst localization and warhead chemistry rather than as a single fixed molecular radius.

Collectively, the effective spatial resolution of PPL is governed by two hierarchical parameters: (i) the fundamental photophysical radius of energy or electron transfer, which requires molecular contact for orbital-overlap-dependent processes such as Dexter energy transfer; (ii) the chemical lifetime and diffusion trajectory of the generated reactive intermediates, ranging from nanosecond-lived carbenes to microsecond-lived singlet oxygen and quinone methides. A comprehensive evaluation of PPL precision must therefore integrate photocatalytic kinetics and intermediate quenching dynamics.

3. Subcellular targeting mechanism

The feature of photocatalytic proximity labeling is the ability to generate reactive intermediates within restricted environments, thereby converting spatial information into covalent molecular signatures. Unlike conventional biochemical fractionation approaches that rely on physical isolation of cellular compartments, photocatalytic labeling records subcellular compositions and maps molecular interactomes directly within living systems. To achieve such spatial precision, the localization of photocatalysts within defined subcellular regions is critical. Therefore, diverse targeting strategies have been developed to deliver photocatalysts to specific subcellular regions, which can be broadly classified into non-genetic and genetic targeting strategies (Figure 3).

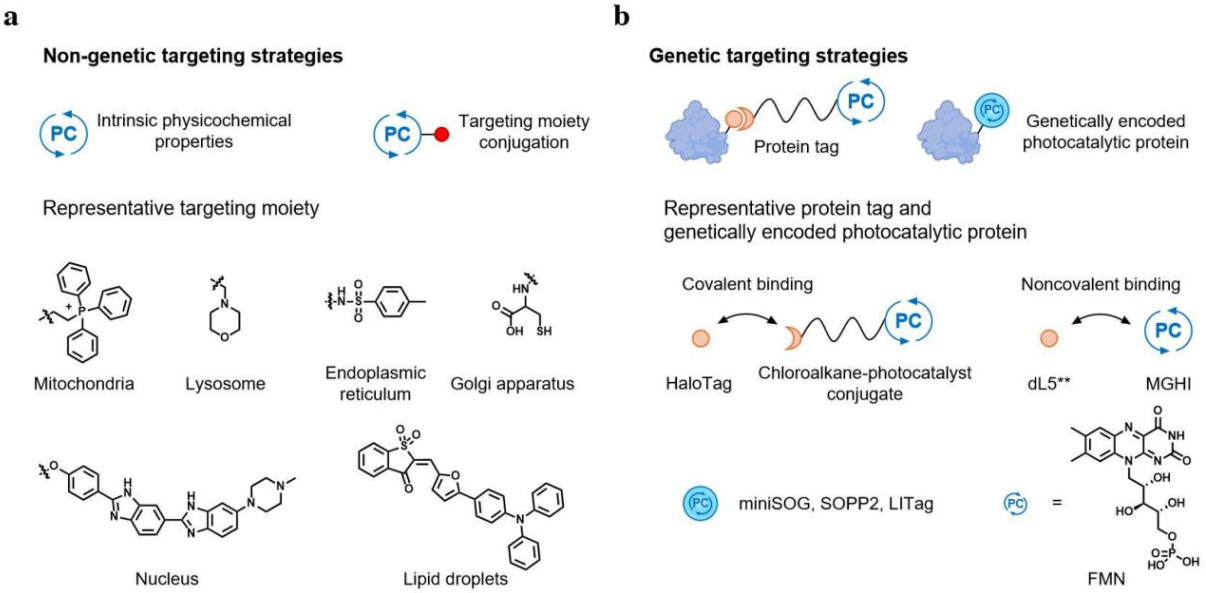

Figure 3. Non-genetic and genetic subcellular targeting strategies. (**a**) Non-genetic targeting strategies for subcellular photocatalytic proximity labeling. Photocatalysts can localize to specific subcellular regions through their intrinsic physicochemical properties or through conjugation with organelle-targeting moieties. Representative targeting motifs and molecular features are shown for mitochondria, lysosomes, the endoplasmic reticulum, Golgi apparatus, nucleus, and lipid droplets. (**b**) Genetic targeting strategies for photocatalytic proximity labeling. Genetically encoded systems achieve spatial control either by recruiting exogenous photocatalysts to genetically expressed protein tags or by directly expressing photocatalytic proteins at defined cellular locations. HaloTag covalently captures chloroalkane-photocatalyst conjugates, whereas the fluorogen-activating protein dL5** noncovalently binds the photosensitizer MG-HI. Alternatively, genetically encoded photocatalytic proteins, including miniSOG, SOPP2, and LITag, utilize the endogenous flavin cofactor FMN as the photosensitizing chromophore for light-triggered proximity labeling.

3.1. Non-genetic targeting strategies

Non-genetic approaches utilize the intrinsic physicochemical properties of photocatalysts or chemically installed targeting motifs to achieve organelle localization without genetic manipulation. These strategies are particularly advantageous for primary cells, patient-derived samples, and other biological systems where genetic modification is technically challenging.

The simplest strategy exploits the inherent physicochemical properties of photocatalysts, including charge, lipophilicity, and hydrophobicity, to achieve selective accumulation within specific organelles. For example, cationic photocatalysts can preferentially accumulate in mitochondria driven by the negative membrane potential across the inner mitochondrial membrane.[39] Following mitochondrial accumulation,

Sustain. Sci. Innov. **2026**, *1*, 103389
https://doi.org/10.54963/ssi.103389

these molecules can associate with the matrix-facing surface of the inner membrane, enabling localized activation of photocatalytic reactions in this compartment.[40]

An alternative strategy introduces specific targeting groups onto photocatalysts to redirect their intracellular distribution. In this approach, photocatalysts serve as reactive modules, whereas appended chemical motifs provide organelle recognition. A representative example is lysosomal targeting using morpholine-containing photocatalysts. Protonation of the morpholine group under the acidic lysosomal environment promotes selective accumulation within lysosomes, enabling photocatalytic labeling under conditions that are challenging for many enzyme-based labeling systems.[41] This modular design separates the functions of localization and chemical reactivity, allowing independent optimization of targeting elements and photocatalytic properties. Consequently, targeting moiety-mediated strategies provide broad adaptability for diverse organelles and biological contexts.

3.2. Genetic targeting strategies

Genetic targeting strategies utilize genetically encoded elements to position photocatalytic activity at defined proteins or cellular regions. Although these approaches require genetic manipulation, they provide genetically programmable and spatially precise recruitment of photocatalysts to defined proteins or subcellular sites, enabling high-resolution mapping of protein-centered interactomes and subcellular molecular landscapes.

Protein tags provide a versatile platform for recruiting photocatalysts to proteins of interest (POIs). In this strategy, a genetically encoded tag is fused to the target protein, while the photocatalyst is chemically conjugated to a complementary ligand that specifically reacts with the tag. Among various systems, HaloTag has been widely employed because it forms an irreversible covalent bond with chloroalkane-functionalized photocatalysts.[42] This strategy enables precise recruitment of photocatalysts to specific proteins, allowing investigation of local protein-protein interaction networks and dynamic molecular assemblies. Compared with organelle-level targeting, protein-tag approaches achieve higher spatial precision by restricting photocatalytic activation to the immediate vicinity of a defined protein.

Alternatively, fully genetically encoded strategies utilize engineered FMN-binding protein domains to localize cellular FMN, with its flavin group serving as the photosensitizer. miniSOG represents one of the most widely used fully genetically encoded PPL platforms, localizing FMN to miniSOG-fused POIs.[25] Upon blue-light irradiation, miniSOG-bound FMN generates $^1O_2$, enabling oxidative labeling of nearby biomolecules. Compared with chemically delivered photocatalysts, genetically encoded photosensitizers provide direct spatial control through protein expression and fusion, making them particularly suitable for studying defined protein environments and organellar microdomains.

Together, these targeting strategies provide complementary solutions for spatial control in photocatalytic proximity labeling. Non-genetic approaches offer broad applicability by avoiding genetic manipulation, whereas genetic strategies enable programmable localization with molecular precision. The combination of chemical catalyst design, targeting architecture, and genetically encoded tools has expanded photocatalytic proximity labeling from organelle-scale profiling to protein-specific interactome mapping, establishing a versatile framework for interrogating molecular organization across diverse biological systems.

