靶向蛋白降解技术调控蛋白稳态的药学机制及其在疾病治疗中的应用

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摘要: 蛋白质稳态 (proteostasis) 是细胞维持正常功能的核心机制, 其本质在于协调蛋白质的合成、折叠、转运与降解的动态平衡。当稳态失衡时, 错误折叠蛋白积累与功能蛋白的缺失将触发病理级联反应, 成为跨疾病谱系的共性病理特征。传统药物开发主要聚焦于抑制致病蛋白的功能, 但大量蛋白因缺乏明确结合位点或功能冗余而难以成药。目前, 靶向蛋白降解技术 (targeted protein degradation, TPD) 的兴起为传统难治性靶点提供了新的干预策略。本文将从蛋白质降解技术分类、分子机制及疾病应用入手, 系统解析 TPD 如何通过重塑蛋白质稳态网络突破“不可成药”瓶颈, 并展望其临床转化前景, 为攻克复杂疾病提供新的治疗方法及理论依据。

关键词: 蛋白质稳态; 靶向蛋白降解技术; 疾病治疗; 药学机制; 泛素−蛋白酶体系统

中图分类号: R914 **文献标识码**: A **文章编号**: 0513-4870(2026)01-0122-13

Pharmaceutical mechanism of targeted protein degradation technology regulating protein homeostasis and its application in disease treatment

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Abstract: Proteostasis is the fundamental process by which cells maintain their normal functions. It involves maintaining the dynamic equilibrium of protein synthesis, folding, transport, and degradation. Disruption of proteostasis leads to the accumulation of misfolded proteins and a deficiency of functional proteins, triggering a pathological cascade—a hallmark of various diseases. Traditional drug development primarily focuses on inhibiting the activity of disease-causing proteins. However, many proteins are considered "undruggable" due to the absence of well-defined binding sites or functional redundancy. Recently, the targeted protein degradation (TPD) has provided a novel therapeutic strategy for traditionally undruggable targets. In this review, we systematically analyze how TPD overcomes the limitations of undruggable targets by remodeling the proteostatic network, covering the classification of protein degradation technologies, molecular mechanisms, and disease applications. Furthermore, we explore the clinical translation potential of TPD technologies, providing novel therapeutic strategies and theoretical frameworks for complex diseases.

Key words: proteostasis; targeted protein degradation; disease treatment; pharmacological mechanism; ubiquitin-proteasome system

收稿日期: 2025-05-31; 修回日期: 2025-08-05.

基金项目: 国家自然科学基金资助项目 (82460765); 陕西省教育厅一般项目 (24JK0730); 陕西省科学技术协会青年人才托举计划项目 (20250351); 延安大学博士科研启动项目 (YDBK2023-75); 陕西省大学生创新创业训练项目 (S202410719175).

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DOI: 10.16438/j.0513-4870.2025-0621

蛋白质稳态作为细胞功能的核心调控机制, 其本质是通过协调蛋白质合成、折叠、转运与降解的动态平衡来维持细胞稳态[1]。在蛋白质合成过程中, 新生成的多肽链于核糖体完成初步组装后, 需经历翻译后修饰以确保其正确折叠并实现生物学功能[2]。此阶段分子伴侣通过ATP水解驱动的构象调整机制, 辅助新生肽链完成空间结构重塑。与此同时, 泛素–蛋白酶体系统 (ubiquitin-proteasome system, UPS) 和自噬–溶酶体途径 (autophagy-lysosomal pathway, ALP) 构成双重质量控制网络, 前者通过泛素化标记选择性降解异常蛋白, 后者借助自噬体包裹清除蛋白聚集体, 二者共同维系蛋白质组的完整性与功能活性[3]。当蛋白质稳态被打破时, 错误折叠蛋白的蓄积与功能蛋白的缺失将引发病理级联反应。例如, 阿尔茨海默病 (Alzheimer's disease, AD) 的特征性病理改变包括β-淀粉样蛋白 (amyloid-beta, Aβ) 异常沉积形成老年斑和Tau蛋白过度磷酸化导致的神经纤维缠结[4]。在肿瘤发生过程中, 致癌蛋白通过异常稳定化持续激活促癌信号通路, 这种蛋白稳态失衡同样见于代谢综合征等多种病理状态[5]。重要的是, 蛋白质稳态失调已超越单一疾病范畴, 成为横跨神经退行性疾病、恶性肿瘤及代谢性疾病的共性病理特征, 已成为疾病治疗和药物开发的热点。传统药物研发模式主要聚焦于抑制致病蛋白的功能, 但大量蛋白因缺乏明确结合位点或功能冗余而难以成药, 被称为“不可成药”靶点[6]。然而, 靶向蛋白降解技术 (targeted protein degradation, TPD) 的兴起, 为传统难治性靶点提供新的干预策略。随着蛋白水解靶向嵌合体、自噬靶向嵌合体等技术的迭代发展, TPD正在重塑药物研发格局, 为癌症、神经退行性疾病及代谢相关疾病开辟新的治疗路径[7-9]。本文将从技术分类、分子机制及临床转化3个层面, 系统解析TPD重塑蛋白网络的核心原理, 探讨其在攻克传统“不可成药”靶点中的实践价值, 为创新药物研发提供理论支撑的同时, 也有望为癌症、神经退行性疾病和自身免疫性疾病等多种疾病的治疗提供新的治疗策略。

