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REVIEW

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Proximity labeling in neuroscience: decoding molecular landscapes for precision neurology

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Abstract

The intricate cellular architecture and dynamic molecular interplay in the nervous system have long challenged mechanistic studies of neurological diseases. Conventional approaches often miss the transient, low-affinity, or spatially confined interactions that underlie neural homeostasis and pathogenesis. Proximity labeling (PL) technologies overcome this limitation by enabling in situ capture of these elusive molecular events within living systems. Through spatially restricted biotinylation, PL methods, including engineered biotin ligases (e.g., TurboID), peroxidases (e.g., APEX2), and emerging photocatalytic platforms, allow high-resolution mapping of proteomes and interactomes within defined subcellular compartments, cell types, and cell-cell interfaces. In this review, we systematically outline the principles of PL and its transformative applications in constructing molecular atlases of the nervous system. We highlight how these tools are revolutionizing our understanding of brain function by elucidating pathophysiological mechanisms in Alzheimer's disease, Parkinson's disease and other neurological disorders. Furthermore, we discuss how PL accelerates the translation of basic research into clinical practice by facilitating the discovery of mechanistic biomarkers and druggable targets. Finally, we address current challenges and future directions, including integration with multi-omics and single-cell methodologies, and conclude that PL can advance precision neurology by bridging molecular neurobiology with therapeutic innovation.

Keywords Proximity labeling, Neurological disorders, Protein-protein interaction, Biomarker discovery, Therapeutic targets, Spatial proteomics

Introduction

The mammalian nervous system executes complex behaviors through specialized, precisely positioned, and interacting cell types [1–3]. A sophisticated network of molecular interactions underpins the functions of neurons and other brain cell types. These interactions modulate signaling pathways, regulate neurotransmitter release, and sustain proper neural connectivity [4]. Disruptions in protein-protein interaction (PPI) network are associated with synaptic communication deficits, protein aggregation, and dysregulated cell death pathways, collectively contributing to the pathogenesis of various neurodegenerative diseases and neurodevelopmental disorders [5–7].

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Spatial compartmentalization ensures molecular complexes and biological processes occur in precise subcellular localizations [8]. The functions of any biomolecule are determined not only by its intrinsic properties but also by its spatial context within the cell [9]. Consequently, systems-level mapping of spatial interaction networks is required to obtain mechanistic understanding of cellular processes [10]. Although traditional methods such as co-immunoprecipitation (Co-IP) and subcellular fractionation can provide some information [11, 12], they have inherent limitations in preserving the spatial context of these interactions and in capturing transient or low-affinity interactions.

Recently, proximity labeling (PL), a cornerstone of "spatiomics", has emerged as a powerful approach to mapping protein proximity networks and interactomes in living systems [13–16]. Newer platforms such as TurboID and ascorbate peroxidase (APEX2), building upon early biotin ligase-based strategies that have characterized synaptic proteomes in living cells and mice [17, 18], enable high-resolution "molecular spatiomics" by capturing PPIs under near-physiological conditions while preserving native membrane integrity and protein complexes [19]. Critically, PL enables mapping of otherwise unpurifiable subcellular regions within their native context (e.g., the synaptic cleft [17]) without physical isolation. This avoids detergent-induced artifacts and improves recovery of fragile membrane proteins, including receptors, ion channels, and transporters. PL has been applied to delineate subcellular-compartment proteomes, cell-type-specific spatial proteomes, cell-surface proteomes, and cell-cell interaction networks [20–23]. Moreover, PL is evolving from a proteomic tool into a dynamic "molecular microscope" for neural-circuit dissection, with potentials to redefine diagnosis and therapy through discovery of mechanistic biomarkers and druggable targets.

PL techniques

Overview of PL

PL enables the mapping of molecular interactions and spatial neighborhoods in living cells and organisms. The core principle of PL involves fusing a protein of interest (POI) or a "bait" to an engineered enzyme that catalyzes the generation of reactive molecules (e.g., biotin-AMP or biotin-phenoxyl radicals) upon substrate addition. These reactive species covalently tag endogenous biomolecules within a short radius (typically ~10–20 nm) to the bait. The biotinylated molecules can then be affinity-purified and identified by mass spectrometry (MS) or next-generation sequencing, allowing for the reconstruction of local molecular landscapes under near-physiological conditions (Fig. 1a) [24–26].

Classification of PL techniques

Current PL platforms are primarily categorized by the enzymes used, each with distinct mechanisms and trade-offs (Fig. 1b).

Biotin ligases, such as BioID, TurboID, miniTurbo, BASU (a mutant BirA* engineered from *Bacillus subtilis*), and AirID, use ATP to convert biotin into a reactive biotin-AMP intermediate that labels proximal lysine residues. TurboID and its derivatives are widely used due to their rapid kinetics (labeling within minutes). However, they can deplete endogenous biotin pools and exhibit basal activity [27–29].

Peroxidases, such as APEX/APEX2 and horseradish peroxidase (HRP), utilize H_2O_2 to generate highly reactive, short-lived biotin-phenoxyl radicals that label electron-rich amino acids (e.g., tyrosine, tryptophan, cysteine, histidine). They offer ultrafast labeling (~ 1 min) and high temporal resolution, making them ideal for capturing rapid biological processes. However, the required H_2O_2 can be cytotoxic and perturb the redox-sensitive pathways, limiting some in vivo applications [15, 30–32].

In Split-PL variants, PL enzyme is split into two inactive fragments, each fused to two different POI proteins or localized to distinct compartments. Proximity-driven reconstitution restores the enzymetic activity and restricts labeling to specific PPIs, compartment interfaces, or known complexes, improving the specificity for conditional or inducible PPIs.

Antibody-based PL, such as biotinylation by antibody recognition (BAR), enables the mapping of PPIs in fixed cells and clinically relevant human tissues without genetic modification [33]. This technique employs a primary antibody to target an endogenous protein, followed by an HRP-conjugated secondary antibody. Upon substrate addition, the HRP enzyme is activated, generating reactive species that can covalently tag nearby proteins [34]. This method allows stringent purification and highly efficient proteomic analysis of native interactomes under pathophysiological conditions, effectively bridging basic and clinical neuroscience. However, the method is critically dependent on antibody specificity and affinity, necessitating rigorous validation. In addition, it offers limited spatial resolution due to the labeling radius that can extend to hundreds of nanometers. Additionally, the requirement of sample fixation and the use of peroxide make it unsuitable for live-cell applications.

Photocatalytic PL (Photo-PL) utilizes diverse light-activated catalysts, including genetically encoded proteins (e.g., miniSOG [35], fluorescent activator protein [36], or light-oxygen-voltage domains [LOV] [21]), transition-metal complexes (e.g., iridium- or ruthenium-based catalysts [37–40]), and organic dyes (e.g., Eosin Y [41], rhodamine 123 [42], dibenzylfluorescein), to generate

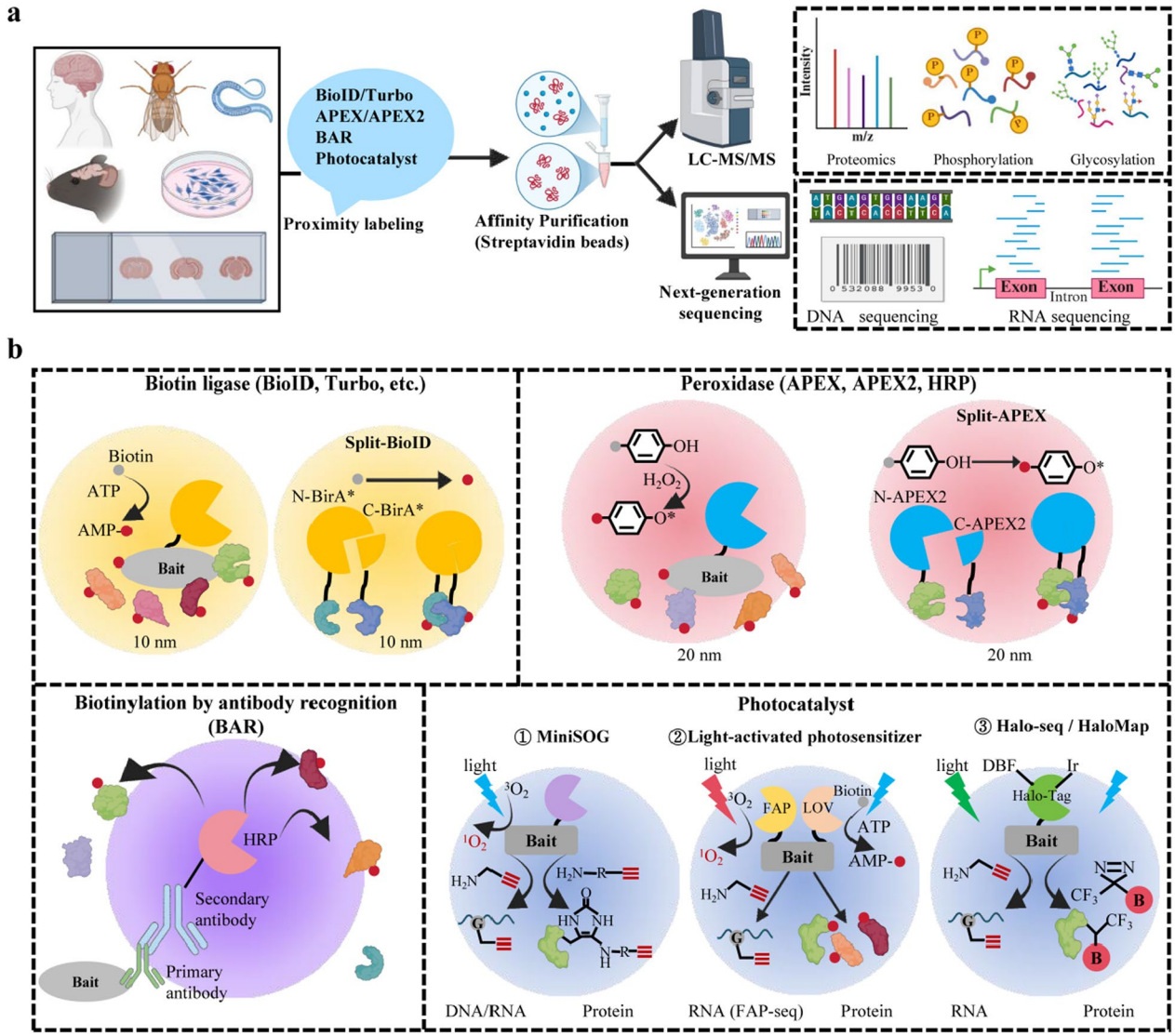


Fig. 1 Overview of proximity labeling (PL) strategies and workflow. **a** General PL workflow. PL is performed in diverse experimental systems (in vitro, in vivo, or ex vivo), followed by enrichment of biotinylated molecules and analysis via mass spectrometry or next-generation sequencing. **b** Classification and schematic representation of major PL techniques. A bait protein is fused to an engineered enzyme capable of catalyzing biotinylation. Upon addition of substrate (e.g., biotin or biotin-phenol), the enzyme labels proximal endogenous biomolecules. Created with BioRender.com