4. Photocatalytic proximity labeling across subcellular compartments

4.1. Mitochondria

Mitochondria are highly dynamic organelles that serve as central hubs for cellular energy metabolism, redox regulation, calcium homeostasis, and apoptotic signaling. Disruption of mitochondrial homeostasis has been increasingly recognized as a hallmark of diverse pathological states, including neurodegeneration, metabolic disorders, cardiovascular diseases, and cancer. Consequently, defining the mitochondrial proteome, transcriptome, and molecular interactomes under physiological and pathological conditions is essential for understanding mitochondrial functions, stress responses, and disease progression. Conventional approaches for mitochondrial molecular profiling, including organelle isolation and enzymatic proximity labeling, are often limited by compromised spatial fidelity or the requirement for genetic manipulation. Photocatalytic proximity labeling overcomes these limitations by combining organelle-selective photocatalyst localization with light-controlled activation, enabling genetically independent and temporally resolved interrogation of mitochondrial molecular landscapes (Figure 4a, Table 1).

One class of photocatalytic mitochondrial proteomics approaches exploited the intrinsic mitochondrial accumulation properties of small-molecule photocatalysts. Huang and coworkers developed CAT-Prox,[37] a bioorthogonal photocatalytic deprotection-enabled proximity labeling strategy, using the mitochondria-targeting iridium catalyst Ir8. The positively charged iridium complex preferentially accumulated in mitochondria, where light irradiation triggered deprotection of a PAB-protected QM probe to generate a highly reactive QM intermediate for covalent protein labeling, enabling in situ mitochondrial proteome profiling in living cells, including hard-to-transfect macrophages.[37] Under optimized cellular conditions, CAT-Prox used 0.2 μM Ir8 and 100 μM QM probes with blue-light irradiation for approximately 10 min. Ir8 showed strong mitochondrial colocalization (Pearson's R up to 0.83),

Sustain. Sci. Innov. 2026, 1, 103389
https://doi.org/10.54963/ssi.103389

while mitochondrial proteins accounted for up to 72% of the enriched proteome. Building upon this strategy, CAT-S[38] introduced a more efficient thioQM labeling chemistry to improve mitochondrial proteome coverage and expand applications to primary biological samples. Under optimized conditions, CAT-S employed 100 nM photocatalysts and 100 μM thioQM probes with 12 min photoirradiation, achieving high mitochondrial targeting and proteomic specificity (Pearson's R up to 0.90; mitochondrial specificity up to 87%). Through bioorthogonal photocatalytic activation, CAT-S enabled mitochondrial proteomic profiling in primary T cells, dissociated mouse tissues, and diabetic mouse kidney samples, demonstrating compatibility with complex living systems inaccessible to conventional genetically encoded approaches.[38]

Beyond transition-metal catalysts, organic photosensitizers have also been explored for mitochondria-targeted photocatalytic proximity labeling. Rhodamine 123 (Rh123), a classical mitochondria-localizing fluorophore, was repurposed as a photocatalyst to activate aryl azide-based labeling probes upon light irradiation.[43] The photoexcited Rh123 generated reactive intermediates that enabled covalent labeling of proximal mitochondrial proteins, allowing dynamic monitoring of mitochondrial proteome remodeling under rotenone-induced oxidative stress.[43] Under optimized cellular conditions, the method employed 20 μM Rh123 and 200 μM AzPh-biotin with 1 h photoirradiation, showing high mitochondrial colocalization (Pearson's R = 0.87) and 60.4% mitochondrial proteomic specificity. This strategy highlights the potential of exploiting the intrinsic organelle-targeting properties of established bioactive fluorophores for genetically independent mitochondrial profiling. To further expand the applicability of mitochondrial photocatalytic labeling, near-infrared (NIR)-activated systems have been developed to overcome the limited tissue penetration and potential phototoxicity associated with visible-light excitation. The PL-NIR (proximity labeling strategy using near-infrared excitation) strategy employed the mitochondria-targeting fluorophore IR780 as a NIR-responsive photocatalyst, which generated reactive oxygen species upon NIR irradiation for mitochondrial protein labeling.[44] Under optimized conditions, PL-NIR employed 2 μM IR780 and 5 mM 3-ethynylaniline (3-EA) with only 90 s NIR irradiation, achieving strong mitochondrial targeting (Pearson's R = 0.83). By utilizing longer-wavelength excitation, PL-NIR improved light penetration and reduced interference from endogenous cellular chromophores, providing a promising approach for mitochondrial proteome analysis in more complex biological environments.[44]

In addition to mitochondrial protein labeling achieved through intrinsic physicochemical targeting, non-genetic photocatalytic strategies have also been extended toward spatially resolved mitochondrial RNA profiling. An aggregation-induced emission (AIE)-based photosensitizer, TFPy, was developed as a mitochondria-targeting photocatalyst, whose aggregation within mitochondria enhanced both fluorescence emission and reactive oxygen species generation.[45] TFPy exhibited strong mitochondrial localization (Pearson's R > 0.8) and mediated proximity labeling through locally generated singlet oxygen, with cellular labeling performed using 5 μM photosensitizer and 3 min photoirradiation. Leveraging its intrinsic mitochondrial localization and light-activated photocatalytic activity, TFPy enabled non-genetic proximity labeling and high-throughput sequencing of mitochondria-associated transcripts.[45] More recently, CAT-seq established a bioorthogonal photocatalytic RNA labeling platform for in situ mitochondrial transcriptome profiling.[46] By integrating a mitochondria-targeting photocatalyst with a QM-based RNA labeling probe, CAT-seq achieved mitochondrial RNA labeling within 15 min of blue-light irradiation, with high spatial colocalization (Pearson's R = 0.82) and a mitochondrial sequencing specificity of 62.9%. CAT-seq enabled selective capture of mitochondrial RNAs and further extended photocatalytic proximity labeling toward synchronous mitochondrial RNA and protein multiomics analysis within the same sample.[46]

Beyond intrinsic physicochemical targeting, conjugation of mitochondria-targeting moieties provides another versatile strategy for directing photocatalytic labeling systems to mitochondria. Triphenylphosphonium (TPP), a mitochondria-targeting cation driven by mitochondrial membrane potential, has been widely employed as a targeting moiety for photocatalytic labeling systems, either through conjugation with photocatalysts[23] or labeling probes.[46] For example, a photooxidation-driven proximity labeling strategy employed a TPP-conjugated eosin derivative (TPP-AcDBF) as a mitochondria-localized photosensitizer.[23] Upon green-light irradiation, the dibromofluorescein (DBF) photosensitizer generated singlet oxygen, which oxidized proximal mitochondrial proteins and enabled covalent capture through nucleophilic labeling reagents.[23] TPP-AcDBF showed strong mitochondrial localization (Pearson's R = 0.88), with cellular labeling performed using 10 μM TPP-AcDBF and 5 mM propargylamine. The optimized labeling conditions yielded up to 78% mitochondrial proteins, enabling mitochondrial proteome profiling in living cells.

Genetically encoded photocatalytic proteins provide an alternative strategy by enabling genetically programmed localization of photocatalytic activity to defined mitochondrial regions. PDPL (photoactivation-dependent proximity labeling) established a genetically encoded photocatalytic proximity labeling platform based on miniSOG.[27] Upon blue-light irradiation, the genetically positioned miniSOG generates singlet oxygen, which activates aniline-based labeling chemistry to covalently capture proximal proteins. Under optimized conditions (1 mM probes, 20 min irradiation), mitochondrial PDPL identified 461 significantly enriched proteins with 78.5% mitochondrial specificity, of which 91.7% of the annotated mito-

Sustain. Sci. Innov. **2026**, *1*, 103389
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chondrial proteins were localized to the matrix or inner mitochondrial membrane. By combining genetic control of photocatalyst localization with light-triggered activation, PDPL enabled spatiotemporally resolved mapping of organellar proteomes.[27] Subsequently, LITag (Light-induced Interactome Tagging) expanded genetically encoded photoproximity labeling by introducing a compact LOV-based photocatalytic module for rapid and controllable protein labeling.[31] Upon blue-light excitation, the FMN cofactor within the engineered LOV domain generates reactive intermediates that activate exogenous probes for covalent proximity labeling. Using a COX4-derived mitochondrial targeting sequence to localize LOV to the mitochondrial matrix, LITag achieved proteomic labeling with only 3 s of irradiation and identified over 160 significantly enriched proteins, all of which were annotated as mitochondrial proteins. Its intrinsic fluorescence further allowed simultaneous visualization of photocatalyst localization and labeling events.[31]