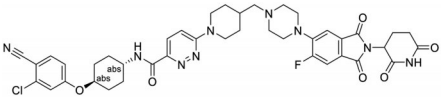
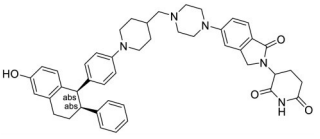
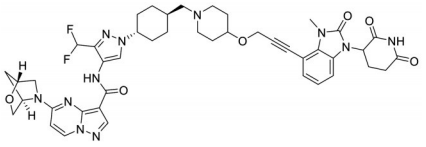
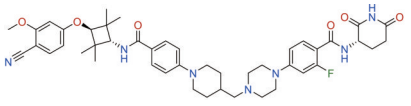
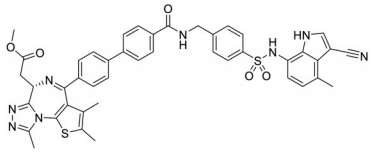
1 靶向蛋白降解技术

1.1 泛素–蛋白酶体系介导的降解

1.1.1 蛋白水解靶向嵌合体 蛋白水解靶向嵌合体 (proteolysis-targeting chimeras, PROTACs) 最早由Sakamoto等[10]于2001年提出并验证。PROTACs作为TPD的核心, 把目标蛋白质和细胞内的“垃圾处理系统”(UPS) 连接起来, 让细胞自己降解目标蛋白, 实现对疾病相关蛋白的精准调控[11]。具体而言, PROTACs是一种双功能分子, 由靶蛋白结合域 (target binding moiety, TBM)、E3泛素连接酶结合域 (E3 ligase binding moiety, EBM) 以及连接两者的化学连接子 (linker) 3个关键部分共同构成[12]。在作用过程中, TBM通过小分子抑制剂或抗体片段特异性识别靶蛋白表面位点, 经结构优化后选择性募集E3泛素连接酶, 最终形成三元复合物。该复合物借助UPS引导靶蛋白被26S蛋白酶体识别并降解, 从而完成对致病蛋白的清除[13,14]。相较于传统占据驱动型抑制剂, PROTACs的催化特性使得在亚化学计量浓度下即可实现持续疗效, 同时降解整个靶蛋白而非单纯抑制活性, 有效规避了因靶蛋白突变导致的耐药性问题[15,16]。在临床应用方面, PROTACs技术已开辟出多条研发管线, 应用范围涉及肿瘤、自身免疫疾病等领域, 聚焦于雄激素受体以及白细胞介素-1受体相关激酶4 (interleukin-1 receptor associated kinase 4, IRAK4) 等核心靶点的降解。例如, 针对前列腺癌的ARV-110、ARV-766处于I/II期临床阶段; 针对乳腺癌的ARV-471已进入临床III期试验; 针对特应性皮炎的KT-474处于II期临床; 针对实体瘤的DT-2216处于I/II期临床, 初步验证了该技术的治疗潜力[17,18]。此外, PROTACs在神经退行性疾病领域也取得了突破性进展, Tau蛋白降解策略为阿尔茨海默病等疾病的干预开辟了新路径[19]。随着PROTACs技术的不断成熟, 其有望通过降解“不可成药”靶点, 重塑药物开发范式 (表1[17,18,20-43], 图1)。

1.1.2 分子胶 分子胶概念最早由Van Duyne等[44]于1991年提出。时隔近20年后, Ito等[45]首次揭示了其在靶向蛋白降解领域的新机制。作为一类新兴的小分子化合物, 其核心作用机制在于诱导或增强蛋白质–蛋白质之间的相互作用[46]。这类化合物可特异性的将靶蛋白与E3泛素连接酶桥接, 形成稳定的三元复合物, 触发靶蛋白的泛素化修饰过程, 最终通过蛋白酶体降解途径实现靶蛋白清除[47]。据统计, 约85%的蛋白质缺乏可成药性结构域或存在空间位阻效应[48]。针对这一难题, 分子胶技术为攻克“不可成药”靶点开辟了新的途径, 其通过重构蛋白质相互作用界面, 突破了传统占位驱动型抑制剂的局限[49]。传统药物的作用模式就像用药把蛋白锁住使其罢工, 但蛋白还留在细胞中, 其仍可能挣脱后继续发挥不良作用。与传统抑制剂不同的是, 分子胶不仅能强化天然存在的蛋白质相互作用, 还可恢复突变导致的功能缺失[50]。以沙利度胺及其衍生物为例, 分子胶通过诱导脑蛋白 (cereblon, CRBN) E3连接酶与特定转录因子Ikaros家族锌指蛋白1 (ikaros family zinc finger protein 1, IKZF1) 和Ikaros家族锌指蛋白3 (ikaros family zinc finger protein 3, IKZF3) 之间的相互作用, 实现靶蛋白的蛋白酶体降解, 在治疗多发性骨髓瘤 (multiple myeloma, MM) 中展现出显著