reactive species such as singlet oxygen [35, 43], quinone methides [36], carbenes [44, 45], or phenoxy radicals [46], for spatially controlled biomolecular labeling in living systems [47]. This approach achieves exceptional spatiotemporal precision and bioorthogonality, enabling high-resolution mapping of dynamic subcellular processes, as demonstrated in mitochondrial proteomics with iridium-based CAT-Prox [37], RNA localization studies using Halo-seq [39], stress granule (SG) dynamics with Halo-Map [40], and T-cell immune-synapse surface networks via Eosin Y-mediated labeling [41]. However, the broader application of Photo-PL in vivo is constrained by limited light penetration in tissues, challenges in probe delivery, and the need to optimize reaction kinetics under physiological conditions.

Applications of PL techniques

PL has evolved into a versatile platform for interactome mapping across all major biomolecule classes—proteins, RNA, DNA, and small molecules, with spatial resolution [34, 48, 49] (Table 1). A critical factor in PL labeling of these biomolecule classes is the selectivity of the labeling

Table 1 Comparison of key PL technologies for spatial molecular landscape mapping

Biomolecules	Method	Enzyme type/Principle	Advantages	Limitations	Applications	Ref.
Protein	Protein molecular profile					
	BioID/TurboID/BASU	Biotin ligase	Non-toxic for in vivo applications.	Poor temporal resolution as a result of low catalytic activity.	Identifying proximal proteins in living cells.	[16]
	APEX/APEX2/HPR	Peroxidase	High temporal resolution, versatility for both protein and RNA labeling.	Limited application in vivo because of the toxicity of H_2O_2.	Mapping proteomes and interactomes rapidly (minutes) in living or fixed cells.	[16]
	BAR	Antibody-targeted, HRP-based technique	Enables mapping interactomes of specific endogenous proteins and PTM profiling in fixed cells and primary human tissues, without genetic manipulation.	Limited by a large labeling radius and a critical dependence on antibody quality, restricting its use to fixed-cell contexts.	Identifying the interactors of lamin A/C in immortalized cell lines, primary cell culture, and primary human muscle and adipose tissues.	[33]
	AMAPEX	Antibody-targeted, APEX2-based technique	Enables labeling of endogenous proteins and specific PTMs without genetic manipulation.	Limited by antibody quality and requires cell permeabilization.	Maps interactomes of specific endogenous protein states, like histone modifications.	[53] [54]
	TyroID	Utilizes recombinant tyrosinase to generate reactive o-quinone intermediates.	High spatiotemporal resolution and in vivo-compatible, minimal perturbation to native biological systems.	Limited to extracellular environments and tyrosine-rich regions, potentially missing proteins information.	Mapping dynamic extracellular proteomes in vivo, such as tumor microenvironments and brain region-specific surfaceomes.	[61]
	HaloMap	Photo-PL, a HaloTag-fused protein to recruit a photosensitizer molecule.	High spatiotemporal control for mapping dynamic processes in living cells.	Requires genetic engineering to express the HaloTag fusion and exogenous delivery of the photosensitizer ligand.	Unraveling intracellular protein interactomes and dynamics of membraneless organelles, like stress granules.	[40]
	MiniSOG	Photo-activated to generate singlet oxygen upon light, covalently labeling neighboring proteins or RNA/DNA.	Enables identification of weak, transient interactions in live cells with high spatiotemporal control.	Requires genetic manipulation and may cause cellular photo damage.	Mapping PPIs and subcellular molecular landscapes in live cells.	[36]
	Cal-ID/CaST	Biotin ligase, calcium-dependent.	Provides permanent, transcription-independent molecular recording of transient Ca^{2+} signals with high spatial resolution.	Requires minutes for detectable labeling to miss transient information, and could bias toward calmodulin-binding proteins.	Capturing calcium-induced biotinylation upon neuronal activation in primary cortical neurons and kainic-acid-induced seizures.	[62]
	Cell-cell interactions					
	QMID	Utilizes enzyme-generated QM electrophiles that diffuse micrometers to covalently label neighboring cells without direct cell-cell contact.	Enables recording of cell spatial organization at cellular-scale resolution (~μm), capturing both direct and indirect cell communications in native tissues.	Limited by the diffusion range and stability of QM electrophiles, potentially labeling non-specific cells beyond the intended proximity range.	Dissecting immune niches and tumor microenvironments by labeling and isolating spatially proximal cells for downstream single-cell analysis.	[67]
	TransitID	Utilizes two distinct PL enzymes targeted to different cellular compartments to sequentially biotinylate proteins that traffic between various locations.	Enables nanometer-resolution mapping of endogenous proteome trafficking dynamics between compartments and even between different cells in co-culture systems.	Requires careful optimization of sequential labeling timing and enzyme targeting, and may miss very rapid or transient trafficking events due to the time needed for biotinylation.	Mapping protein trafficking between organelles (e.g., cytosol-mitochondria) and intercellular communication between immune and cancer cells.	[69]

Table 1 (continued)

Biomolecules	Method	Enzyme type/Principle	Advantages	Limitations	Applications	Ref.
	LIPSTIC	Utilizes sortase A to catalyze transpeptidation between a labeled substrate and cell surface proteins upon receptor-ligand engagement.	Enables monitoring of dynamic cell-cell interactions in vivo with single-cell resolution and compatibility with downstream analysis.	Requires genetic engineering to express sortase-acceptable substrates and limited to extracellular interactions.	Quantifying transient intercellular communication events in immunology (e.g., T cell-DC interactions).	[68]
	FucoID	Expresses site-specific fucosyltransferase (sFT) in cells or uses antibody conjugates (Ab-sFT) to confirm cell-cellinteractions.	Enables revealing interactions of different molecular pairs, such as peptide-major histocompatibility complex-T cell receptor, chimeric antigen receptor-antigen, and PD-1–PD-L1.	Limited by its dependence on having a purified population of "bait" cells for the standard method, restricting its use to study specific cell types in complex tissues or clinical samples.	Identifying unique gene expression changes in cells interacting with $HER2^+$ bladder cancer cells among $CD4^+$ and $CD8^+$ T cells.	[66] [71]
	gLCCC	Expresses a synthetic receptor system (synNotch) to observe cell-cell interactions.	A synthetic Notch system can permanently label in vivo cell-cell contact histories, enabling the study of dynamic interactions.	Limited to genetically pre-defined sender and receiver cells, precluding the detection of interactions in unmodified systems.	Monitoring and tracing dynamic cell-cell contacts across diverse in vivo contexts, including embryonic development, tissue homeostasis, and tumor growth in mice.	[72]
RNA	RNA-centric (identifying the proteins interacting or proximal with an RNA of interest)					
	TRIBE	ADAR deaminase fused with a protein of interest (POI), mediating A-to-I editing of interacting RNAs.	Does not require antibody purification and crosslinking.	Exogenous RBP expression can cause artifacts, and RNA tagging exhibits 3′-end bias.	Identifying the in vivo RNA interactome of specific RNA-binding proteins.	[75]
	APEX-RIP/Proximity-Clip	APEX is coupled with RNA immunoprecipitation (RIP) or crosslinking and immunoprecipitation (CLIP) methodologies.	It bypasses antibody purification, recovers localized RNAs, and uses UV crosslinking for direct interactors.	UV crosslinking enhances specificity at the cost of efficiency and necessitates IP-grade antibodies or genetic tagging.	Mapping the spatial RNA-protein interactome.	[76] [77]
RNA	RaPID	Aptamer-recruited biotinylation (MS2-BioID/MS-APEX2)	Avoids crosslinking artifacts and enables direct in vivo biotinylation of proximal proteins.	Requires RNA tagging, may capture indirect interactors.	Working with exogenous RNA, identifies RBPs associated with an RNA of interest.	[28] [78]
	TAPRIP	Utilizes CIRTS3 RNA-targeting system fused to miniTurbo to biotinylate proteins interacting with specific RNA structures.	High-efficiency, biocompatible mapping of RNA-protein interactomes without requiring RNA extraction or crosslinking.	Limited by the delivery efficiency of CIRTS3-miniTurbo system and non-specific labeling due to miniTurbo's basal activity.	Profiling protein interactomes of non-coding RNAs (e.g., circRNAs) and functional RNA structures (e.g., G-quadruplexes) in live cells.	[79]
	CBRPP	A dCas13-PBL enzyme (e.g., TurboID or APEX) fusion to be guided to a specific endogenous RNA sequence to biotinylate proximal proteins.	High specificity in living cells, eliminating the need for cross-linking or in vitro manipulation.	Limited to the efficient expression and delivery of the large dCas13-PBL fusion construct, which can challenge cellular viability and require optimized delivery systems.	Identifying proteins that interact with or are in proximity to specific non-coding RNAs or mRNA transcripts.	[80]
	Protein-centric (identifying the RNAs interacting or proximal with a POI)					
	APEX-seq	Direct RNA biotinylation, no crosslinking	Fast (~1 min), high spatial efficiency, and is amenable to in vivo applications.	It cannot distinguish direct from indirect interactions, and the biotin-phenoxyl radicals may compromise RNA integrity.	Characterizing the RNA composition of specific regions.	[81] [82]