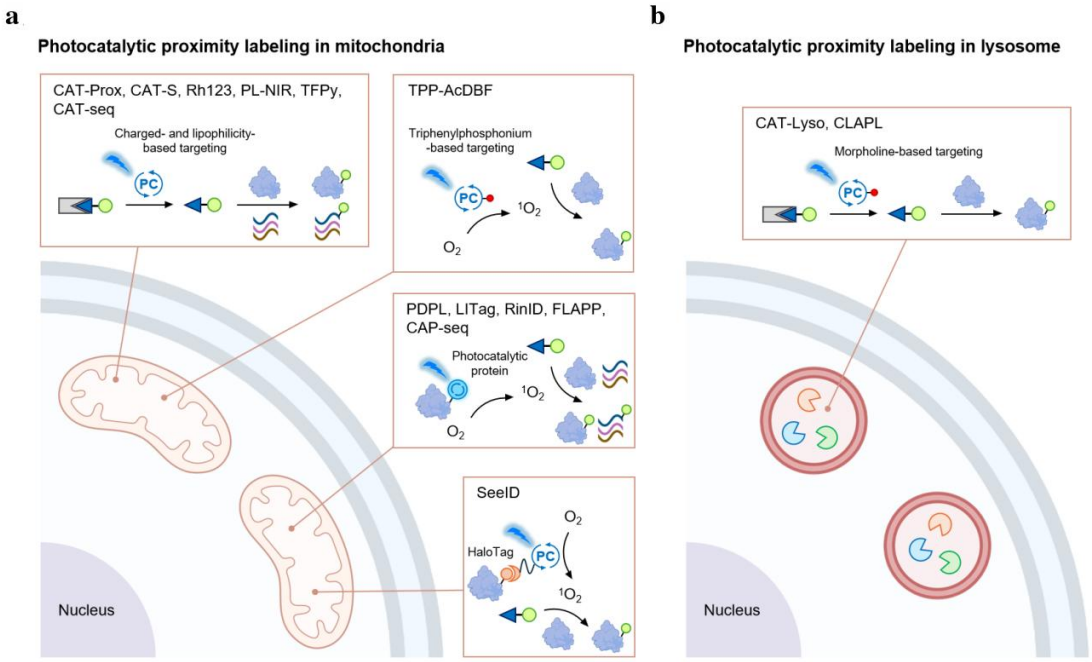


Figure 4. Photocatalytic proximity labeling in mitochondria and lysosomes. (**a**) Representative photocatalytic proximity labeling strategies for mitochondrial molecular profiling. Non-genetic approaches exploit either the intrinsic mitochondrial accumulation of photocatalysts, as exemplified by CAT-Prox, CAT-S, Rh123, PL-NIR, TFPy, and CAT-seq, or conjugation with the mitochondria-targeting triphenylphosphonium (TPP) moiety, as exemplified by TPP-AcDBF. These systems enable photocatalytic activation or photooxidation-mediated labeling for mitochondrial proteome and transcriptome profiling. Genetic strategies position photocatalytic activity within mitochondria through genetically encoded photocatalytic proteins, as exemplified by PDPL, LITag, RinID, FLAPP, and CAP-seq, enabling spatially resolved protein and RNA profiling. Protein-tag-mediated targeting, exemplified by HaloTag-based SeeID, further enables photocatalytic mapping of dynamic mitochondrial protein interactomes. (**b**) Representative photocatalytic proximity labeling strategies for lysosomal proteome profiling. CAT-Lyso and CLAPL employ morpholine-based lysosomal targeting to selectively localize photocatalytic activity within acidic lysosomal compartments. CAT-Lyso utilizes photocatalytic activation of a thioquinone methide precursor for covalent labeling of proximal lysosomal proteins, whereas CLAPL combines singlet-oxygen-mediated photocatalytic labeling with cross-linking-assisted amplification to enhance lysosomal proteome coverage.

Building upon genetically encoded miniSOG-based photocatalysis, RinID (reactive oxygen species induced protein labeling and identification) further applied this strategy toward high-specificity mitochondrial proteome profiling.[28] By targeting the photocatalytic module to the mitochondrial matrix, RinID enabled selective generation of reactive intermediates within mitochondria and subsequent enrichment of proximal proteins for mass spectrometry analysis. Under optimized cellular conditions using 20 mM propargylamine and 15 min of blue-light irradiation, RinID identified 477 mitochondrial proteins with 94% specificity. This approach provided a genetically encoded strategy for resolving mitochondrial molecular landscapes with high spatial specificity.[28] More recently, FLAPP (fluorogen-activating protein mediated photocatalytic proximity labeling) expanded genetically encoded photocatalytic proteomics toward NIR excitation.[47] In this strategy, a genetically targeted fluorogen-activating protein (FAP) recruits an iodinated malachite green derivative as a photosensitizing

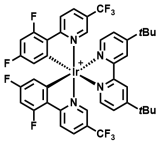
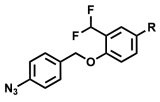
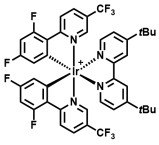
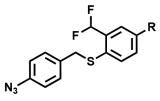
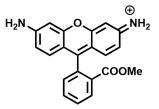
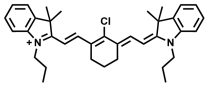
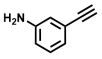
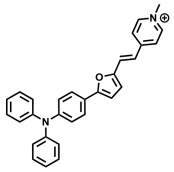
Sustain. Sci. Innov. **2026**, *1*, 103389
https://doi.org/10.54963/ssi.103389

cofactor, forming an activated photocatalytic complex upon binding. Under 660 nm NIR irradiation, the complex generates singlet oxygen for proximity-dependent protein labeling. Using 500 nM MG-HI and 10 min of irradiation, mitochondrial matrix-targeted FLAPP achieved 96% spatial specificity. This genetically encoded NIR-responsive system further improved compatibility with complex biological samples through deeper tissue penetration and reduced background excitation.[47]

In parallel with protein profiling, genetically encoded photocatalysts have been adapted for mitochondrial transcriptome analysis. CAP-seq (chromophore-assisted proximity labeling and sequencing) utilized a miniSOG photocatalyst genetically targeted to the mitochondrial matrix through COX4 fusion.[26] Upon blue-light illumination, miniSOG generated singlet oxygen to oxidize RNA nucleobases, enabling subsequent probe-mediated enrichment and sequencing of mitochondrial RNAs. Under optimized conditions using 10 mM propargylamine and 20 min of irradiation, CAP-seq enriched all 13 mitochondrial mRNAs and both mitochondrial rRNAs, while showing minimal enrichment of abundant cytosolic transcripts. This strategy therefore achieved highly selective mitochondrial transcriptome profiling.[26] Beyond RNA profiling, genetically encoded photocatalysts have also been explored for mitochondrial genome analysis. MiniSOG-based photooxidative labeling platforms have achieved spatially restricted mitochondrial DNA tagging. Using 5 mM propargylamine under blue-light irradiation for 15 min, mitochondria-targeted photosensitizers selectively oxidatively modified guanosine bases on mitochondrial DNA, resulting in approximately 3.5-fold enrichment of the mitochondrial genome over nuclear genomic background with negligible cytotoxicity.[48]

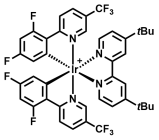
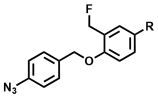
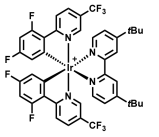
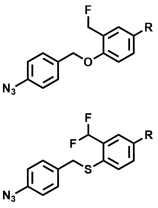
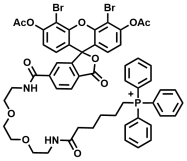
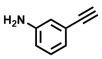
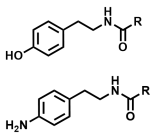
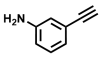
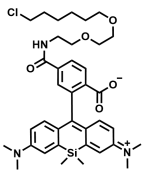
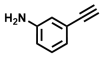
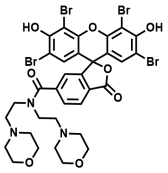
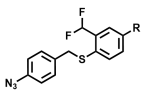
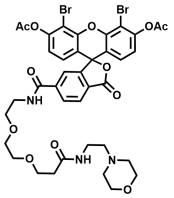
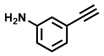
Beyond mitochondrial molecular profiling, genetically encoded photocatalytic labeling has also enabled dynamic mitochondrial interactome analysis. SeeID (Silicon-rhodamine-enabled Identification) employed a HaloTag-compatible silicon rhodamine (SiR)-based NIR photocatalytic system to combine live-cell fluorescence imaging with proximity labeling.[49] Cellular labeling was performed using 1 μM SiR-CA and 500 μM 3-EA under 660-nm irradiation for 30 min, with high spatial specificity demonstrated by strong colocalization between labeling signals and Halo-tagged subcellular markers (Pearson's R up to 0.94). By tracking Halo-Parkin translocation during mitophagy and coupling imaging-guided labeling with LC-MS/MS analysis, SeeID revealed dynamic changes in the mitochondrial Parkin interactome, including the transient recruitment of proteasome-associated proteins during early mitophagy stages.[49] This strategy highlights the potential of photocatalytic proximity labeling for resolving spatiotemporal mitochondrial interaction networks beyond static molecular profiling.