Table 1 Core principles and current research status of targeted protein degradation (TPD) technologies. UPS: Ubiquitin-proteasome system; IBG: Intramolecular bivalent glutarate; BET: Bromodomain and extraterminal domain; TRIM: Tripartite motif; EGFP: Enhanced green fluorescent protein; TAC: Targeting activated chimeras; RNase: Ribonuclease; MYC: Myelocytomatosis cellular oncogene; JUN: V-jun avian sarcoma virus 17 oncogene homolog; PROTAC: Proteolysis-targeting chimeras; AR: Androgen receptor; DBD: DNA-binding domain; ARTC: Androgen receptor targeting chimera; BTK: Bruton's tyrosine kinase; CI: Cation independent; EGFR: Epidermal growth factor receptor; ATTEC: Autophagosome tethering compound; LD: Lipid droplets; PD: Programmed death; DUBTAC: Deubiquitinase-targeting chimera; DUB: Deubiquitinating enzyme; CFTR: Cystic fibrosis transmembrane conductance regulator; TAG: Triacylglycerol

E3 ligase-dependent/ independent manner	Technology	Key mechanism	Research progress/example	Ref.
E3 ligase-dependent manner	PROTACs	Ubiquitinating the target protein by spacially linking the E3 ligase to the target protein and directing it to UPS degradation	ARV-110 (prostate cancer; breast cancer; phase II clinical study)  ARV-110  ARV-471  KT-474  ARV-766	[17,20, 21]
	Molecular glues	Mediating protein-protein interactions and inducing either the degradation or stabilization of target protein	Thalidomide analogs have been approved for the treatment of hematological tumors; Monte rosa is collaborating with Novartis to develop molecular glue degraders	[22]
	IBG	Simultaneously engaging and connecting two adjacent domains of the target protein in cis to enhance surface complementarity with E3 ligases for productive ubiquitination and degradation	 IBG1 (BET protein degradation and cancer cell killing)	[18,23]
	TRIM-Away	Recruiting antibody-bound target proteins for degradation by the proteasome	*α*EGFP TRIMbody (specifically degrading intracellular EGFP in HEK293T)	[24-26]
	TransTAC	Driving rapid co-internalization of a target protein of interest and TfR1 from the cell surface, and enabling target protein entry into the lysosomal degradation pathway	Diversing membrane proteins; lung cancer	[27-29]
	RIBOTAC	Recruiting and locally activating RNase L	MYC-RIBOTAC (breast cancer), JUN-RIBOTAC (pancreatic tumour cell)	[30,31]
	Ab-PROTAC	Directing protein degradation specifically in HER2+ cells	Selective degradation of BRD4 in breast cancer cells	[32]
	Peptide-PROTAC	Recruitmenting of MDM2 induces AR and AR-V7 degradation by targeting the DNA-binding domain (DBD) of the androgen receptor (AR)	dsARTC (prostate cancer)	[33-35]
	Trivalent PROTAC	Trivalent ligand design (target protein + E3 ligase + co-binding domain)	Efficient degradation of BTK (DC50 < 1 n mol·L^{-1})	[36]

Continued

E3 ligase-dependent/ independent manner	Technology	Key mechanism	Research progress/example	Ref.
	BIOPROTAC	Bifunctional small molecules induce recombination of natural E3 ligase complexes	Degradation of IKZF1/3; treatment of multiple myeloma	[37]
E3 independent degradation technology	LYTAC	Bifunctional molecules bind target proteins to lysosomal receptors (CI-M6PR) for degradation via the endocytosis-lysosomal pathway	The Bertozzi team developed LYTAC to degrade EGFR	[23]
	AUTAC	Bifunctional molecules bind target proteins to autophagic tags and induce lysosomal degradation after autophagosome encapsulation	Second-generation AUTAC degrades FKBP12 with 100-fold higher efficiency; Rube Ocarina's team develops polyQ·ATTECs	[38]
	ATTEC	Bifunctional molecules bind target proteins to LC3, a key autophagy protein, and induce lysosomal degradation after autophagosome encapsulation	LD-ATTEC degrades lipid droplets to improve obesity; LLC355 degrades DDR1 to inhibit tumour migration	[39]
	AbTAC	Antibodies bind to target proteins and then mediate endocytosis to lysosomal degradation *via* cell surface receptors (e.g. CI-M6PR)	SignalTAC platform incorporates lysosomal sorting signals; degrades HER2; 3-fold increase in efficiency	[40]
	GlueTAC	Modification of nanobodies to introduce unnatural amino acids, form covalent binding to enhance endocytosis stability, and couple cell-penetrating peptides with lysosomal sorting sequences	Degradation of PD-L1; enhancing tumour immunotherapy	[41]
	DUBTAC	Deubiquitinase (DUB) recruits chimeras and stabilises target proteins	Stabilisation of CFTR ΔF508 mutant restores cystic fibrosis protein function	[42]
	AceTAG	Acetylation tag-mediated degradation system	Tau protein degradation using acetyltransferase to tag target proteins	[43]

疗效[51]。除了促进蛋白质降解外, 分子胶还参与调节蛋白质功能。特定分子胶能够稳定丙酮酸激酶 (pyruvate kinase isozyme type M2, PKM2) 四聚体构象, 增强其代谢酶活性, 为癌症代谢重编程的干预提供了新的思路[52] (表 1, 图 1)。