Table 1 (continued)

Biomolecules	Method	Enzyme type/Principle	Advantages	Limitations	Applications	Ref.
	CAP-seq	Light-activated proximity-dependent photo-oxidation of RNA nucleobases.	High spatial specificity in live cells.	Requires genetic engineering to express the photosensitizer fusion protein, limiting its application in primary samples.	Investigating subcellular local transcriptomes.	[83]
	dCas13-APEX2/CRUIS	PL enzyme (PafA, BioID, BASU, APEX2) fuses with catalytically inactive dCas13 to biotinylate proteins interacting with an endogenous transcript.	High-specificity, genetic-code-guided mapping of the proteome and transcriptome surrounding specific endogenous RNA.	Requires transfection/expression of multiple large constructs, potential off-target effects.	Identifying proteins and RNAs that interact with or are near nuclear or cytoplasmic RNAs, such as lncRNAs, mRNAs, or viral RNAs.	[84] [85]
	PARIS	UV-activated psoralen to crosslink base-paired RNAs, which are then ligated and sequenced to map interactions.	Achieving of near-base pair resolution in determining RNA structures and interactions directly in living cells.	The requirement for psoralen treatment and UV irradiation, which can be cytotoxic and perturb cellular physiology.	Mapping RNA secondary structures and interaction networks in vivo.	[86]
	Halo-seq	A photoactivatable molecule to label proximal RNAs, which are then purified via click chemistry and sequencing.	Higher efficiency in analyzing small, precisely localized RNA populations (e.g., in suborganellar regions).	Requires precise optical control and might have limited penetration depth in thicker tissues or entire organisms.	Mapping and quantifying RNA localization and the dynamics.	[39]
DNA	DNA-centric (identifying proteins associated with a specific DNA sequence)					
	GLoPro	Peroxidase, dCas9-guided targeting and APEX2-mediated catalytic labeling to biotinylate proteins proximal to a specific genomic locus.	High-specificity, CRISPR-guided profiling of locus-specific protein complexes without crosslinking or harsh extraction.	Limited by dCas9 efficiency and specificity, and by APEX2's small labeling radius which may miss larger complexes.	Mapping dynamic protein recruitment and regulatory complexes at specific genomic loci (e.g., enhancers, promoters) in native chromatin contexts.	[87]
	CASPEX/C-BERST	Combining CRISPR-dCas9 targeting with APEX2 to biotinylate proteins associated with a defined genomic sequence in live cells.	Enables rapid, unbiased, and high-throughput profiling of proteomes at specific genomic loci without crosslinking or genetic manipulation of endogenous loci.	Limited by the off-target potential of dCas9/gRNA and a small labeling radius that can miss functional distal interactions.	Defining the subnuclear proteome at repetitive genomic elements (e.g., telomeres, centromeres) to annotate novel regulatory factors.	[88] [89]
	CAPTURE	Utilizing a biotinylated, nuclease-deficient Cas9 (dCas9) guided by sgRNAs to target specific genomic loci.	High-resolution, unbiased identification of protein complexes and long-range interactions at a single-copy genomic locus in its native chromatin context.	Limited by the efficient delivery and expression of the large dCas9-sgRNA machinery, and may perturb native cell physiology.	Mapping the proteomic composition and chromatin interactome of specific regulatory elements, such as telomeres, enhancers, and disease-associated loci.	[90]
	ChromID	Biotin ligase, fusing engineered chromatin readers (eCRs) to BASU to label proteins proximal to specific chromatin modifications.	Enables high-specificity mapping of protein interactomes at defined epigenetic marks in living cells.	Requires customized synthetic readers (eCRs), potentially limiting broad applicability and introducing artifacts.	Identifying chromatin-dependent protein interactome and applied to distinct chromatin modifications in mouse stem cells.	[91]
	SelectID	A dCas9-methylation binding domain-TurboID fusion to biotinylate proteins at specific methylated DNA loci.	Enables highly specific proteomic profiling of specific DNA sequences with defined epigenetic marks.	Limited by chromatin accessibility and off-target binding	Discovering novel regulators and readers at specific methylated genomic elements.	[92]
	Protein-centric (identifying the DNAs associated with a POI)					
	ALaP-seq	APEX2 is fused to a POI to detect associated DNA.	Direct, high-resolution mapping of chromatin interactions with nuclear compartments in live cells.	Lower specificity than ChIP-seq, inability to distinguish direct vs. indirect tethering.	Uncovering spatial transcriptional hubs and dissect epigenetic exclusion mechanisms.	[94]

Table 1 (continued)

Biomolecules	Method	Enzyme type/Principle	Advantages	Limitations	Applications	Ref.
	DamID-seq	Fusing Dam methyltransferase and a DNA-binding protein to methylate adenines in GATC motifs near protein-DNA interaction sites.	Does not require antibodies or crosslinking, providing high-resolution genome-wide mapping of protein-DNA interactions with high sensitivity.	Limited by Dam methyltransferase specificity and the requirement for genetic fusion.	Mapping genome-nuclear lamina interactions and other protein-DNA binding events in living cells with high precision and sensitivity.	[95]
Small molecule	Molecular landscape					
	Photo-activated PL (PAPL)	Photocatalytic, generates reactive species that label lipids upon light activation.	Enables organelle-selective analysis of lipid transport and composition.	Requires introduction of exogenous components and may perturb native systems.	Quantitatively mapping lipid transport and metabolism between specific organelles.	[50]
	Small molecule-Protein interactions					
	DrugID	Biotin ligase, conjugates a drug to a biotin ligase to identify its binding and proximal proteins in live cells.	Mapping drug interactomes de novo in live cells at physiological doses with minimal material.	The drug-enzyme conjugate may alter the native behavior of the drug.	Mapping in vivo drug interactomes, including small molecules (e.g., JQ1) and oligonucleotides (e.g., ASOs).	[96]
	PROCID	HaloTag-mediated proximity biotinylation for target identification.	Enables direct, live-cell mapping of dynamic drug-protein interactions with high specificity.	Requires chemical conjugation of small molecules to HaloTag ligands, may miss transient interactions.	Identifying unknown drug targets and binding sites in live cells, accelerating drug mechanism studies.	[97]
	BioTAC	Biotin ligase, a small-molecule-guided platform to identify proximate proteins in living cells.	In-situ identification of both direct and complex binding proteins within native cellular environments.	Limited by background signal and chimera-induced functional alterations.	Mapping the cellular interactomes of therapeutic small molecules to elucidate mechanisms of action.	[98]
	POST-IT	HaloTag-fused Pup ligase to directly transfer Pup to proximal proteins upon binding to a small molecule in live cells.	Enables non-diffusive, highly specific tagging of drug-protein interactions in live cells, overcoming limitations of lysate-based methods.	Requires optimization to prevent self-pupylation and achieve efficient small-molecule conjugation.	Identifying novel drug targets and off-targets in native physiological contexts, including complex in vivo models (zebrafish embryos).	[99]

chemistry. For example, PL labeling of proteins is often directed at specific reactive amino acids. In contrast, the labeling of nucleic acids is less specific. The generated radicals (e.g., from APEX) react promiscuously with the electron-rich nucleobases of proximal RNAs or DNAs. PL labeling of lipids presents a distinct challenge due to the hydrocarbon-dominated structure. A recent study demonstrated photocatalytic lipid labeling using a lipophilic azide probe. Upon blue light exposure, organelle-localized photocatalysts activate the probe to generate triplet nitrenes, which then selectively label nearby lipids with nucleophilic head-groups (e.g., phosphatidylethanolamine) via covalent bonding [50]. The primary advantage of these approaches is the ability to capture spatially resolved interactomes in live cells. However, there is a key limitation due to the inherent chemical bias; nucleic acid labeling lacks base specificity, and lipid labeling often under-represents saturated and neutral lipid classes that lack these reactive moieties. In the following sections, we will elaborate on these diverse applications (Fig. 2, Table 1), underscoring the role of PL as a foundational technology for multidimensional molecular mapping.

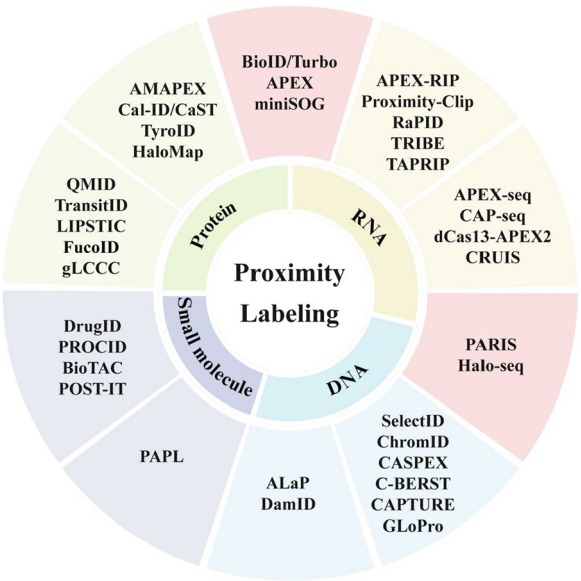


Fig. 2 Applications of PL techniques for spatial interactome mapping. PL methods are categorized by target molecule class: Proteins (e.g., AMAPEX, Cal-ID/CaST, TyroID, HaloMap for identifying protein-protein interactions; QMID, TransitID, LIPSTIC, FucoID, gLCCC for mapping cell-cell interactions), RNA (e.g., APEX-RIP, Proximity-Clip, RaPID, TRIBE, TAPRIP for identifying RNAs interacting with a POI; APEX-seq, CAP-seq, dCas13-APEX2, CRUIS for mapping RNA-binding proteins), DNA (e.g., ALaP and DamID for mapping chromatin interactions; SelectID, ChromID, CASPEX, C-BERST, CAPTURE, GLoPro for identifying proteins associated with specific DNA loci), and Small molecules (e.g., PAPL for identifying cellular organelle lipids; DrugID, PROCID, BioTAC, POST-IT for capturing small molecules and their interacting partners). The red modules highlight multi-class detection: protein/RNA (BioID/Turbo, APEX, miniSOG) and RNA/DNA (PARIS, Halo-seq). Created with BioRender.com

Mapping dynamic proteomes and interactomes in living systems

A primary application of PL is the characterization of local proteomes and PPI networks within living systems. By capturing biotinylated proteins for mass spectrometry, PL can define the molecular composition of subcellular compartments, membrane contact sites, and transient signaling complexes that are inaccessible to conventional methods [51]. Comprehensive summaries are available elsewhere [16, 19, 34, 52].