Table 1. Photocatalytic proximity labeling platforms across distinct subcellular environments.

Technique	Targeting Mechanism	Photocatalyst	Labelling Probe	Labeling Targets	Light Source	Subcellular Compartments
CAT-Prox[37]	Intrinsic properties			Protein	450 nm blue LED	Mitochondria
CAT-S[38]	Intrinsic properties			Protein	450 nm blue LED	Mitochondria
Rh123- mediated labeling[43]	Intrinsic properties			Protein	515 nm green LED	Mitochondria
PL-NIR[44]	Intrinsic properties			Protein	808 nm NIR light	Mitochondria
TFPy- mediated labeling[45]	Intrinsic properties			RNA	480 nm blue light	Mitochondria

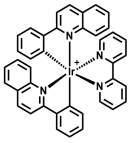
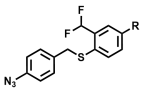
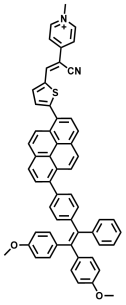
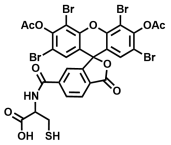
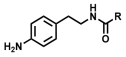
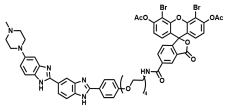
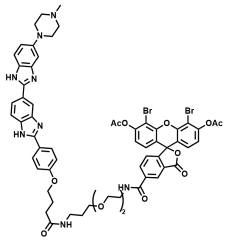
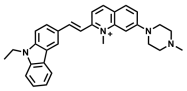
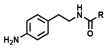
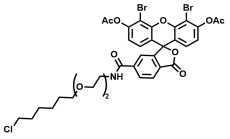
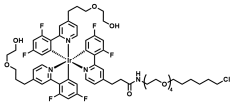
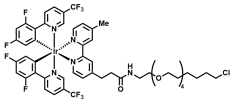
Sustain. Sci. Innov. **2026**, *1*, 103389
https://doi.org/10.54963/ssi.103389

Table 1. *Cont.*

Technique	Targeting Mechanism	Photocatalyst	Labelling Probe	Labeling Targets	Light Source	Subcellular Compartments
CAT-seq[46]	Intrinsic properties			RNA	450 nm blue LED	Mitochondria
CAT-ortho[46]	Intrinsic properties			RNA and Protein	450 nm blue LED	Mitochondria
TPP- AcDBF-mediated labeling[23]	TPP			Protein	500–510 nm green light	Mitochondria
PDPL[27]	Genetically fused miniSOG	flavin		Protein	460 nm blue light	Mitochondria; ER; Nucleus
LITag[31]	Genetically fused LOV*	flavin		Protein	440 nm blue light	Mitochondria; Nucleus (nucleoplasm, nuclear lamina, nucleolus)
RinID[28]	Genetically fused miniSOG	flavin		Protein	460–470 nm blue LED	Mitochondria, ER, Nucleus, Stress granules
FLAPP[47]	Genetically fused dL5**	dL5**-MG-HI		Protein	660 nm NIR light	Mitochondria; ER; Nucleus (nucleoplasm, nuclear lamina)
CAP-seq[26]	Genetically fused miniSOG	flavin		RNA	Blue LED	Mitochondria; ER
miniSOG-mediated DNA labeling[48]	Genetically fused miniSOG/ SOPP2	flavin		DNA	Blue LED	Mitochondria; Nucleus (nucleoplasm, nuclear lamina, nucleolus)
SeeID[49]	Genetically fused HaloTag			Protein	660 nm NIR LED	Mitochondria, ER, Nucleus, Lysosome
CAT-Lyso[50]	Morpholine			Protein	520 nm green LED	Lysosome
CLAPL[51]	Morpholine			Protein	500–510 nm green light	Lysosome

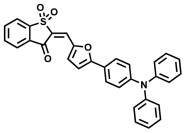
Sustain. Sci. Innov. **2026**, *1*, 103389
https://doi.org/10.54963/ssi.103389

Table 1. *Cont.*

Technique	Targeting Mechanism	Photocatalyst	Labelling Probe	Labeling Targets	Light Source	Subcellular Compartments
CAT-ER[52]	Intrinsic properties			Protein	450 nm blue LED	ER
FAP-seq[24]	Genetically fused FAP	FAP-MG-HI		RNA	660 nm NIR light	ER, Nucleus
AIE-PhoPL[53]	Intrinsic properties			Protein	500–510 nm green light	Golgi apparatus
CAT-Golgi[54]	Cysteine			Protein	520 nm green light	Golgi apparatus
CS@Ce6-RB-mediated labeling[55]	chondroitin sulfate	CS@Ce6-RB		Protein	White light	Golgi apparatus
Hoechst-DBF[56]	DNA binding			Protein RNA	~530 nm LED	Nucleus
Hoechst-DBF[57]	DNA binding			Protein	512 nm LED	Nucleus
NCP[58]	DNA binding			Protein	White LED	Nucleus
HaloTag DBF[59]	Genetically fused HaloTag			Protein RNA	~485 nm LED	Nucleus
µMap, µMap-seq[60]	Genetically fused HaloTag			Protein RNA	450nm LED	Nucleus (nucleoli, nuclear lamina, paraspeckles, Cajal bodies, PML bodies)
CAP seq[61]	Genetically fused miniSOG	flavin		RNA	~470 nm LED	Stress granules
CAP-seq[62]	Genetically fused miniSOG	flavin		RNA	~470 nm LED	Stress granules; Processing bodies
HaloMap[63] (µMap)	Genetically fused HaloTag			Protein	450 nm LED	Stress granules

Sustain. Sci. Innov. **2026**, *1*, 103389
https://doi.org/10.54963/ssi.103389

Table 1. *Cont.*

Technique	Targeting Mechanism	Photocatalyst	Labelling Probe	Labeling Targets	Light Source	Subcellular Compartments
BRET-ID[64]	Genetically fused LOV domain	flavin		Protein	Nluc BRET	Stress granules
LipoID[65]	Intrinsic properties			Protein	White light	Lipid droplets

4.2. Lysosome

Lysosomes are essential degradative and recycling organelles that maintain cellular homeostasis through macromolecule degradation, nutrient sensing, autophagy regulation, membrane repair, antigen presentation, and cell death signaling. Beyond their canonical degradative functions, lysosomes serve as dynamic signaling hubs that coordinate cellular metabolism and stress responses. Therefore, comprehensive characterization of the lysosomal molecular landscape is critical for understanding cellular adaptation under physiological and pathological conditions.

However, lysosomal molecular profiling remains technically challenging due to the unique biochemical properties of the lysosomal lumen. The highly acidic environment and abundant proteolytic enzymes within lysosomes limit the applicability of many proximity labeling enzymes, which are primarily restricted to the cytosolic surfaces of lysosomal membrane proteins. Photocatalytic proximity labeling provides a chemically robust alternative by enabling small-molecule photocatalysts to operate within harsh lysosomal environments. In contrast to mitochondria-targeting strategies that often exploit intrinsic physicochemical properties, lysosomal photocatalytic labeling has mainly relied on morpholine-based targeting to achieve selective accumulation within acidic compartments (Figure 4b).

CAT-Lyso established a non-genetic photocatalytic strategy for in situ lysosomal proteome profiling by adapting bioorthogonal photocatalytic chemistry to the acidic lysosomal lumen.[50] CAT-Lyso employs a morpholine-containing lysosome-targeting eosin photocatalyst with a thioQM precursor. Upon light activation, the photocatalyst generates a highly reactive thioQM intermediate within lysosomes, enabling efficient covalent labeling of proximal lysosomal proteins under physiological conditions.[50] Under optimized cellular conditions (10 μM LysoCat, 50 μM probe, 15 min irradiation), LysoCat exhibited marked lysosomal accumulation (Pearson's R = 0.82), with 81% of identified proteins assigned to the luminal side, demonstrating superior spatial fidelity under harsh physiological conditions that typically degrade engineered enzymes.[50]

Complementarily, CLAPL (cross-linking-assisted photocatalytic proximity labeling) introduced a chemical amplification strategy to improve the depth of lysosomal proteome profiling.[51] Using the morpholine-functionalized photosensitizer MP-AcDBF, CLAPL generated singlet oxygen-mediated labeling events within lysosomes and subsequently employed cross-linking chemistry to connect weakly labeled proteins with pre-labeled species.[51] Under optimized conditions, CLAPL used 5 μM MP-AcDBF with 5 min green light irradiation, showing strong lysosomal localization (Pearson's R = 0.83). This amplification strategy enhanced the detection of low-abundance and transient lysosomal proteins from 197 to 238, thereby expanding the coverage of lysosomal proteomic analysis.[51]

4.3. Endoplasmic reticulum

The endoplasmic reticulum (ER) is the central hub of the secretory pathway and plays essential roles in protein synthesis, folding, maturation, lipid biosynthesis, calcium storage, and cellular stress responses. As the primary site responsible for maintaining protein homeostasis, the ER continuously monitors the folding status of newly synthesized proteins through an integrated network of molecular chaperones, folding enzymes, and quality-control machinery. Perturbation of ER homeostasis induces the unfolded protein response (UPR), which determines cellular adaptation or progression toward apoptosis. Therefore, resolving the spatial and temporal dynamics of the ER proteome is essential for understanding cellular stress adaptation, metabolic regulation, and disease-associated signaling pathways.