1.2 溶酶体途径

1.2.1 溶酶体途径嵌合体 溶酶体途径嵌合体 (lysosome-targeting chimera, LYTAC) 是一种基于溶酶体降解机制开发的新型 TPD, 通过内吞–溶酶体途径介导细胞外及膜蛋白的降解[53]。其核心结构由两个功能域构成, 一是特异性靶向目标蛋白的抗体或小分子配体; 二是与溶酶体靶向受体的配体, 二者通过 linker 共价连接。LYTAC 与目标蛋白结合后, 形成的复合物被细胞膜内吞, 并在溶酶体靶向受体的引导下转运至溶酶体进行降解[54]。相较于传统蛋白酶体途径仅能降解胞内蛋白的局限, LYTAC 无需依赖 E3 泛素连接酶, 可降解细胞外蛋白、膜蛋白以及蛋白聚集体等传统方法难以干预的靶点[55]。Ahn 等[23]基于 LYTAC 通过将抗表皮生长因子受体 (epidermal growth factor receptor, EGFR) 抗体与阳离子依赖性甘露糖-6-磷酸受体 (cation-independent mannose-6-phosphate receptor, CI-M6PR) 配体进行偶联, 成功实现了对 EGFR 的溶酶体降解。与此同时, Luo 等[56]利用葡萄糖转运蛋白 (glucose transporter 1, Glut1) 作为溶酶体靶向受体, 将 Glut1 配体与程序性死亡配体 1 (programmed cell death ligand 1, PD-L1) 抗体进行偶联, 成功实现了对膜蛋白 PD-L1 的靶向降解。这些研究验证了 LYTAC 技术在扩展蛋白降解靶点范围方面具有显著优势 (表 1, 图 1)。

1.2.2 自噬靶向嵌合体 自噬靶向嵌合体 (autophagy-targeting chimera, AUTAC) 作为一种基于 ALP 的前沿 TPD, 在蛋白降解领域具有重要意义[57]。其核心作用机制在于诱导自噬体对目标蛋白进行选择性包裹并转运至溶酶体实现降解[58]。AUTAC 由特异性结合目标蛋白的配体与模拟 *S*-鸟苷化 (*S*-guanylation) 的降解标签这两大关键部分构成, 其中降解标签通过介导目标蛋白的赖氨酸 63 位点 (lysine 63, K63) 多聚泛素化修饰发挥关键作用。经 K63 位点多聚泛素化修饰的靶蛋白被自噬受体 SQSTM1/p62 特异性识别, 进而募集至自噬体膜结构, 最终在溶酶体腔内完成降解过程[24]。相较于依赖 E3 泛素连接酶的 PROTAC 技术, AUTAC 具有显著的技术优势。其作用机制不依赖 E3 连接酶系统, 突破了传统降解技术对胞内蛋白酶体途径的依赖,

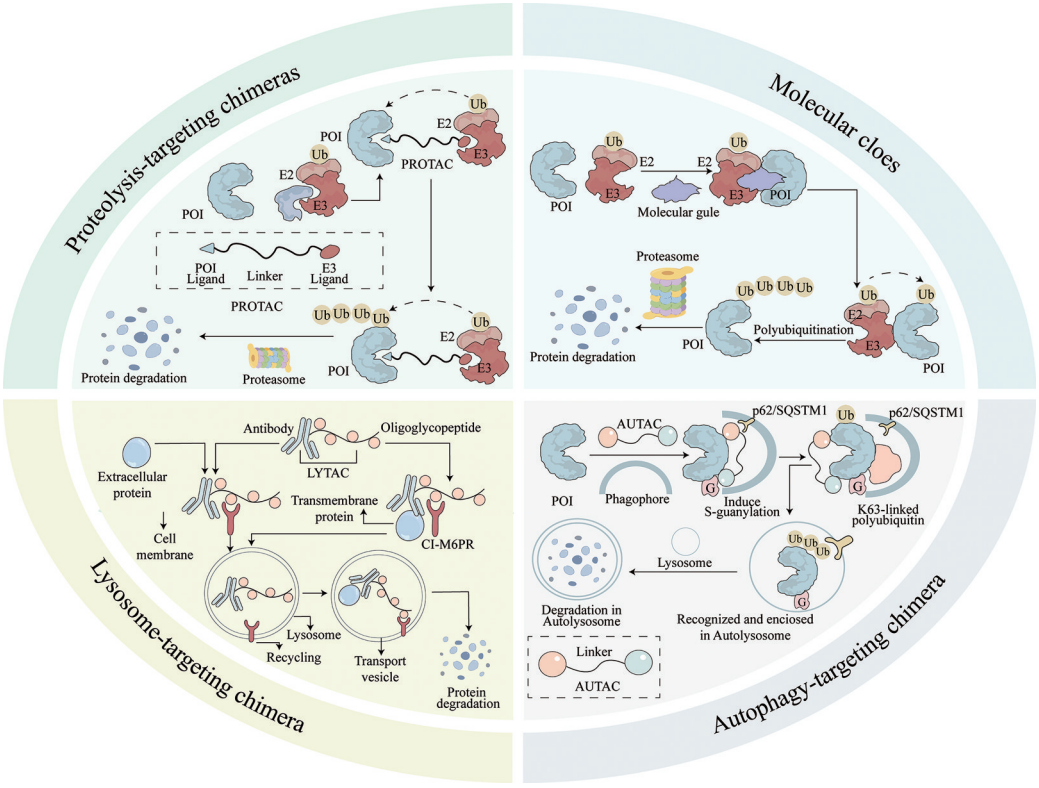


Figure 1 The classifications and mechanisms of targeted protein degradation (TPD) technology. POI: Proteins of interest; Ub: Ubiquitin; LYTAC: Lysosome-targeting chimera; AUTAC: Autophagy-targeting chimera; SQSTM1/p62: Sequestosome 1; E2: E2 ubiquitin conjugating enzyme; E3: E3 ubiquitin ligase