Key innovations have significantly expanded the scope and context of proteomic mapping. Antibody-based PL techniques (e.g., BAR [33], AMAPEX [53, 54]) enable interactome discovery in fixed cells and primary human tissues without the need for genetic manipulation. PL also excels in mapping dynamic post-translational modifications (PTMs) [55], using strategies ranging from photoactivatable TurboID/BioID-based profiling of phosphorylation [56, 57] and glycosylation to direct enzymatic labeling of PTMs like O-GlcNAcylation in live cells [58–60]. For dynamic, in vivo applications, engineered enzymes like TyroID can map extracellular proteomes, such as brain region-specific surfaceomes [61], while photoactivated platforms (e.g., miniSOG [36], HaloMap [40]) provide exceptional spatiotemporal control for processes like SG assembly. Furthermore, activity-dependent systems (such as calcium-dependent BioID [Cal-ID]) create permanent, transcription-independent records of transient signaling events, such as calcium signals and neuronal activity [62].

PL can also be integrated with other technologies. CLEM (correlative light and electron microscopy) platforms, such as fast light-EM examination, leverage the electron-dense precipitates generated by PL enzymes (e.g., APEX2), enabling seamless correlation of dynamic tracking of proteins in living cells with the high-resolution ultrastructural mapping within the native cellular architecture [31, 63]. Combining with synchronized trafficking systems, such as the retention using selective hooks (RUSH) system, enables the capture of transient interactors for cargo proteins along the secretory pathway. This approach maps their trafficking interactome for targets like SARS-CoV-2 proteins and lysosomal enzymes under physiological and pathological conditions [64, 65].

PL technologies offer a powerful approach to dissecting cell-cell interactions, ranging from stable adhesions to transient signaling events [66]. They have varying spatial resolutions depending on the operation principles. Diffusible labeling systems such as QMID (quinone methide-assisted identification of cell spatial organization)

enable micrometer-scale mapping of cellular neighborhoods and indirect communication [67], while receptor-engagement detectors like LIPSTIC (Labelling Immune Partnerships by SorTagging Intercellular Contacts) provide single-cell resolution of specific ligand-receptor interactions in real-time [68]. For tracing protein exchange between cells, sequential enzymatic labeling approaches including TransitID offer nanometer-scale precision [69]. Recent innovations include self-sufficient peroxidase systems that generate H_2O_2 endogenously, enabling sensitive recording of cell-cell contacts under physiological conditions, which is ideal for neural and immune studies [70]. The toolkit further expands to include engineered enzyme systems (FucoID) for identifying specific interaction pairs [71] and synthetic biology platforms (gLCCC) that permanently record contact histories between defined cellular partners [72]. Together, these complementary strategies enable comprehensive mapping of cell-cell communications, bridging nanoscale interaction events to macroscopic cellular behaviors and their resultant functional phenotypes.

Resolving RNA-protein interactions and local transcriptomes

PL has revolutionized the study of RNA biology by enabling the mapping of RNA-protein interactions and subcellular RNA localization in living cells, using RNA-centric and protein-centric strategies.

The RNA-centric strategy is designed to identify proteins associated with specific RNA molecules, yielding precise views of RNA-binding protein (RBP) networks [73, 74]. Techniques like TRIBE (Targets of RNA-binding proteins Identified By Editing) use RNA editing enzymes to mark the bound transcripts [75]. These editing sites are then identified through high-throughput sequencing, revealing the targets of the RBP. APEX-RIP/Proximity-CLIP [76, 77] and RaPID [28, 78]/TAPRIP [79] employ proximity biotinylation, with or without crosslinking, to capture RNA-binding proteins. Extending to endogenous transcripts, CBRPP (CRISPR-based RNA proximity proteomics) targets native RNAs directly based on the fusion of dCas13 to PL enzyme [80].

The protein-centric methods, such as APEX-seq and CAP-seq, use peroxidase- or photosensitizer-based labeling to identify all RNAs near a bait protein or organelle, enabling transcriptome-wide mapping of RNA localization with high spatial and temporal resolution [81–83]. Several techniques enable the precise investigation of specific RNAs. For example, dCas13-APEX2/CRUIS (CRISPR-based RNA-United Interacting System) has been used to profile the proximal proteome near telomerase RNA and hTR [84, 85]. Additional modalities like PARIS (Psoralen Analysis of RNA Interactions and Structures) [86] and Halo-seq [39] further enable the study of RNA structures and the dynamics of precisely localized RNA populations. Collectively, these tools have uncovered fundamental principles of RNA regulation and compartmentalization.

Profiling chromatin-associated proteomes and genomic landscapes

PL enables high-resolution profiling of the protein complexes associated with specific genomic loci and chromatin states in live cells. CRISPR/dCas9-guided systems such as GLoPro (genomic locus proteomics) [87], C-BERST (dCas9-APEX2 Biotinylation at genomic Elements by Restricted Spatial Tagging) [88, 89], and CAPTURE (CRISPR affinity purification in situ of regulatory elements) [90], which fuse a PL enzyme to dCas9, can direct the PL enzyme to defined DNA sequences, biotinylating proximal proteins, thereby revealing the proteomic landscape of promoters, enhancers, and repetitive elements. Complementing this, chromatin reader-based approaches, such as ChromID (chromatin-dependent protein identification) [91] and SelectID (selective profiling of epigenetic control at genome targets identified by dCas9) [92], map interactomes at specific epigenetic marks. Beyond protein-centric mapping, photosensitizer protein-based labeling enables crosslink-free profiling of chromatin architecture. This method revealed lamina-associated domains that covered ~37.6% of the genome in the nuclear lamina of human embryonic kidney 293 T cells [93]. Meanwhile, ALaP-seq [94] and methylation-based techniques (DamID-seq) [95] have been used to identify DNA regions associated with a nuclear bait protein or to map genome-wide protein-DNA interactions, respectively. These methods have advanced our understanding of nuclear architecture and gene regulation, though challenges remain in minimizing steric interference and improving resolution for closely spaced genomic features.

Charting metabolic networks and drug interactomes

PL is being increasingly applied to map small-molecule interactomes. Photo-activated PL (PAPL) generates reactive species to label proximal lipids, enabling organelle-selective analysis of lipid composition and transport [50]. For mapping drug-protein interactions, enzyme-conjugation strategies (e.g., DrugID [96], PROCID [97]) employ covalent conjugation of a drug with a labeling enzyme, allowing unbiased identification of binding and proximal proteins in live cells. Newer platforms like BioTAC (biotin targeting chimera) [98] and POST-IT (Pup-On-target for Small molecule Target Identification Technology) [99] further enhance specificity by minimizing diffusion-driven background, enabling highly precise target

identification in physiological contexts and accelerating drug mechanism-of-action studies.

Taken together, these diverse and innovative PL modalities provide an unparalleled toolkit for constructing multi-omic molecular maps in living systems. They enable interrogation of patiotemporal dynamics of interactions across all major biomolecular classes in vivo, advancing our understanding of cellular processes and disease mechanisms.

Construction of molecular atlas in the nervous system

The cellular diversity and intricate subcellular architecture have long complicated molecular profiling in the CNS. While the single-cell RNA-seq technology resolves neuronal subtypes, and Cre-lox strategies enable gene manipulation [100], these approaches cannot fully capture proteomes within intact subcellular compartments or at cell-cell interfaces. Traditional biochemical fractionation disrupts delicate structures [101], and physical isolation methods, such as laser-capture microdissection (LCM) or fluorescence-activated cell sorting (FACS), can erode morphological context and dilute transient interactions [102, 103]. PL technologies overcome these barriers by enabling high-resolution, organelle-, cell-type-, and interface-specific molecular mapping within native environments.

Mapping organelle proteomes and interactions

PL has been instrumental in mapping the molecular composition and dynamic interactions of intracellular organelles. For mitochondria and ER, engineered enzymes such as APEX2 and TurboID enable spatially restricted labeling of organelle proteomes [104–106]. Interactome studies in non-neuronal models have identified RTN4IP1 (reticulon 4-interacting protein 1, also known as optic atrophy-10, OPA10) as a crucial mitochondrial oxidoreductase essential for coenzyme Q synthesis [107]. Studies using the split-TurboID tool and peroxidase-mediated proximity biotinylation, respectively, have mapped protein composition of ER-mitochondria contact sites (e.g., involving ABCD3 and LBR, SYNJ2BP-RRBP1) in HEK 293 T cells [108, 109]. These findings provide an essential molecular framework for investigating energy metabolism and organelle communication in neurons, and identifying processes critical for neurotransmission and neuronal survival.

Within the ER, APEX labeling has revealed structures like PERK/COPII-dependent ER whorls that modulate translation during stress [110]. Peroxidase (HRP/APEX2)-based mapping has revealed stress-induced protein mistargeting, including ATF6-dependent ER-import defects [111]. In situ secretory protein labeling via ER-anchored TurboID (iSLET) has enabled dynamic tracking of tissue-specific secretory proteins in the mouse liver [112]. This implies that iSLET is a potential tool for studying secretion of neuropeptides and neuromodulators. For RNA-protein interactomes, TRIBE has identified neuron-specific targets of RNA-binding proteins [74, 113], and the discovery of ER-localized glycoRNAs has challenged conventional models of the secretory pathway [114].

Lysosome-focused PL approaches (e.g., LAMP1-APEX, Lyso-TurboID) have uncovered novel membrane proteins (e.g., SCAMP3, a secretory carrier-associated membrane protein) [115, 116] and repair mechanisms such as the phosphoinositide-initiated membrane tethering and lipid transport (PITT) pathway [117] and TBC1D15-driven tubulation [118] in various cell models. While these studies were performed in non-neuronal models, they are highly relevant to neuroscience, as lysosomal integrity is critically implicated in neurodegeneration [116, 119]. In neurons, ER-lysosome contact mapping has demonstrated that P180 and kinesin-1 directly regulate axonal lysosome trafficking in neurons [120], a finding that directly links PL-defined organelle interactions to neuronal-specific functions.