Photocatalytic proximity labeling provides a genetically independent strategy for dynamic ER profiling by enabling light-controlled generation of reactive intermediates within the ER microenvironment. Compared with conventional approaches, photocatalytic systems offer precise temporal control and enable in situ interrogation of ER molecular changes under different physiological and pathological states (Figure 5a).

A representative non-genetic photocatalytic strategy for ER profiling is CAT-ER, which integrates an ER-targeting iridium photocatalyst with QM chemistry for time-resolved ER proteome analysis.[52] Upon light activation, the photocatalyst triggers photochemical deprotection of the QM precursor, generating a highly reactive intermediate that covalently labels proximal ER proteins.[52] Under optimized cellular conditions, CAT-ER used 100 nM photocatalysts and 50 μM probes with

Sustain. Sci. Innov. **2026**, *1*, 103389
https://doi.org/10.54963/ssi.103389

15 min photoirradiation. CAT-ER showed strong ER localization (Pearson's R = 0.82), and 84% of the proteins identified by proteomics were assigned to the secretory pathway. By avoiding genetic manipulation and enabling temporally controlled activation, CAT-ER allowed dynamic ER proteome profiling across diverse cell types, including hard-to-transfect systems, and revealed stage-dependent remodeling of the ER proteome during cellular stress progression.[52]

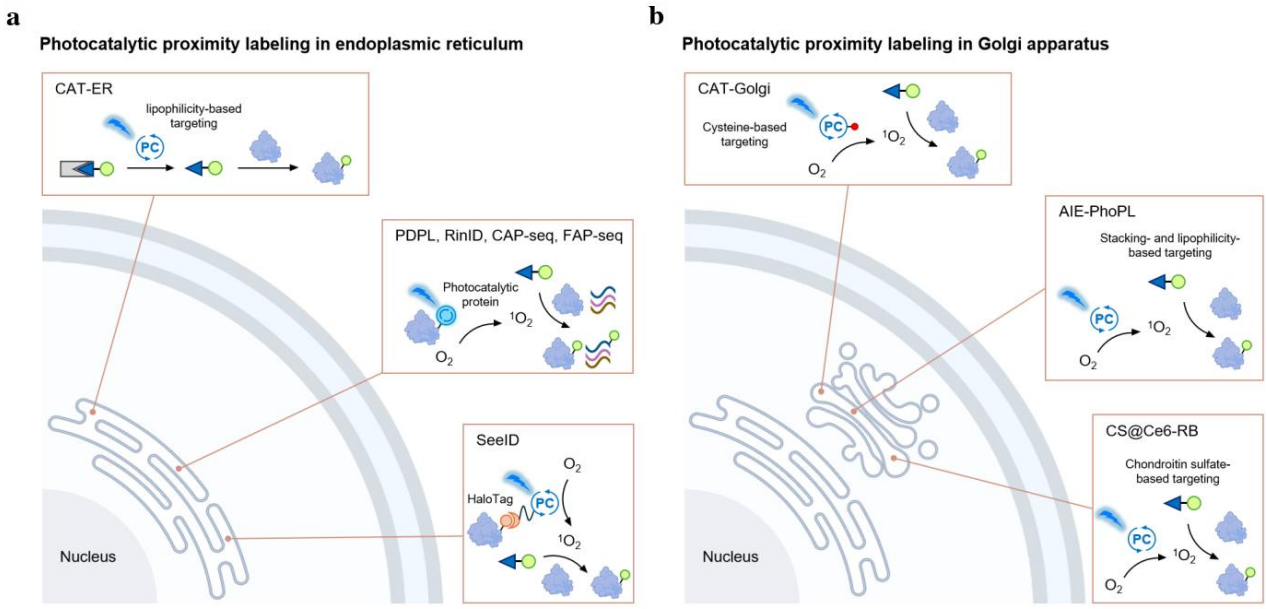


Figure 5. Photocatalytic proximity labeling in the endoplasmic reticulum and Golgi apparatus. (**a**) Representative photocatalytic proximity labeling strategies for molecular profiling in the endoplasmic reticulum (ER). The non-genetic CAT-ER strategy exploits the intrinsic lipophilicity of an ER-localizing iridium photocatalyst to enable light-triggered activation of reactive probes for time-resolved ER proteome profiling. Genetic strategies employ genetically targeted photocatalytic proteins, as exemplified by PDPL, RinID, CAP-seq, and FAP-seq, for spatially resolved profiling of ER-associated proteins and RNAs. Protein-tag-mediated targeting, represented by HaloTag-based SeeID, further enables NIR photocatalytic labeling of ER-associated molecular environments. (**b**) Representative non-genetic photocatalytic proximity labeling strategies for Golgi molecular profiling. CAT-Golgi employs cysteine-based targeting to direct a photocatalyst to the Golgi apparatus for singlet-oxygen-mediated protein labeling. AIE-PhoPL exploits the intrinsic molecular stacking and lipophilicity of an aggregation-induced emission (AIE)-derived photocatalyst for spontaneous Golgi localization and photooxidative protein labeling. CS@Ce6-RB employs chondroitin sulfate-mediated targeting to localize a nanophotosensitizer containing Ce6 and rose bengal to the Golgi apparatus, enabling singlet-oxygen-mediated proximity labeling and Golgi proteome profiling.

Genetically encoded photocatalytic proteins have also been applied for ER proteome profiling. PDPL[27] and RinID,[28] based on genetically targeted miniSOG photocatalysis, enabled spatially resolved ER protein mapping by directing the photocatalytic module to ER compartments. PDPL identified 911 significantly enriched proteins from the ER outer membrane with 73% organelle specificity, while RinID achieved high spatial specificity for both the ER membrane and lumen, with 93% and 97% of the identified proteins, respectively, annotated to the secretory pathway.

Beyond protein profiling, genetically encoded photocatalytic systems have also expanded toward ER-associated RNA landscapes. CAP-seq[26] enabled ER-proximal transcriptome profiling by targeting miniSOG to the cytoplasmic side of the ER membrane, enriching 372 mRNAs with a strong preference for secretory pathway transcripts. FAP-seq[24] further introduced a near-infrared genetically encoded RNA proximity labeling platform based on an FAP and MG-HI.[24] Under optimized conditions, FAP-seq used 125 nM MG-HI and 1.5 mM propargylamine with 1 min photoirradiation. The FAP–MG-HI complex generates singlet oxygen upon irradiation, enabling RNA proximity labeling and subsequent transcriptome profiling. ER-associated RNAs were preferentially enriched in ER-FAP cells, whereas cytosolic and mitochondrial RNAs showed minimal enrichment, demonstrating high spatial specificity.[24]

Protein-tag-mediated strategies provide another route for ER-targeted photocatalytic labeling. SeeID utilized a HaloTag-compatible SiR-based NIR photocatalytic system, enabling ER-targeted proximity labeling and visualization-guided mapping of associated proteomes and protein interaction networks.[49] Using Halo-Sec61β for ER membrane targeting, SeeID identified 284 high-confidence ER membrane proteins, 90% of which were

Sustain. Sci. Innov. **2026**, *1*, 103389
https://doi.org/10.54963/ssi.103389

annotated as secretory pathway proteins, demonstrating high spatial specificity.

4.4. Golgi apparatus

The Golgi apparatus is a central hub of the secretory pathway that regulates protein and lipid modification, sorting, and trafficking. Given its dynamic remodeling during cellular stress, differentiation, and autophagy, spatially resolved profiling of the Golgi proteome is essential for understanding intracellular trafficking and Golgi-associated cellular regulation. Several non-genetic photocatalytic strategies have recently enabled in situ Golgi proteome profiling through distinct targeting mechanisms (Figure 5b).