可靶向降解非酶蛋白、转录因子等, 且在降解过程中自噬受体SQSTM1/p62直接募集目标蛋白, 可实现对线粒体的选择性降解[59]。在靶向蛋白降解应用方面, AUTAC适用性广泛, 可降解多种致病蛋白及细胞器。例如, 鲁伯埙团队[25]开发的亨廷顿蛋白降解靶向嵌合体, 能特异性识别亨廷顿蛋白的延展多聚谷氨酰胺链, 实现突变蛋白的降解。该技术在肿瘤治疗领域同样取得突破, 成功降解了溴结构域蛋白4 (bromodomain-containing rrotein 4, BRD4) 等致癌蛋白, 并在代谢相关疾病模型中有效降低烟酰胺磷酸核糖转移酶 (nicotinamide phosphoribosyltransferase, NAMPT) 水平[60,61]。AUTAC有望克服当前蛋白降解技术局限, 为多种疾病的治疗干预开辟新途径 (表1, 图1)。

1.3 其他

自噬体连接化合物技术 (autophagosome-tethering compounds, ATTEC) 基于细胞ALP, 通过设计双功能分子实现靶标蛋白与微管相关蛋白1A/1B轻链3 (microtubule-associated protein 1A/1B light chain 3, LC3) 的桥接, 进而触发自噬体对病理蛋白的包裹及向溶酶体的转运降解[62]。该技术突破了传统PROTAC技术对UPS的路径依赖, 拓展可干预靶标范围, 尤其适用于脂滴 (lipid droplets, LD) 等非蛋白类生物大分子的靶向清除。另外, 在肥胖小鼠模型中, LD-ATTEC通过疏水相互作用特异性识别LD, 诱导其自噬降解而不影响细胞膜脂质, 且表现出良好的血脑屏障渗透性, 为其在神经系统相关疾病中的应用提供了可能[63]。值得一提的是, 分子内二价胶 (intramolecular bivalent glue, IBG) 作为新兴靶向降解技术, 通过双功能分子顺式结合靶蛋白相邻的两个结构域, 诱导构象改变以增强与E3泛素连接酶的相互作用, 从而实现高效靶向蛋白降解[18]。AbTAC技术则融合抗体的高选择性与溶酶体降解机制, 通过抗体与靶蛋白结合后, 利用细胞表面受体CI-M6PR介导内吞过程, 将复合物运输至溶酶体进行降解[64]。TRIM-Away技术利用细胞内源性E3泛素连接酶TRIM21与抗体Fc段的特异性结合, 通过泛素化标记抗体−靶蛋白复合物, 直接诱导蛋白酶体降解[65]。该技术无需基因修饰, 可在数分钟内清除天然蛋白质, 尤其适用于长寿蛋白或转录后修饰蛋白的快速敲低[32]。例如, 在卵母细胞研究中, 通过电转导入特异性抗体即可实现目标蛋白的极速降解, 为发育生物学研究提供了新思路[66]。其他新兴技术如GlueTAC通过改造纳米抗体引入非天然氨基酸, 形成与靶蛋白的共价结合, 增强内吞稳定性, 并耦联细胞穿膜肽与溶酶体分选序列, 实现膜蛋白的高效降解[67] (表1)。

2 蛋白质稳态在疾病治疗中的作用机制

2.1 神经退行性疾病

2.1.1 阿尔茨海默病 在AD的病理进程中, 蛋白质稳态失衡作为核心致病机制, 其与年龄增长及遗传易感因素密切相关[68]。随着机体衰老, 细胞内蛋白质质量控制系统的多层级防御功能逐渐衰退, 导致Aβ和Tau蛋白等关键蛋白发生异常折叠与聚集, 形成具有神经毒性的寡聚体及纤维化沉积物[69]。近期研究揭示[70], 由纤维蛋白原 (fibrillarin, FIB-1) 与核仁蛋白56 (nucleolar protein 56, NOL-56) 组成的核仁复合物FIB-1-NOL-56在维持蛋白质稳态中发挥关键调控作用。该复合物通过调节转化生长因子-β (transforming growth factor-beta, TGF-β) 通路, 参与细胞内蛋白折叠、降解及分泌等过程。抑制FIB-1-NOL-56活性可显著降低Aβ肽及异常Tau蛋白的毒性作用, 在增强UPS对错误折叠蛋白的识别与降解的同时, 还能提高自噬–溶酶体途径对蛋白聚集体的清除能力。针对靶向雄激素受体的PROTAC药物ARV-713通过脂质纳米颗粒包裹可实现肝靶向递送, 提示AD治疗需开发脑组织特异性递送系统, 如受体介导的转胞吞作用或外泌体载体[71]。未来, 基于PROTAC药物的精准干预策略, 有望突破AD治疗瓶颈 (表2)[70,72-79]。