PL has also illuminated the proteomic architecture of membraneless compartments. CAP-seq mapped SG transcriptomes, revealing enrichment of AU-rich RNAs [121], while APEX2-based SG proteomics identified core constituents such as G3BP1 and autophagy-related factors implicated in amyotrophic lateral sclerosis (ALS) [122]. Critically, in neuronal subcompartments, PL has identified key organizers like SCRIB [123, 124] in the axon initial segment (AIS), and Pdlim7 as a functional component of the spines [125]. These findings provide mechanistic insights into polarized trafficking and synaptic dysfunction. In addition, TurboID labeling proteomics has identified myelin basic protein (MBP) proximity interactions with adhesion proteins, solute carriers, vesicle-transport machinery, and ferroptosis-linked metabolic regulators, suggesting broader roles of MBP in myelin integrity [126].

Collectively, the unique advantages of PL, including its tunable spatial resolution (achieved by varying labeling radii through enzyme engineering or time-controlled activation), precise temporal control, and broad system compatibility (as demonstrated in diverse models such as iPSC-derived neurons [116] and primary tissues [108]), have advanced our understanding of organelle interplay, underscoring the promise of integrated spatial omics for decoding neuronal function and pathology.

Cell-type-specific molecular census

PL systems are increasingly tailored for cell-type-specific profiling within the nervous system. For neuronal subtypes, LOV-TurboID enables light-controlled, high-precision labeling in the mouse brain and cultured neurons [21]. BioID and TurboID have been used to map interactomes of neurotransmitter receptors (e.g., AMPA receptor [AMPAR], γ-aminobutyric acid sub-type A receptor), revealing developmental shifts in receptor-associated partners [127]. Chemogenetic activation coupled with APEX2 proximity labeling in striatal neurons has uncovered activity-dependent proteome remodeling [128, 129]. In dopaminergic neurons, TurboID identified Kv7.2/7.3 channels as interactors of dopamine and glutamate transporters, suggesting their roles in modulating neurotransmitter uptake relevant to Parkinson's disease (PD) and epilepsy [130]. Adeno-associated viruse (AAV)-mediated, cell-specific TurboID delivery has facilitated comprehensive proteomic profiling of neurons and astrocytes, identifying approximately 10,000 unique proteins with high reproducibility [131].

PL has also facilitated circuit mapping and activity recording. A study using Cre-dependent APEX2 proximity labeling in corticostriatal neurons has profiled axonal proteome dynamics across postnatal development, linking altered kinase activity to neurodevelopmental phenotypes [129]. Cal-ID, an enzyme that biotinylates nearby proteins within minutes in response to elevated local calcium levels, has been used to record neuronal activity with high spatial resolution and molecular specifivity [62]. Irala et al. [132] used TurboID fused to neurocan (NCAN) termini to delineate distinct cortical interactomes in vivo, showing that the NCAN C-terminus promotes inhibitory synapse formation.

Regarding synapse organization and intercellular communication, a study using BioID in Cx36-EGFP mice and zebrafish uncovered >50 previously unrecognized proteins at electrical synapses, including the scaffold protein Sipa1l3, which shapes synaptic connectivity [133]. Pupylation-based interaction labeling (PUPIL) has been used to map gap junction networks in the mouse brain, offering a non-invasive approach to study neural connectivity [134]. At chemical synapses, a PL study using PSD-95-fused and gephyrin-fused BirA (an *E.coli* biotinylation enzyme) to target the proteomes of excitatory and inhibitory postsynapses, respectively, comprehensively defined 121 excitatory and 181 inhibitory postsynaptic proteins, revealing new regulators of trafficking and signaling [18]. In a notable application, BAR was used to define the physiological interactome of pS129-alpha-synuclein in the healthy mouse olfactory bulb [135]. The identified partners, enriched for presynaptic functions, reposition this pathological epitope as part of normal biology and point to a potentially vulnerable circuit in synucleinopathies. A low-toxicity tyrosine-labeling system (BmTyr) efficiently mapped endogenous interactomes of metabotropic glutamate receptor (Grm1) and dopamine receptor (Drd2) in the mouse brain via ligand-tethered PL [136].

Beyond neurons, PL has illuminated glial signaling. In BV-2 microglia, TurboID fused to Kv1.3 revealed distinct N- and C-terminal interactomes under inflammatory conditions, implicating pathways involving STAT1 and Toll-like receptor (TLR) 2 [137]. A BioID-based study showed that the LPS-induced Neu1 translocation sustains neuroinflammation by desialylating TLR4, highlighting a potential therapeutic target [138]. TurboID profiling in microglial and neuronal lines has revealed native-state proteomes (~60% coverage) with distinct inflammatory signatures, offering systems-level views of neuroinflammatory responses [139].

Together, PL is a powerful tool to resolve cell-type-specific proteomes, elucidate synaptic organization, and uncover disease-relevant mechanisms across neural systems.

Cell-cell interaction mapping

PL has revolutionized proteomic mapping at cell-cell interfaces within the nervous system, revealing molecular foundations for synaptic and neuro-glial communication. Using spatially restricted enzymatic tagging, Loh et al. profiled excitatory and inhibitory synaptic cleft proteomes with >89% specificity, identifying Mdga2 as a regulator of Neuroligin-2 at inhibitory synapses [17]. Earlier HRP-fusion work targeting synaptic adhesion molecules (e.g., SynCAM1) identified 39 excitatory cleft proteins, including Neuroligin-3 and Neurexin-1, alongside novel candidates such as receptor tyrosine-protein phosphatase zeta [140].

Subsequent innovations enabled systematic dissection of neuro-glial contacts. The Split-TurboID system adapted to astrocyte-neuron interfaces has enabled in vivo labeling at astrocyte-synapse junctions and revealed previously unappreciated protein networks [48, 141]. Another study combining cell type-specific in vivo biotinylation of proteins (CIBOP) and viral delivery produced cell-type-resolved maps of neuronal and astrocytic proteomes with regional specificity, revealing proteomic differences between Camk2a-positive neurons and Aldh1l1-positive astrocytes [141, 142]. BioID2-based protocols enable detailed subcellular proteomics in intact astrocytes and neurons while preserving the morphology [62, 142]. In disease models, HRP-based PL in 5×FAD mice revealed Aβ accumulation at the myelin-axon interface and disrupted signaling pathways linked to lipid metabolism and axonal outgrowth [143].

Collectively, PL has become an indispensable approach to decoding the molecular architecture of neural cell-cell interfaces under physiological and pathological conditions.

Applications in neurological disease research

The complexity and inaccessibility of the human nervous system have long impeded a mechanistic understanding of neurological diseases. Traditional methods often fail to capture the spatiotemporal dynamics of molecular events that drive the pathogenesis. PL is transforming neurological disorder research by pinpointing the precise subcellular context and interactors of pathogenic proteins, mapping organelle- and circuit-specific dysfunctions that underlie cellular vulnerability, and directly nominating mechanistic biomarkers and druggable targets (Fig. 3, Table 2).

Elucidating disease mechanisms with spatiotemporal precision

In Alzheimer's disease (AD), PL has revolutionized the study of tau and Aβ pathology. In a study dissecting the role of tau, split-TurboID identified over 700 interactors of the microtubule-binding repeat domain of tau (TauRD), which demonstrate a surprising enrichment for RNA-binding and spliceosome proteins. This finding implicates a novel mechanism where tau disrupts nuclear pathways beyond its classical role in microtubule stability [144]. Complementary APEX-based labeling in human iPSC-derived neurons has mapped tau interactions with synaptic-vesicle proteins during activity-dependent tau secretion, providing a potential mechanism for activity-regulated tau secretion and spread [145]. Furthermore, BioID2 uncovered an interaction between tau and N-ethylmaleimide-sensitive factor (NSF), which regulates AMPAR trafficking. This interaction provides a direct molecular link between tau pathology and the synaptic plasticity deficits underlying memory loss in AD [146]. Notably, a study combining an *O*-GlcNAc binding activity with TurboID proximity labeling in *Drosophila* identified components of the translational machinery as substrates of *O*-GlcNAcylation, suggesting that *O*-GlcNAcylation modulates regional translational activity in the brain and thus impact cognitive function [147]. Beyond tau, HRP-based PL in human post-mortem brains and mouse

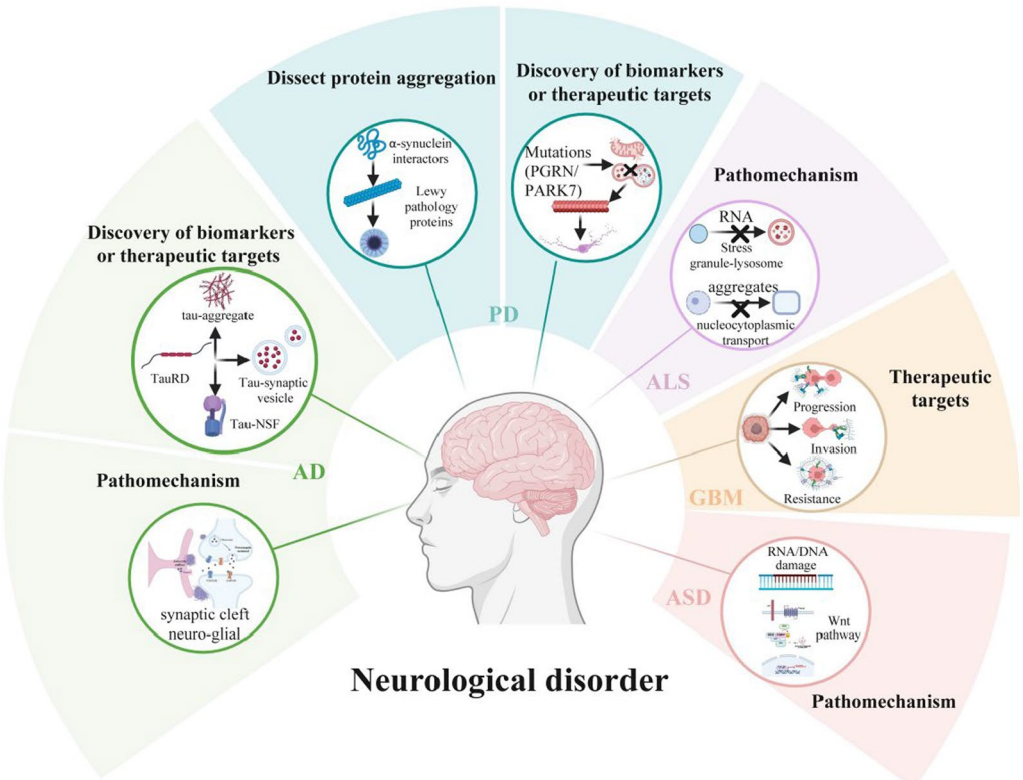


Fig. 3 PL-based approaches enable systematic investigation of disease-specific mechanisms, proteomic landscapes-guided biomarkers and druggable targets across major neurological disorders, including Alzheimer's disease (AD), Parkinson's disease (PD, ALS, glioblastoma (GBM), and autism spectrum disorder (ASD). Created with BioRender.com