AIE-PhoPL (aggregation-induced emission luminogen-mediated photocatalytic proximity labeling strategy) represents a catalyst-intrinsic targeting strategy for Golgi proteome profiling.[53] It utilizes an aggregation-induced emission luminogen-derived photocatalyst (TPE-PyT-CPS), whose molecular architecture and optimized lipophilicity promote spontaneous Golgi localization. Upon green-light irradiation, the photocatalyst generates singlet oxygen through energy transfer and radical species through single-electron transfer, enabling proximal modification of histidine and tyrosine residues. Under optimized conditions, AIE-PhoPL used 5 μM TPE-PyT-CPS and 5 mM 3-EA with 5 min irradiation. TPE-PyT-CPS showed strong Golgi localization (Pearson's R = 0.91), while proteomic analysis achieved up to 80% specificity for the Golgi-associated secretome. AIE-PhoPL enabled in situ profiling of Golgi-associated secretomes in living cells and hard-to-transfect macrophages.[53]

Alternatively, targeting moiety conjugation provides a modular strategy for Golgi-directed photocatalytic labeling. CAT-Golgi employs a cysteine-conjugated eosin photocatalyst (GolgiCat) together with an aniline probe, where cysteine modification facilitates selective accumulation within Golgi membranes.[54] Upon light activation, GolgiCat generates reactive intermediates that initiate proximal protein labeling. Under optimized conditions, CAT-Golgi used 10 μM GolgiCat and 100 μM aniline probes with green light irradiation for 8 min. GolgiCat showed strong Golgi localization (Pearson's R = 0.85), while proteomic analysis achieved up to 74% specificity for secretory pathway proteins. CAT-Golgi enabled quantitative Golgi proteome profiling across multiple cell types and revealed dynamic Golgi remodeling during Golgiphagy.[54]

Beyond small-molecule photocatalysts, nanomaterial-based targeting provides another non-genetic approach for Golgi labeling. A Golgi-targeting nanophotosensitizer (CS@Ce6-RB) integrates chondroitin sulfate with chlorin e6 and rose bengal photosensitizers.[55] The targeting component facilitates Golgi accumulation, while the photosensitizers generate reactive oxygen species upon light activation to drive proximal protein labeling. CS@Ce6-RB exhibited strong Golgi localization (Pearson's R = 0.936), and under optimized conditions, labeling was performed with 0.05 mg/mL CS@Ce6-RB and 5 mM 3-EA under white-light irradiation for 5 min. Proteomic analysis identified 410 Golgi-annotated proteins in HeLa cells, enabling dynamic analysis of Golgi proteome remodeling during cancer metastasis.[55]

4.5. Nucleus

The nucleus is a highly organized compartment where genome regulation is coordinated through dynamic interactions among chromatin, nuclear lamina, transcriptional machinery, RNA molecules, and phase-separated nuclear condensates. Such spatial organization plays essential roles in cellular functions under both physiological and pathological conditions, and resolving the molecular composition and organization of nuclear microenvironments is critical for understanding nuclear regulation.[66–69] PPL, with its light-controlled activation and spatially restricted labeling, provides a powerful strategy for interrogating nuclear organization with high spatial and temporal precision. Nuclear PPL approaches can be broadly organized according to their targeting strategies, ranging from DNA-targeting small-molecule approaches to genetically programmed targeting of POI-defined nuclear structures (Figure 6a, Table 1).

Small-molecule-guided PPL approaches for the nucleus have primarily exploited chromatin-associated DNA as an endogenous nuclear landmark to enrich photocatalysts within nuclear microenvironments. Li and colleagues developed a DBF–Hoechst conjugate, in which the DNA minor groove-binding dye Hoechst 33342 directed the photosensitizer DBF to chromatin regions for light-triggered labeling of proximal proteins and RNAs.[56] Using a similar DBF–Hoechst conjugate, Tamura and colleagues established a PPL strategy in which photogenerated singlet oxygen oxidized an o-phenylenediamine (PDA)-based biotin probe to enable protein labeling within nuclear microenvironments.[57] In living HeLa cells, 5 μM AcDBF-Hoechst and 1 mM Bt-PDA enabled nucleus-restricted labeling under 512 nm irradiation for 10 min; quantitative proteomics further identified 10 proteins enriched by at least 2-fold, all of which were annotated as nuclear proteins. More recently, Luo and colleagues developed a nucleus-targeted photosensitizer (NCP) that integrates DNA-binding and photosensitization capabilities. Upon white-light irradiation, NCP (5 μM) activated a biotin-aniline probe through photo-oxidation, enabling efficient profiling of the nuclear proteome.[58]

While small-molecule approaches provide efficient access to nuclear environments, genetically targeted photocatalytic systems offer greater targeting flexibility and spatial programmability for investigating the molecular composition of defined subnuclear structures. As early proof-of-concept studies, Li and colleagues employed HaloTag-based systems to target DBF to the nuclear compartment through H2B-Halo or nu-

Sustain. Sci. Innov. **2026**, *1*, 103389
https://doi.org/10.54963/ssi.103389

clear localization signal (NLS)-Halo constructs, enabling mapping of nuclear-associated RNAs.[59,70] In the initial Halo-DBF system, cells were treated with 5 μM Halo-DBF and 1 mM propargylamine, followed by 500 nm irradiation for 15 min. H2B-Halo preferentially enriched chromatin-associated RNAs, whereas the more diffusely localized NLS-Halo shifted the enrichment toward nucleoplasmic and nucleolar RNAs, demonstrating subnuclear spatial resolution. Following these applications, Ding and colleagues developed a modified approach using SOPP2 (singlet oxygen photosensitizing protein-2) and a phenethylamine probe for proximity-dependent DNA labeling.[48] In addition to mitochondrial DNA profiling, this strategy enabled light-triggered labeling of local genomic DNA at the nuclear lamina and revealed lamina-associated domains (LADs), providing a high-resolution view of chromosome organization and demonstrating the potential of photocatalytic chemistry for studying genome architecture. Subsequent studies extended miniSOG-based PPL to nuclear protein mapping. In addition to nuclear proteome profiling using H2B-miniSOG and NLS-miniSOG, PDPL enabled spatiotemporally resolved profiling of BRD4-associated protein networks and suggested a hypothetical role of BRD4 in regulating liquid–liquid phase separation (LLPS) in nuclear compartments.[27] By varying blue-light irradiation from 2 to 20 min, PDPL resolved time-dependent BRD4 protein neighborhoods, with the 2-min condition preferentially capturing the most proximal interaction network. Other genetically encoded approaches, including LITag, RinID, and FLAPP, have further demonstrated utility for nuclear proteome profiling.[28,31,47] LITag enabled nuclear photolabeling within only 1–3 s, whereas H2B-targeted RinID used 10 mM probes with 15-min blue-light irradiation and achieved 92% nuclear specificity. FLAPP further extended nuclear profiling to 660-nm irradiation, with cellular labeling performed using 500 nM MG-HI and 1 mM 3-EA for 10 min, achieving up to 96% spatial specificity.

Recent advances have further expanded PPL toward spatiotemporally resolved characterization of nuclear biomolecular organization at finer spatial scales. Building upon photocatalytic labeling chemistry developed for other cellular compartments, the MacMillan group applied μMap and μMap-seq to investigate nuclear-associated proteomes and transcriptomes. In 2023, Seath and colleagues developed a chromatin-targeted μMap strategy that enabled traceless installation of an Ir photocatalyst into the nuclear microenvironment through protein trans-splicing. Specifically, isolated nuclei expressing chromatin proteins fused to the CfaN split-intein fragment were incubated with 0.5 μM CfaC-Ir for 1 h at 37 °C, followed by labeling with 200 μM diazirine-biotin under blue-light irradiation for up to 90 s. This approach achieved short-range (~10 nm) protein labeling within chromatin environments and enabled investigation of chromatin neighborhoods in isolated nuclei.[71] In 2025, Knutson and colleagues further extended μMap to profile protein compositions of diverse subnuclear structures, including nucleoli, nuclear lamina, paraspeckles, Cajal bodies, and promyelocytic leukaemia (PML) bodies, and developed μMap-seq for parallel transcriptomic mapping of these structures.[60] Using 10 μM of the optimized Ir photocatalyst, proximity labeling was performed with 5 min blue-light irradiation, yielding 337 enriched proteins, 86% of which were annotated as nuclear proteins.

Collectively, these studies demonstrate that PPL enables multi-scale analysis of nuclear organization, ranging from global nuclear omics profiling to the characterization of subnuclear structures and microenvironments. By integrating precise spatial and temporal control with proteomic, transcriptomic, and genomic readouts, PPL provides a versatile framework for dissecting nuclear biomolecular networks under physiological and pathological conditions.