2.1.2 帕金森病 帕金森病 (Parkinson's disease, PD) 作为典型的神经退行性疾病, 其核心病理机制源于α-突触核蛋白 (α-synuclein, α-syn) 异常聚集引发的蛋白质稳态失衡。在生理状态下, α-syn以可溶性单体形式参与突触前膜神经递质释放调控及DNA损伤修复过程[73]。目前, Gain Therapeutics开发的口服变构蛋白调节剂GT-02287可穿越血脑屏障 (blood-brain barrier, BBB), 通过恢复溶酶体蛋白酶、葡萄糖苷酶功能而减少α-syn聚集, 具有改善PD患者的运动及认知功能的作用[80]。这种机制与传统的靶向蛋白降解技术不同, 其核心价值在于修复功能受损的酶, 而非清除异常蛋白。因此, 纠正蛋白稳态失衡, 致力于靶向蛋白技术的药物研发, 可为PD的治疗提供新思路 (表2)。

2.2 免疫系统类疾病

2.2.1 类风湿性关节炎 在类风湿关节炎的发病进程中, 滑膜成纤维细胞 (fibroblast-like synoviocytes, FLS) 异常增殖与骨侵蚀作为核心病理环节, 由蛋白质折叠失衡和UPS失调共同驱动[81,82]。具体而言, 人类白细胞抗原-DRβ1基因 (human leukocyte antigen-DRβ1, HLA-DRβ1) 突变导致抗原呈递细胞 (antigen-presenting cell, APC) 对瓜氨酸化蛋白的识别障碍, 进而错误呈递自身抗原并过度激活$CD4^+$ T细胞, 破坏辅助性T细胞17 (T helper17 cell, Th17)/调节性T细胞 (T regulatory cell, Treg) 免疫平衡[83]。同时FLS内持续的内质网应激使未折叠蛋白反应 (unfolded protein response, UPR) 失效, 转而激活促生存信号以抵抗凋亡[84]。针对上述机制, TPD通过多途径协同干预。在纠正免疫失衡方面, CRBN降解剂 (来那度胺衍生物) 通过降解转录因子IKZF1/3, 抑制FLS中丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK)/核因子-κB (nuclear factor-κB, NF-κB) 信号传导, 进而下调基质金属蛋白酶-1/3/9及炎症因子如白细胞介素-6 (interleukin-6, IL-6)、肿瘤坏死因子 (tumor necrosis factor-α, TNF-α) 的表达, 减轻滑膜侵袭[85]。此外, BTK-PROTAC与IRAK4-PROTAC分别靶向降解B细胞关键信号蛋白及巨噬细胞炎症复合体核心组分, 协同阻断致病性自身抗体产

Table 2 Mechanisms and applications of protein homeostasis in neurological and immune system diseases. FIB: Fibrillarin; NOL: Nucleolar protein; TGF: Transofrming growth factor; NF: Nuclear factor; TNF: Tumor necrosis factor; IL: Interleukin; JAK: Janus kinase; STAT: Signal transducer and activator; SYK: Spleen yrosine kinase; AAG: Allylamino geldanamycin

Disease type	Mechanism of protein homeostasis imbalance	Related drug	Target/pathway	Ref.
Alzheimer's disease	Abnormal function of the nucleolar complex FIB-1-NOL-56; abnormal aggregation of tau protein	Nucleolar complex inhibitors	TGF-β signaling transduction; protein folding and degradation	[70]
	Autophagy dysfunction; proteasome dysfunction; abnormal aggregation of tau protein	Bafilomycin-A (BafA1), MG-132, PD150606	NF-κB signaling pathway; ubiquitin-proteasome system	[72]
Parkinson's disease	Abnormal aggregation of α-syn; abnormalities in the UPS	Ubiquitin-proteasome activators	Ubiquitin-proteasome system; mitochondrial autophagy pathway	[73-75]
Rheumatoid arthritis	Release of TNF-α and IL-6 exacerbates immune attacks	Anti-TNF-α monoclonal antibodies	IL-6/JAK-STAT signaling pathway	[76,77]
Systemic lupus erythematosus	BTK-dependent B-cell activation leads to increased secretion of autoantibodies; proteasome-mediated NF-κB activation promotes the transcription of inflammatory factors; excessive activation of SYK kinase exacerbates inflammation and autoantibody production	BTK inhibitors, SYK inhibitors, immunoproteasome regulators	JAK-STAT pathway; BTK protein; immunoproteasome	[78]
Non-alcoholic fatty liver disease	Prefolded albumin forms albumin bodies in the cytoplasm, capturing prefolded CPT2 and leading to mitochondrial homeostasis imbalance	17-AAG (Hsp90 inhibitor)	Hsp90-albumin body axis	[79]

生并有效恢复Th17/Treg平衡[86]。再者, 靶向肿瘤坏死因子受体相关因子6 (tumor necrosis factor receptor-associated factor 6, TRAF6)/IκB激酶 (IκB kinase, IKK)的PROTAC可阻断E3连接酶TRAF6介导的K63泛素化链异常激活, 可有效抑制NF-κB核转位以及下游炎症反应[83]。值得注意的是, 新型TNF-α-PROTAC利用肿瘤抑制蛋白VHL介导的胞外蛋白降解, 使滑膜液中TNF-α水平降低超过80%, 从而有效阻断M1型巨噬细胞极化, 取得优于传统单抗疗法的治疗效果[87] (表2)。