Table 2 Advances in neurological disorders by PL technologies

Disease	Approach	Target	Sample	Main finding	Refs.
AD	split TurboID	Tau microtubule repeat domain (TauRD)	HEK293 cells	Identified 700+ TauRD interactors (RNA-binding/spliceosome proteins) linking nuclear RNA processing to tau pathology.	[144]
	APEX	Human tau	Human iPSC-derived neurons	Identified activity-dependent tau-synaptic vesicle interactions, mapping binding to vesicle cytosolic domains.	[145]
	BioID2	Tau	Primary neurons, mouse brains	Identified tau-NSF interactions regulating AMPAR trafficking and synaptic plasticity underlying memory.	[146]
	Turbo	*O*-GlcNAcylation	*Drosophila* mushroom body	*O*-GlcNAcylation impacts cognitive function via regulating regional translational activity in the brain.	[147]
	HRP	Dystrophic neurites (spheroid)	Human postmortem and mouse brains	Revealed mTOR-mediated protein turnover and cytoskeletal dysregulation in dystrophic neurites drives spheroid pathology.	[148]
	HRP	Myelin-axon interface	Human brains and 5×FAD mice	Demonstrated Aβ accumulation at myelin-axon interfaces disrupts neuro-glial signaling and paranode structure.	[143]
	ProPPr	Phospho-tau	FFPE tauopathy brain tissues	Cross-disease tau-aggregate proteomics identified disease-specific interactors (VPS35/LAMP2/GSK3α) and a role of microglial ferritin in CBD.	[170]
	CIBOP	Parvalbumin interneurons (PV-INs)	Human brains and 5×FAD mice	PV interneuron proteomics linked mitochondrial/synaptic/mTOR dysfunction to early AD, revealing risk/resilience-associated proteins.	[172]
PD	TurboID	Histone H3.3	HEK293T cells	PARK7 translocates to chromatin upon Cys106 ligation.	[173]
	APEX2	Dopaminergic neurons	Mouse brains	Dopaminergic neuron proteome mapping revealed axonal localization of key ion channels.	[174]
	APEX, BAR	Lysosomes	iPSC-derived neurons and mouse brains	Progranulin deficiency disrupts lysosomal function via v-ATPase/hydrolase/pH dysregulation, impairing proteostasis.	[175]
	UltraID	α-Synuclein	HEK293T cells and iPSC-derived neurons	Identified 38 α-synuclein interactors (endolysosomal/membrane proteins) supporting membrane-mediated early aggregation.	[166]
	BAR	Total and pathological α-synuclein	Human brains	Identified 261 Lewy pathology proteins (e.g., HBB) and vesicular/mitochondrial dysregulation in synucleinopathies.	[152]
	BAR	α-Synuclein	Human brains	Identified 79 PD/DLB-linked vesicle/SNARE proteins and 3 MSA markers (CBR1/CRYAB/GFAP) associated with metabolic/oxidative pathways.	[171]
ALS	APEX2	Fused in sarcoma (FUS)	HEK293T cells	FUS N-terminal phosphorylation shifts interactome to cytoplasmic mRNA regulators (e.g., MOV10) and nuclear DNA repair factors, disrupting RNA homeostasis.	[154]
	APEX	Superoxide dismutase 1(SOD 1)	HEK293T cells and N2a cells	ALS-mutant SOD1 (G85R/G93A) aberrantly binds XPO5, disrupting pre-miRNA export and Dicer processing to impair miRNA biogenesis.	[156]

Table 2 (continued)

Disease	Approach	Target	Sample	Main finding	Refs.
	APEX	Profilin 1 (PFN1)	HEK293T cells and N2a cells	ALS-mutant PFN1 (C71G/M114T) binds splicing factors (hnRNPC/U2AF2), inducing pathogenic Alu exonization.	[155]
	APEX2	Tubulin-binding protein STMN2	U2OS cells and iPSC-derived neurons	STMN2 neuroprotection in ALS involves dynamic tubulin/membrane-state switching at trans-Golgi networks.	[158]
	APEX2	LAMP1-positive lysosomes	Human iPSC-derived neurons	ANXA11 mediates RNA granule-lysosome tethering, a transport mechanism disrupted by ALS mutations.	[159]
	APEX2	Stress granules (SG)	Human iPSC-derived neurons, *Drosophila*	Identified 150 novel SG components with cell-type-specific profiles, showing neuronal SGs are uniquely enriched in chaperones/autophagy factors.	[122]
	BioID	TDP-43	Human brains, iPSC-derived neurons, Neuro-2A	TDP-43 aggregates sequester nuclear pore components (Nups/TFs), disrupting nucleocytoplasmic transport.	[154]
	BioID2	C9orf72-derived dipeptide repeat proteins	Human postmortem brains	C9orf72 DPR interactomes revealed polyGA aggregates sequester VCP, impairing autophagy in ALS/FTLD.	[168]
ASD	TurboID	DDX3X	Mouse primary neural progenitors	DDX3X mutations impair neurodevelopment through RNA/DNA damage pathways, with severe cases causing neuronal death.	[160]
	BioID2	Synapsin1	Mouse primary neurons	Identified 41 ASD gene networks disrupting mitochondrial/Wnt/MAPK pathways and correlating with clinical severity.	[161]
GBM	BioID2	Epithelial membrane protein 3 (EMP3)	U-118 glioblastoma cells	EMP3 sustains oncogenic EGFR/CDK2 signaling in GBM by blocking RAB7-mediated degradation via TBC1D5, driving proliferation and therapy resistance.	[176]
	PAPL	EGFR	Glioblastoma tissue, GBM43 cells	Live-cell and GBM tissue EGFR interactomes unveiled spatially distinct microenvironment interactions.	[177]
	Turbo-ID	ACP1, AURKB	GBM43 cells	Cortactin links ACP1-AURKB in GBM invasion via serine-phospho/tyrosine-dephospho regulation.	[178]

brains revealed mTOR-driven proteostasis defects and cytoskeletal dysregulation within dystrophic neurites, offering direct insights into the mechanisms of spheroid pathology [148]. Additionally, in HT22 cells, BioID mapping of the beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) interactome, upstream in the amyloid cascade, identified time-resolved proximal proteins, informing the dynamic regulation of amyloidogenic processing [149].

In PD, complex and dynamic interactomes of α-synuclein have been revealed by PL. APEX2 mapping in neurons identified 225 α-synuclein-proximal proteins involved in membrane trafficking and RNA binding, many of which overlap with known PD risk factors [150]. Crucially, PL studies have compared molecular interactions for wild-type versus pathological (e.g., A53T, pSer129) α-synuclein. Analysis of human tissues using the BioID system revealed transcriptional adapter 2-alpha (TADA2α) as a novel binding partner of α-syn, and found a much stronger interaction between α-synuclein A53T and TADA2α than that between wild-type α-synuclein and TADA2α [151]. The BAR technique labeling total and pathological α-synuclein showed disease-specific interactions of pSer129 α-synuclein with vesicular proteins [152]. PAPL extended these findings by enabling organelle-specific profiling and nominating novel Parkin substrates (e.g., Ssu72/SNW1) with relevance to PD pathogenesis [143].

In ALS and frontotemporal dementia, PL has been used to study RNA-binding protein pathology. APEX-based approaches revealed that ALS-linked mutants of SOD1 and profilin 1 (PFN1) have aberrant interactions with the miRNA biogenesis machinery (Exportin 5) and mRNA splicing factors (hnRNPC, U2AF2), respectively. This finding directly connects these mutations to RNA dysregulation [155, 156]. Furthermore, using stress-context-dependent APEX2 proximity mapping in iPSC-derived neurons, we found that the interactions of TDP-43 with specific splicing factors (e.g., SRRM2) within membrane-less organelles were significantly altered. Integrated with single-nucleus RNA-seq, this approach identified NUFIP2 as an interactor with TDP-43 that promotes TDP-43 aggregation and HNRNPC as a TDP-43 splicing regulator that can be modulated to rescue TDP-43-mediated toxicity [157]. PL has also elucidated dynamic molecular shifts underlying ALS pathogenesis. In iPSC-derived neurons, APEX2 mapping revealed that STMN2, a protein critical for neuronal integrity, undergoes a disease-associated shift from the tubulin-bound to the membrane-associated state [158]. PL has also elucidated critical organelle communication defects in ALS. APEX2 mapping identified annexin A11 (ANXA11) as a key tether between RNA granules and lysosomes, a mechanism essential for RNA transport and degradation that is disrupted by ALS-linked *ANXA11* mutations [159].