4.6. Other cytosolic organelles

Beyond the major membrane-bound organelles discussed above, the cytosol contains a diverse array of specialized organelles and dynamic subcellular structures that participate in various cellular activities. Examples include membraneless organelles (MLOs), such as stress granules (SGs) and processing bodies (PBs),[72–74] and lipid droplets (LDs), which are surrounded by a phospholipid monolayer. Their specialized molecular environments and dynamic organization make these cytosolic compartments attractive targets for PPL, which enables biomolecular mapping with high spatial and temporal precision.

To date, genetically targeted PPL approaches have been applied to SGs and PBs (Figure 6b), which are highly dynamic RNA–protein condensates involved in RNA regulation and cellular stress responses.[75] Building upon CAP-seq strategies previously developed for other cellular compartments, Ren and colleagues characterized the SG-associated transcriptome in living cells using a G3BP1-miniSOG construct.[61] RNA labeling was performed with 10 mM propargylamine under blue-light irradiation for 15 min, with labeling signals showing strong colocalization with the SG marker G3BP2. Subsequent applications of CAP-seq targeting additional SG scaffolds (TIA1 and G3BP2) and the PB marker DDX6 revealed heterogeneous RNA distributions within SGs and PBs.[62] Using the same labeling conditions, multibait CAP-seq identified distinct bait-proximal transcriptomes with high reproducibility (Pearson's R > 0.97). These studies demonstrated the capability of PPL to resolve dynamic transcriptomic landscapes associated with distinct condensate states. Beyond transcriptomic mapping, the HaloMap platform extended the μMap strategy to dynamic profiling of the SG-associated proteome in living cells by combining HaloTag-mediated targeting with an intracellularly installed Ir-based photosensitizer. HaloMap employed 5 μM Ir photocatalyst and 500 μM biotin-diazirine,

Sustain. Sci. Innov. **2026**, *1*, 103389
https://doi.org/10.54963/ssi.103389

followed by 450-nm irradiation for 10 min, enabling highly localized labeling of HaloTag-G3BP1-associated SG proteins. HaloMap revealed ubiquitin-related regulators and identified the autophagy-associated ubiquitin receptor TOLLIP as a potential mediator of SG disassembly.[63] More recently, a bioluminescence-triggered PPL strategy was developed for in vivo proteomic applications. This strategy, termed BRET-ID, uses a genetically encoded POI–LOV–NanoLuc (Nluc) fusion, in which Nluc bioluminescence activates LOV-bound FMN via bioluminescence resonance energy transfer (BRET), enabling proximity labeling without external light irradiation and the first proteomic mapping of SGs in living mice.[64] For SG profiling in cells, BRET-ID achieved labeling with 75 μM furimazine for only 5 min and identified 674 significantly enriched SG-associated proteins, while showing strong spatial overlap with the SG marker FXR1.

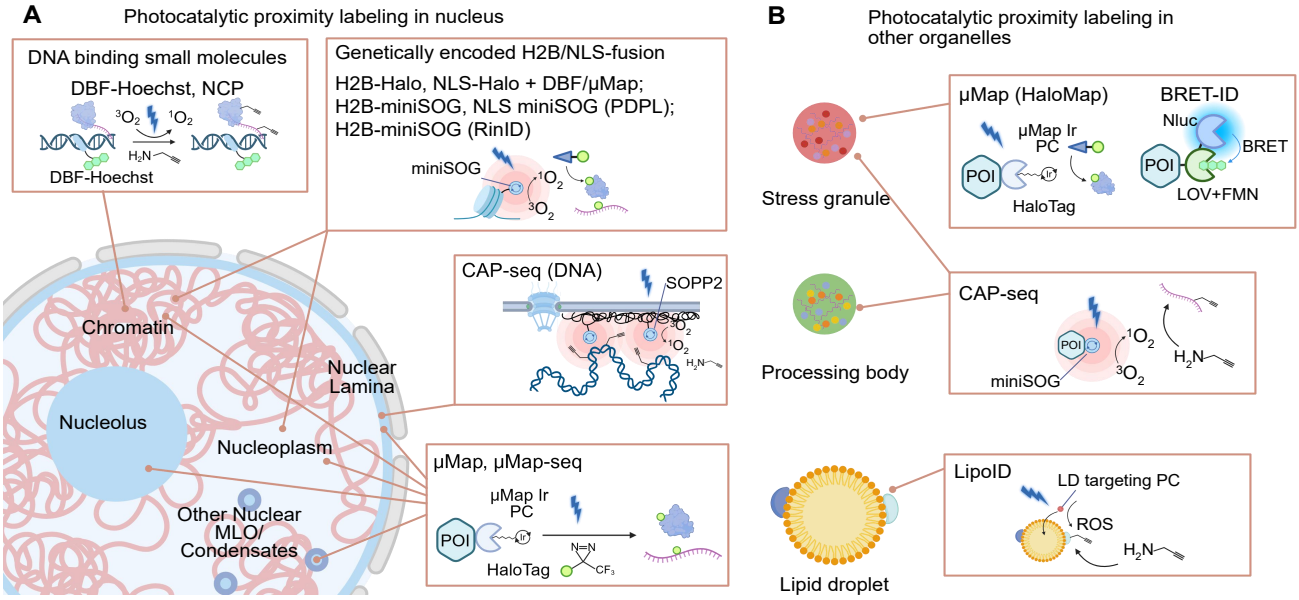


Figure 6. Photocatalytic proximity labeling in the nucleus and cytosolic MLOs. (**a**) Representative photocatalytic proximity labeling strategies for molecular profiling in the nucleus. Small-molecule PPL strategies exploit DNA-binding photosensitizers, either through conjugating Hoechst and DBF or using a photosensitizer with intrinsic DNA-binding capacity. Genetic strategies employ POI fusions to target different nuclear compartments, e.g., H2B for chromatin, NLS for nucleoplasm (whole nucleus), lamin A for nuclear lamina. (**b**) Representative photocatalytic proximity labeling strategies for other cytosolic organelles. For stress granules (SGs), the most typical POI for PPL is G3BP1 (CAP-seq and μMap), while alternative POIs TIA1 and G3BP2 were also used by CAP-seq. For processing bodies (PBs), DDX6 fusion was used in a CAP-seq strategy. A small-molecule photosensitizer was developed for the lipid droplet-associated proteome.

Beyond genetically encoded targeting strategies, a small-molecule-targeted PPL strategy, termed LipoID, has been developed for lipid droplets (LDs) (Figure 6b),[65] which are dynamic lipid storage organelles involved in lipid metabolism and cellular homeostasis.[76] LipoID employs an LD-targeted small-molecule photosensitizer B6 (1 μM) to enable proximity labeling of LD-associated proteins through propargylamine incorporation upon white-light irradiation. Photoactivated B6 generates type I ROS, which mediate covalent labeling of proximal proteins. The study identified CLINT1 as a previously uncharacterized LD-associated protein and revealed interorganellar interactions between LDs and mitochondria.

Together, these studies highlight the versatility of PPL for mapping specialized cytosolic organelles and subcellular structures at both proteomic and transcriptomic levels. The combination of precise spatial targeting and temporal control positions PPL as a powerful approach for dissecting the dynamic organization and regulation of organelle-associated molecular networks.

5. Conclusion

Positioned at the interface of chemistry and biology, photocatalytic proximity labeling offers a versatile paradigm for spatially and temporally resolved multiscale molecular mapping within native cellular contexts. Chemically, PPL harnesses diverse small-molecule catalysts or photocatalytic proteins to generate short-lived reactive intermediates (e.g., carbenes, QMs, and $^1O_2$), achieving broad biomolecular targeting with minimal perturbation, with activation wavelengths now extending from the visible to near-infrared light. Biologically, the non-genetic targeting modalities of PPL overcome traditional constraints, facilitating in situ molecular profiling in hard-to-transfect cells, intact tissues, and human clinical specimens.

Sustain. Sci. Innov. **2026**, *1*, 103389
https://doi.org/10.54963/ssi.103389

From a sustainability perspective, PPL also provides a foundation for more resource-conscious molecular profiling. Its light-controlled reactivity, compatibility with mild physiological conditions, and applicability to non-genetically modified biological systems can streamline experimental workflows and reduce dependence on intensive sample processing. Consequently, these combined strengths position PPL as a crucial platform for the systematic dissection of subcellular multi-omics, as well as complex protein–protein and protein–RNA interactomes, across diverse living systems.