2.2.2 系统性红斑狼疮 系统性红斑狼疮 (systemic lupus erythematosus, SLE) 的蛋白质稳态失衡表现为免疫复合物沉积与自身抗体过量产生。患者B细胞异常活化导致抗核抗体及抗双链DNA抗体过量分泌, 形成的免疫复合物沉积于肾小球基底膜, 通过激活补体释放补体过敏毒素3a (complement anaphylatoxin 3a, C3a)及补体过敏毒素5a (complement anaphylatoxin 5a, C5a)等炎症介质, 诱发局部炎症反应[88]。同时, 患者外周血单核细胞中自噬−溶酶体系统功能障碍可导致自噬流受阻, 造成损伤线粒体积累及线粒体DNA泄漏至胞质, 进而异常激活2′,3′-环鸟苷酸−腺苷酸 (2′,3′-cyclic GMP-AMP, 2′,3′-cGAMP)环状合成酶−干扰素基因刺激因子, 促使I型干扰素 (type I interferon, IFN-I)大量分泌并形成正反馈循环[89]。在临床上, 羟氯喹 (自噬调节剂) 碱化溶酶体pH值以抑制自噬体−溶酶体融合, 减少核苷酸结合寡聚结构域样受体蛋白3 (nucleotide-binding oligomeric structural domain-like receptor protein 3, NLRP3)炎症小体激活及白细胞介素-1β (interleukin-1β, IL-1β)释放[90]。而UPS抑制剂 (如来氟米特) 通过阻断B细胞活化因子 (B-cell activating factor, BAFF)与其受体BAFF-R结合, 从而抑制浆细胞分化和抗体分泌[91]。相比之下, TPD技术可提供更精准的调控。一方面, CRBN E3泛素连接酶配体 (如沙利度胺衍生物) 通过降解spalt样转录因子4, 直接清除过度活化的B细胞与浆细胞, 减少致病性自身抗体生成[92]; 另一方面, 分子胶降解剂 (如靶向G1/S期转换因子1的化合物) 可诱导病理性T/B细胞凋亡, 重建免疫耐受[93]。IRAK4-PROTAC (KT-474) 则通过抑制TLR7/9下游信号传导, 有效降低血清中α干扰素水平[94]。随着这些技术的进一步发展和应用, 有望突破传统免疫抑制剂在治疗SLE方面的局限性, 为患者带来更好的治疗选择和预后 (表2)。

2.2.3 多发性硬化症 多发性硬化症 (multiple sclerosis, MS) 的发病机制根植于蛋白质稳态失衡与神经免疫调节异常的双重病理基础。在MS患者中枢神经系统中, 针对星形胶质细胞终足区离子通道的自身免疫攻击构成核心病理环节, 水通道蛋白4 (aquaporin 4, AQP4) 及内向整流钾通道蛋白4.1 (inwardly rectifying potassium channel 4.1, KIR4.1) 作为关键自身抗原, 其异常自身抗体可破坏BBB完整性, 导致T淋巴细胞浸润, 进而引发髓鞘脱失与轴索损伤[91]。错误折叠蛋白的累积与自噬功能的缺陷可触发少突胶质细胞内质网应激与线粒体损伤, 进而激活NLRP3炎症小体并促进炎症因子释放[95]。传统干预策略虽能部分缓解免疫浸润或炎症反应, 但难以根本性逆转蛋白质稳态紊乱。例如, 通过溶酶体途径降解鞘氨醇-1-磷酸受体1可阻断淋巴细胞向中枢神经系统的迁移[96]。靶向GlialCAM的单克隆抗体或NLRP3抑制剂可抑制炎症反应, 但上述途径均未解决蛋白质稳态失衡的核心问题[97]。相较之下, TPD技术展现出多维度治疗优势, 其可通过降解炎症信号枢纽蛋白 (抑制B细胞活化与小胶质细胞介导的髓鞘吞噬)[98]、清除致病性蛋白聚集体 (利用LYTAC降解p62或PROTAC靶向突变蛋白脂质蛋白以恢复自噬流及分子伴侣介导的自噬功能)[99]、解除髓鞘再生抑制 (降解LINGO-1促进少突胶质细胞分化)[100]以及调控氧化应激 (Keap1-PROTAC稳定核因子E2相关因子2并激活血红素加氧酶1/醌氧化还原酶1等保护性基因)[101], 为MS的治疗提供了新的方法。

2.3 肿瘤

2.3.1 血液肿瘤 UPS功能失调及异常蛋白累积是血液肿瘤病理进程的核心机制[102]。在MM中, 自噬标志物SQSTM1/p62阳性蛋白聚体的蓄积与AUTAC介导的泛素化蛋白降解障碍直接相关, 凸显自噬-UPS交互调控在疾病发生中的关键地位[103]。据报道, CRBN依赖性降解剂 (如来那度胺衍生物) 可通过降解转录因子IKZF1/3抑制干扰素调节因子4 (IFN regulatory factor, IRF4)/骨髓细胞瘤病毒致癌基因 (myelocytomatosis viral oncogene, MYC) 轴; 而基于CRBN E3泛素连接酶的组蛋白去乙酰化酶7 (histone deacetylase 7, HDAC7) 降解剂B14, 可通过介导HDAC7的特异性泛素化降解, 展现出强效的抗肿瘤活性, 为MM治疗提供了新靶点策略[104]。在慢性淋巴细胞白血病 (chronic lymphocytic leukemia, CLL) 中, USP7抑制可导致乳腺癌易感基因1/2泛素化修饰紊乱和RAD18蛋白稳定性的丧失, 从而诱发DNA损伤应答崩溃[105]。同时, 骨髓细胞瘤病毒致癌基因 (myelocytomatosis viral oncogene, MYC) (尤其是C481S突变体) 通过持续激活断点簇区域 (breakpoint cluster region, BCR) 信号驱动疾病进展。值得注意的是, PROTAC技术可高效降解野生型及突变型布鲁顿酪氨酸激酶 (Bruton′s tyrosine kinase, BTK), 阻断下游迁移信号并逆转依鲁替尼耐药[106]。此