In autism spectrum disorder (ASD), PL is systematically bridging genetic risk loci to convergent molecular pathways. TurboID in mouse neural progenitors revealed that *DDX3X* mutations cause variant-specific disruptions in RNA metabolism and DNA damage response, with severe mutations leading to neuronal death [160]. A BioID2-based interaction network covering 41 ASD risk genes revealed convergent disruptions in mitochondrial, Wnt, and MAPK signaling pathways, which correlate with clinical severity [161]. Another study using BioID2 identified Ankyrin-G as a major interactor of the deubiquitinase OTUD7A (Ovarian tumor domain-containing protein 7 A), thereby linking proteostasis dysregulation to impaired neuronal development [162]. PL also identified activity-dependent neuroprotective protein (ADNP) as an R-loop suppressor. Dysfunction of ADNP drives R-loop/CTCF accumulation and impairs neuronal differentiation, while zinc-finger/homeodomain proteins were nominated in the study as broader R-loop regulators [163].

Collectively, these studies highlight PL as a powerful tool to reveal early pathogenic events at high spatial and temporal resolutions, including protein mislocalization, RNA dysregulation, and organelle miscommunication.

Dissecting protein aggregation and proteostasis failure

A paramount strength of PL lies in the ability to resolve the composition and dynamics of pathogenic aggregates and dysfunctional organelles, which are hallmarks of neurodegenerative diseases. Innovative PL methods have been developed to specifically target these processes. AggID, a photo-induced proximity labeling and crosslinking approach, has selectively profiled intracellular aggregates, uncovering HSP70-mediated proteostasis networks and autophagy activation as a response to proteotoxic stress [164]. As mentioned, UltraID-LIPA has provided a temporal map of α-synuclein oligomerization [165], implicating endolysosomal and membrane-associated partners in the initial oligomerization events. Furthermore, the upsFP-tag (conjugating the ultra-photosensitized fluorescent protein chromophore to HaloTag) technology which leverages the radical-mediated labeling mechanism, enabled dynamic interactome profiling of TDP-43 during liquid-liquid phase separation, offering a new tool to study ALS [166]. The AggID and UltraID-LIPA techniques, with the ability to profile the earliest stages of aggregation, provide opportunities for very early therapeutic intervention.

PL is also critical for understanding the functional consequences of aggregation. DenseMAP has resolved SG-specific interactomes of m6A readers (YTHDF1/2) and nucleolar proteomes, highlighting the role of SUMOylation in maintaining nucleolar homeostasis [167]. BioID2 has mapped the interactome of C9orf72-derived dipeptide repeat proteins (DPRs), showing that polyGA aggregates sequester and impair the function of valosin-containing protein (VCP), a key regulator of autophagy, thereby driving neurodegeneration [168]. Similarly, split-APEX has revealed tau interaction with VCP during aggregation, linking impaired protein quality control to AD pathogenesis [169]. These studies move beyond cataloging aggregate constituents to reveal how sequestration disrupts cellular quality control systems.

Discovering disease-specific biomarkers

By defining in situ, disease-specific interactomes directly in human post-mortem tissues, PL provides a powerful and direct route for biomarker discovery. ProPPr (probe-dependent proximity profiling) applied to formalin-fixed paraffin-embedded (FFPE) tissues of four distinct tauopathies revealed unique tau-aggregate proteomes for each disease. VPS35 (vacuolar protein sorting-associated protein 35) and LAMP2 (lysosome-associated membrane glycoprotein 2) were identified as specific interactors in corticobasal degeneration (CBD). In addition, ferritin light chain (FTL)-positive microglia were revealed to be present in CBD astrocytic plaques. These results offer

potential diagnostic markers to differentiate between clinically overlapping tauopathies [170].

In synucleinopathies, BAR has been used to identify 261 proteins associated with Lewy bodies in human brains, with HBB (hemoglobin subunit beta) emerging as a key marker of vesicular and mitochondrial dysfunction in PD and dementia with Lewy bodies (DLB) [142]. A subsequent BAR study further differentiated PD/DLB from multiple system atrophy (MSA), identifying 79 PD/DLB-specific SNARE/vesicle proteins and three MSA-specific markers (CBR1, CRYAB, GFAP) linked to metabolic detoxification pathways [171]. These findings highlight the potential of PL to generate histopathology-defined molecular biomarkers that could improve diagnostic accuracy and stratify patients for targeted therapies.

Identifying novel therapeutic targets

By mapping disease-relevant protein networks with high precision, PL has accelerated the identification of novel, druggable targets for neurological disorders and brain cancers.

In AD, cell-type-specific PL in 5×FAD mice using the CIBOP system revealed mitochondrial and synaptic proteome dysfunction in parvalbumin interneurons (PV-INs) early in disease, nominating mTOR and related pathways as potential targets for early intervention [172].

In PD, TurboID revealed that the PD-associated protein PARK7/DJ-1 undergoes redox-sensitive nuclear translocation via modification at Cys106, implicating nuclear oxidative stress signaling as a potential therapeutic avenue [173]. Moreover, APEX2 mapping in dopaminergic neurons uncovered aberrant axonal localization of specific ion channels, suggesting new approaches to correcting neuronal excitability defects [174]. Similarly, APEX/BAR PL in iPSC-derived neurons demonstrated that progranulin deficiency disrupts lysosomal function via v-ATPase dysregulation, highlighting lysosomal pH modulation as a potential therapeutic strategy for frontotemporal dementia and other neurodegenerative disorders [175].

In glioblastoma (GBM), PL has been used to map oncogenic signaling networks with therapeutic implication. BioID2 revealed that epithelial membrane protein 3 (EMP3) sustains oncogenic EGFR signaling by interacting with the endocytic regulator TBC1D5 to block RAB7-mediated EGFR degradation, driving proliferation and therapy resistance [176]. This mechanism presents EMP3 and its interactions as a promising target to overcome kinase inhibitor resistance. Another study using red-light-activated photocatalytic PL spatially resolved the EGFR interactome within primary GBM tissues, uncovering tumor microenvironment-specific interactions that could be exploited therapeutically [177]. Furthermore, TurboID identified cortactin as a critical node linking ACP1 and AURKB in GBM invasion, where coordinated phosphorylation/dephosphorylation regulates tumor motility, suggesting dual kinase-phosphatase inhibition as a novel therapeutic approach [178].

Collectively, these advances underscore the capacity of PL not only to map disease-relevant networks at high resolution, but also to directly nominate tractable targets across a wide spectrum of neurological disorders.

Challenges and future perspectives

While PL has revolutionized molecular mapping in neuroscience, several inherent limitations must be acknowledged. A primary challenge is the spatial resolution of PL. The typical labeling radius (10–20 nm) captures a 'proximitome' of proteins that are merely near the bait, complicating the distinction between direct interactors and proximal neighbors. This necessitates orthogonal validation (e.g., Co-IP or surface plasmon resonance) to confirm direct physical interactions. Emerging methods are addressing this core limitation. For instance, SRPL (super-resolution proximity labeling) enhances specificity by minimizing background [179], while other frameworks leverage direct biotinylation site analysis to help distinguish direct binders from proximal neighbors [180]. Despite these advances, further innovation in spatial precision remains a critical future direction.

Other technical hurdles include confounding background signals from endogenous biotin or basal enzyme activity (e.g., TurboID), the substantial size of enzyme tags (~28–35 kDa) which may perturb the native function of bait proteins, and practical constraints for in vivo applications such as limited penetration and substrate delivery, and peroxide-associated toxicity (for APEX2). Furthermore, the analytical pipeline presents its own challenges; large-scale MS datasets demand robust statistical frameworks and meticulously designed controls (e.g., enzyme-alone, catalytically dead, mislocalized mutants) to reliably distinguish true interactors from background noise and establish principled significance thresholds.

These limitations, however, are powerful drivers of innovation. The future of PL lies in addressing these challenges through three interconnected avenues (Fig. 4).

(1) Precision engineering of next-generation labeling systems

Future progress in PL hinges on a concerted, multidisciplinary effort to engineer next-generation enzymes and labeling chemistries, aimed squarely at overcoming current limitations in specificity, efficiency, and