Despite remarkable progress, realizing the full potential of photocatalytic proximity labeling requires overcoming several ongoing technical and biological hurdles (Figure 7). First, advancing the core chemical and molecular toolkits remains a primary objective. Next-generation materials must feature long-wavelength responsiveness for deeper tissue penetration, elevated quantum yields to minimize phototoxicity and light doses, and orthogonal activation modes for multiplexed profiling. Pushing the boundary of PPL toward more physiologically authentic models and in vivo systems, though initially demonstrated,[49] requires continued innovation to capture rapid signaling dynamics and complex molecular networks within native tissue architectures. In parallel, probe chemistry must evolve toward smaller, bioorthogonal reporter groups, scarless labeling strategies, and microenvironment-responsive chemoselectivity tailored to disease contexts. Furthermore, the scope of labeled substrates must be systematically broadened; while there is initial progress,[77] expanding efficient tagging to other essential biomolecules beyond proteins and nucleic acids, including complex glycans as well as small-molecule cellular metabolites, represents a crucial frontier that demands further development.

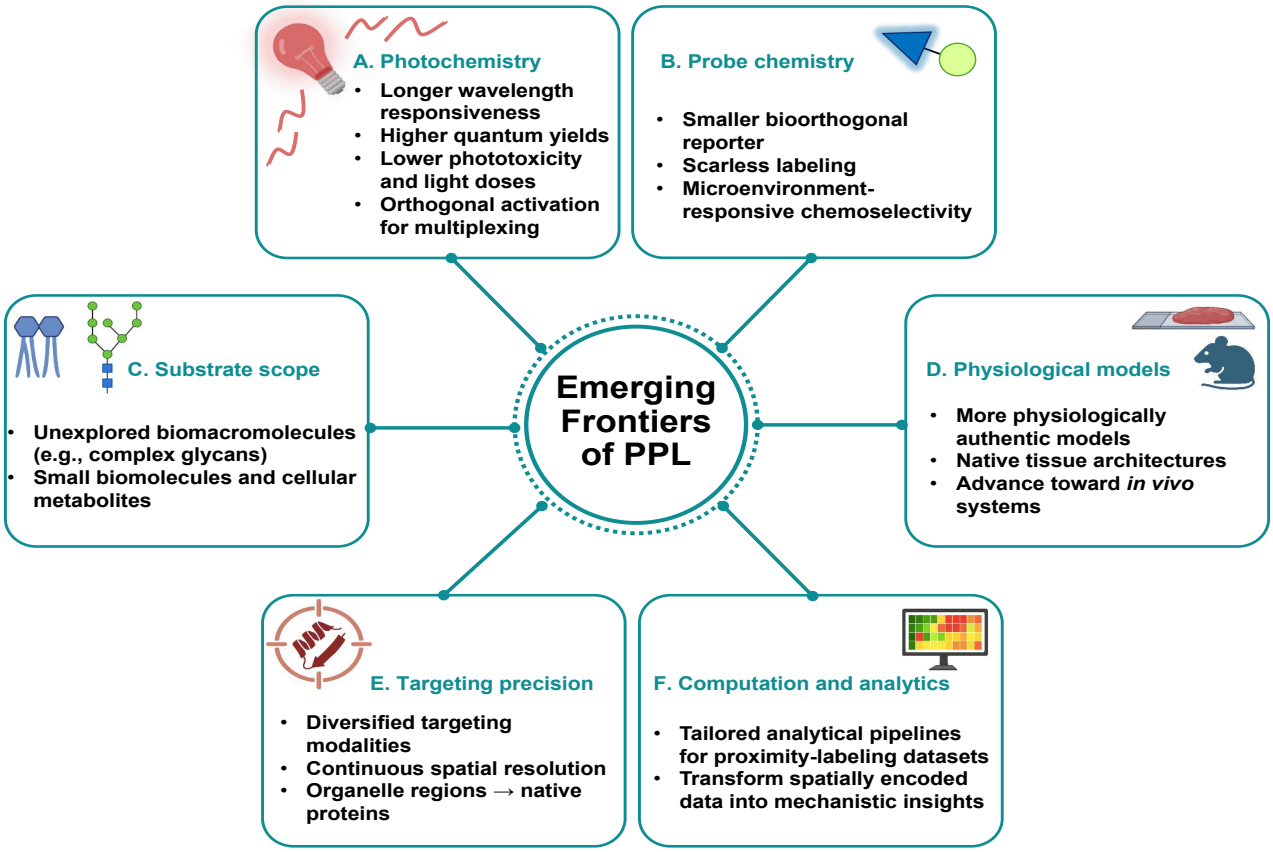


Figure 7. Emerging frontiers and future directions for PPL. Future development of photocatalytic proximity labeling is expected to converge across six complementary directions, including photochemistry, probe chemistry, substrate scope, physiological models, targeting precision and computation and analytics.

Second, expanding targeting paradigms and biological applicability constitutes a parallel imperative. Existing PPL platforms enable versatile subcellular labeling, with emerging strategies exploiting protein–ligand interactions or targeted peptides to direct catalytic centers.[78–80] A key goal for future tool development is to further diversify these targeting mechanisms, thereby achieving a continuous spectrum of spatial resolution that seamlessly spans from broad subcellular organelle regions down to individual native proteins. Besides, integrating advanced computational tools with chemical innovations will be essential for translation. Tailored analytical pipelines specifically designed to interpret proximity-labeling

Sustain. Sci. Innov. **2026**, *1*, 103389
https://doi.org/10.54963/ssi.103389

datasets are required to transform spatially encoded chemical information into mechanistic insights.

In summary, photocatalytic proximity labeling establishes a robust technological foundation for multiscale, in situ biomolecular mapping by synergizing chemical catalyst innovation with native biological context. The modularity of PPL bridges the gap between molecular precision and broad physiological accessibility. As the field advances toward long-wavelength NIR activation, scarless probe designs, and specialized computational decoding pipelines, continuous refinement of photoredox kinetics and light-delivery protocols will further reinforce the resource efficiency, mildness, and environmental compatibility of spatial omics technologies. By intersecting chemical biology with immunology, neuroscience, and translational medicine, PPL is well poised to transform our mechanistic understanding of spatial biological organization in health and disease.

Author Contributions

Conceptualization, Y.Z. and X.F.; writing—original draft preparation, Y. Z., N.Z., and K.F.; writing—review and editing, Y.Z., N.Z., K.F. and X.F.; supervision, Y.Z. and X.F.; project administration, Y.Z. and X.F.; funding acquisition, Y.Z. and X.F. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

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AI Use Statement

During the preparation of this work, the authors used Deepseek for English language editing and grammar polishing. The authors subsequently reviewed and edited the content as necessary and take full responsibility for the final content of the published article.

Conflict of Interest

The authors declare no conflicts of interest.

Abbreviations

$^1O_2$	singlet oxygen
3-EA	3-ethynylaniline
$^3O_2$	triplet oxygen
AIE	aggregation-induced emission
AIE-PhoPL	aggregation-induced emission luminogen-mediated photocatalytic proximity labeling strategy
APEX	Ascorbate peroxidase
BioID	proximity-dependent biotin identification
BRET	bioluminescence resonance energy transfer
CAP-seq	chromophore-assisted proximity labeling and sequencing
CAT-Prox	bioorthogonal and photocatalytic deprotection-enabled proximity labeling
CLAPL	cross-linking-assisted photocatalytic proximity labeling
DBF	dibromofluorescein
DET	Dexter energy transfer
dSTORM	direct stochastic optical reconstruction microscopy
ER	endoplasmic reticulum
FAP	fluorogen-activating protein
FLAPP	fluorogen-activating protein mediated photocatalytic proximity labeling
FMN	flavin mononucleotide
LAD	lamina-associated domain
LC-MS/MS	liquid chromatography–tandem mass spectrometry
LD	lipid droplet
LITag	Light-induced Interactome Tagging
LLPS	liquid–liquid phase separation
LOV	light-oxygen-voltage
MG-HI	iodinated malachite green
miniSOG	mini Singlet Oxygen Generator
MLO	membraneless organelle
NCP	nucleus-targeted photosensitizer
NIR	near-infrared
NLS	nuclear localization signal
Nluc	NanoLuc
PAB	para-azidobenzyl
PB	processing bodies
PDA	o-phenylenediamine
PDPL	photoactivation-dependent proximity labeling
PL-NIR	proximity labeling strategy using near-infrared excitation
PML	promyelocytic leukaemia
POI	protein of interest
PPL	photocatalytic proximity labeling
QM	quinone methide
Rh123	Rhodamine 123
RinID	reactive oxygen species induced protein labeling and identification
ROS	reactive oxygen species
SeeID	Silicon-rhodamine-enabled Identification
SET	single electron transfer
SG	stress granule
SiR	silicon rhodamine
SOPP2	singlet oxygen photosensitizing protein-2
thioQM	thioquinone methide
TPP	triphenylphosphonium
TTET	triplet–triplet energy transfer
UPR	unfolded protein response
μMap	MicroMap

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