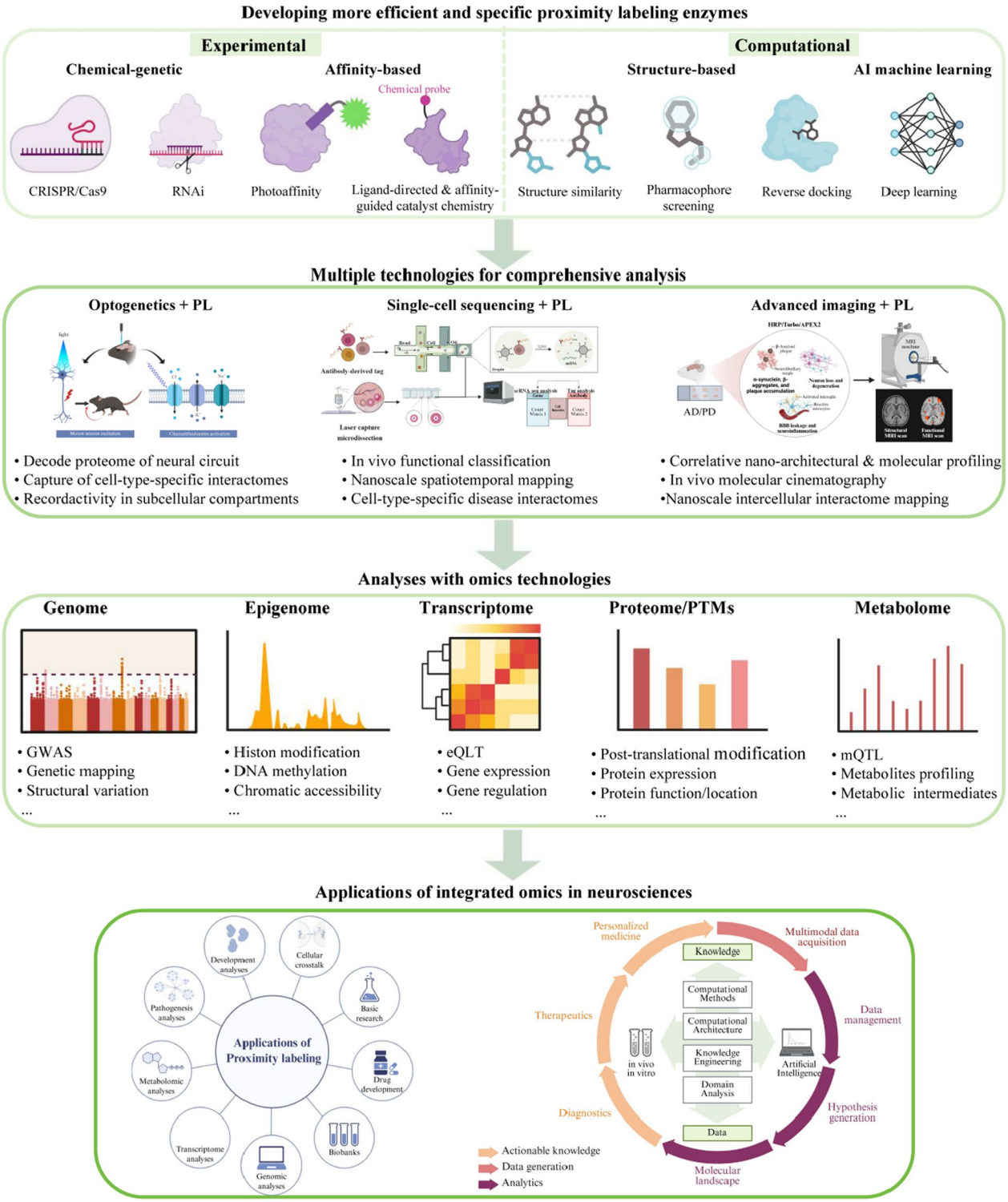


Fig. 4 Future directions of PL technologies. Advances in PL will rely on the development of highly efficient and specific enzymes, combined with integration into multi-modal frameworks including optogenetics, single-cell sequencing, advanced imaging, and multi-omics approaches (genomics, transcriptomics, proteomics, PTMs, metabolomics). These innovations will enable deeper investigation into developmental and pathological mechanisms, accelerate biomarker discovery and drug development, and support the integration of multimodal data for mapping comprehensive molecular landscapes in neuroscience. Created with BioRender.com

spatiotemporal control. By synergizing computational design (leveraging artificial intelligence and deep learning to predict enzyme mutants with enhanced properties), structural biology (enabling rational design based on enzyme-substrate complexes), and chemical biology (developing novel, membrane-permeant probes and photo-caged substrates), we anticipate the creation of a versatile toolkit of "designer" enzymes.

The key goals of this endeavor include development of smaller tags to minimize bait perturbation, orthogonal enzymes for simultaneous multi-compartment labeling, and conditionally activated enzymes controlled by light (optogenetics) or small molecules for exquisite spatiotemporal control. Concurrently, innovations of advanced probes and substrates will be crucial to enhance specificity, reduce background labeling, and ultimately enable the precise capture of transient, low-affinity, or organelle-specific interactions that are currently beyond reach.

(2) Deep integration with multi-omics and spatial technologies for systems-level interactomics

The full potential of PL will be realized through its deep integration with multi-omics technologies and cutting-edge spatial mapping techniques. This synergy is crucial to transition from static catalogs of interactions to a dynamic, systems-level understanding of molecular networks. For instance, combining cell-type-specific PL with single-cell sequencing can deconvolute the proteomic complexity of heterogeneous tissues like the brain, directly linking genetic variants from genome-wide association studies to local protein interaction networks within specific neuronal populations [181]. Furthermore, correlating PL data with spatial transcriptomics and advanced imaging (e.g., expansion microscopy, cryo-electron tomography) [31, 63] will enable the construction of "molecular cartographies"—comprehensive maps that define protein communities and their relationships within the native nano-architectural context. This integrated approach is pivotal for elucidating the spatial underpinnings of diseases like Alzheimer's and Parkinson's, where subtle alterations in local interactomes precede overt pathology.

A parallel and critical frontier is the progression toward single-cell PL proteomics. While bulk PL provides a population-averaged view, emerging methods are pushing the resolution to the single-cell level. Current approaches, such as combining PL with single-cell mass cytometry or carrier-based ultra-sensitive proteomics, are beginning to reveal cell-to-cell heterogeneity in protein proximity networks. The ultimate goal of true single-cell PL-proteomics, which integrates PL, cell sorting or cell capture, and nanoscale proteome analysis, will be indispensable for mapping interactome variations across individual cells within complex tissues. This resolution is crucial for dissecting rare cell types and transient cellular states in development and disease.

The realization of these technological advances, however, is critically limited by a parallel bioinformatic challenge: the current underrepresentation of PL-derived 'proximitomes' in canonical protein interaction databases (e.g., STRING, BioGRID and IntAct). This gap stems from the fundamental distinction between 'proximity' and 'direct interaction', a lack of standardized data formats, and the highly context-dependent nature of PL results. To bridge this divide, a community-driven initiative is essential to create specialized databases or modules that curate PL data as a distinct class of evidence, tagged with rich experimental metadata (e.g., bait, cell type, condition). Establishing such a standardized framework will allow researchers to contextualize new findings, validate PL data against known complexes, and construct unified networks that integrate physical, genetic, and spatial interaction evidence. This bioinformatic integration is the keystone that will transform PL from a powerful discovery tool into a foundational, systems-level resource for biology.

(3) Toward functional and dynamic analysis in living organisms

The ultimate frontier for PL is to evolve from providing static molecular snapshots to recording the real-time dynamics of proteome organization and function within living organisms. Achieving this goal necessitates the integration of PL with technologies that provide direct functional readouts. For instance, combining optogenetics with PL can capture activity-dependent interactome remodeling in stimulated neurons, while coupling PL with metabolic tracing can reveal how metabolic fluxes reshape local protein environments. The development of robust, non-perturbative in vivo PL methods will further enable researchers to track cell-cell communication and the modulation of intercellular interactions in disease models over time. This integrated direction moves beyond merely cataloging "who is there" to understanding "what they are doing" in a physiological context, directly linking molecular proximity to biological function and paving the way for discovering novel functional biomarkers and therapeutic targets.

A central challenge in this endeavor is the functional interpretation of PL-generated candidate lists, specifically the distinction of biologically meaningful interactions from incidental proximity within the labeled 'proximitome'. Moving from a candidate list to validated biology

requires a hierarchical, multi-layered validation strategy. This process begins with bioinformatic triage, where candidates are prioritized using enrichment scores, correlation with public datasets, and pathway analysis. The ensuing biochemical validation phase employs orthogonal methods like Co-IP to confirm direct or stable physical associations for high-confidence candidates.

Underpinning this entire validation roadmap is a rigorous analytical pipeline for data analysis and hit prioritization. The proteomic output of a PL experiment—often encompassing hundreds to thousands of candidates—demands a systematic, multi-layered workflow to distinguish high-confidence proximal proteins from background. This process begins with foundational statistical rigor, involving robust pre-processing, normalization against critical negative controls (e.g., catalytically dead enzymes), and differential abundance analysis to generate a primary list of significantly enriched proteins. Subsequently, an advanced prioritization phase is implemented to overcome common proteomic biases and distinguish biologically meaningful interactions. This includes applying abundance-corrected scoring systems (e.g., SAINT score) to effectively deprioritize ubiquitous proteins like tubulin; filtering candidates based on subcellular context and cross-referencing with external databases to enhance biological plausibility; and conducting functional enrichment analysis to shift focus from individual hits to coherent biological pathways. This comprehensive bioinformatic workflow generates a tractable shortlist of high-confidence candidates, creating a direct bridge to the downstream experimental validation cascade and ensuring a solid foundation for subsequent functional studies.

To definitively establish functional relevance, a suite of cell-based and in vivo assays is paramount. This begins with visually confirming and quantifying the putative interaction in situ using techniques such as proximity ligation assay, fluorescence resonance energy transfer, or bioluminescence resonance energy transfer, complemented by high-resolution microscopy to verify co-localization within the same subcellular compartment. Beyond mere proximity, the functional consequence of the interaction must be assessed through direct perturbation, for instance, using siRNA or CRISPR knockout of the candidate protein, to measure the impact on the localization, stability, or downstream phenotypic outputs of the bait protein. Ultimately, the gold standard for validation is demonstrating the physiological relevance of the interaction within the complex milieu of a living model organism, thereby bridging molecular proximity to tangible biological function.

As these technological and analytical frameworks mature, PL will be uniquely positioned to bridge fundamental neurobiology and clinical translation, transforming spatial hypotheses into mechanistically grounded insights and enabling precision-medicine strategies for neurological diseases.

Conclusion

PL has become a cornerstone methodology in neuroscience, enabling high-resolution mapping of molecular architecture within specialized neural microdomains, including synaptic clefts, postsynaptic densities, and organelle contact sites. By capturing transient, low-affinity, and spatially confined interactions under near-physiological conditions, PL has revealed previously inaccessible protein networks and time-resolved interactomes, yielding critical insights into normal circuit function and the pathogenesis of neurological disease.

Future promising directions lie in addressing persistent challenges through deep integration. Coupling PL with spatial transcriptomics, single-cell proteomics, and advanced imaging will enable the construction of comprehensive molecular atlases. Furthermore, applying PL directly to human tissues and clinically annotated cohorts holds the potential to yield in situ biomarkers and nominate druggable targets. In sum, by seamlessly bridging fundamental neurobiology and clinical translation, PL is poised to serve as a foundational pillar for precision neurology, advancing our understanding of the nervous system and accelerating development of targeted diagnostics and treatments for a broad spectrum of neurodegenerative and neuropsychiatric disorders.

Abbreviations

AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
APEX	Ascorbate peroxidase
ASD	Autistic spectrum disorder
BAR	Biotinylation by antibody recognition
CNS	Central nervous system
ER	Endoplasmic reticulum
FTLD	Frontotemporal lobar degeneration
GBM	Glioblastoma
LD	Lipid droplet
MS	Mass spectrometry
PD	Parkinson's disease
PL	Proximity label
POI	Protein of interest
PPI	Protein-protein interaction
PTMs	Post-translational modifications
RBP	RNA-binding protein
SG	Stress granules

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Author contributions

X.G. conceptualized and designed the review, drafted and revised the manuscript. J.L. and P.C. conducted the literature collection and classification. Data sorting was performed by X.W, L.Z. and Y.S. Manuscript review and editing

were done by H.S. and Q.Y. All authors have read and approved the final manuscript.

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Declarations

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