外, BET-PROTAC (如ARV-825) 可通过降解BRD2/3/4抑制MYC转录, 协同增强CLL细胞杀伤效应[107]。在慢性髓系白血病中, 其致病核心BCR-Abelson酪氨酸激酶 (abelson tyrosine kinase, ABL) 融合蛋白通过诱导USP7酪氨酸磷酸化, 增强其去泛素化酶活性以拮抗磷酸酶和张力蛋白同源物 (phosphatase and tensin homolog, PTEN) 的肿瘤抑制功能, 形成促白血病细胞存活的信号轴[108]。而基于纳米载体的BCR-ABL靶向PROTAC可高效降解T315I等耐药突变体, 阻断信号转导和转录激活因子5 (signal transducers and activators of transcription 5, STAT5)/CT10激酶调控样蛋白 (CT10 regulator of kinase-like protein, CRKL) 信号传导并延缓耐药克隆进化[109,110] (表3)[111-122]。

2.3.2 实体瘤 在霍奇金淋巴瘤研究中, Lue等[123]揭示新型降解剂KT-413通过UPS介导白介素-1受体相关激酶4 (interleukin-1 receptor-associated kinase 4, IRAK4) 降解, 阻断NF-κB信号通路激活, 同时上调I型干扰素反应以增强免疫清除, 最终诱导肿瘤细胞程序性死亡。在乳腺癌研究领域, Gan等[124]开发的多靶点降解剂可选择性降解内质网应激分子伴侣及细胞周期蛋白依赖性激酶1/4, 直接破坏肿瘤细胞生存的核心机制。此外, Bai等[125]报道的降解剂BETd-260可通过诱导溴结构域蛋白4 (bromodomain-containing protein 4, BRD4) 泛素化降解, 并与B细胞淋巴瘤-xL (B-cell lymphoma-extra large, BCL-xL) 抑制剂产生协同致死效应, 有效抑制肿瘤细胞生长。除上述靶点外, CRBN依赖性分子胶降解剂 (如沙利度胺衍生物) 可同步降解IKZF1/3与酪蛋白激酶1α, 抑制ER$^+$乳腺癌增殖与干细胞干性维持[126]。CDK9-PROTAC (BSJ-03-123) 通过阻断RNA聚合酶II磷酸化, 快速下调促生存蛋白, 增强聚ADP-核糖聚合酶抑制剂敏感性[127]。另外, BCL-xL-PROTAC利用CRBN的表达差异规避血小板毒性, 为转移性乳腺癌提供了高安全性的治疗方案[128]。在甲状腺乳头状癌中, Zhang等[129]发现泛素化因子E4A (ubiquitination factor E4A, UBE4A) 与多聚嘧啶tract结合蛋白1的泛素化调控轴存在显著负相关

Table 3 Mechanisms and applications of protein homeostasis in neurological and immune system diseases. ALK: Anaplastic lymphoma kinase; PTEN: Phosphatase and tensin homolog deleted on chromosome ten; AKT: Ak strain transforming; PLC: Phospholipase C; PKC: Protein kinase C; MEK: Mitogen activated protein kinase; ERK: Extracellular signal regulated kinase; BCL: B-cell lymphoma; BAFF: B-cell activating factor

Disease type	Mechanism of protein homeostasis imbalance	Related drug	Target/pathway	Ref.
Lung cancer	Overexpression of HSP90 stabilizes oncogenic client proteins	HSP90 inhibitor (tanespimycin)	HSP90-client proteins (EGFR, ALK)	[111]
	Abnormal proteasome activity leads to the accumulation of misfolded proteins	Bortezomib, carfilzomib	UPS	[112]
	Overactivation of autophagy sustains tumor cell survival	Chloroquine, hydroxychloroquine	LC3-II/p62 autophagy pathway	[113]
Multiple myeloma	Accumulation of ubiquitinated proteins; repression of proteasome subunit gene transcription, blocking protein degradation	CB-5083 (a novel anticancer agent targeting p97)	Nrf1 transcription factor, proteasome subunits	[114]
	Overexpression of MYC protein drives cell growth and tumor development; insufficient 20S proteasome activity leads to the accumulation of misfolded proteins	20S proteasome activator	20S proteasome, MYC protein, apoptosis signaling pathway	[115]
Bladder cancer	Overexpression of the E3 ubiquitin ligase RNF126 degrades the tumor suppressor protein PTEN	RNF126 inhibitor	EGFR/PI3K/AKT signaling pathway	[116]
	Overexpression of USP1 enhances deubiquitinating activity, stabilizes the oncogenic transcription factor c-MYC, and disrupts protein degradation balance	USP1 inhibitor	USP1, c-Myc protein	[117]
Prostate cancer	Inhibition of UPS function blocks the degradation of AR/AR-V7	HSP70 inhibitor	HSP70, AR/AR-V7, UPS pathway, AR signaling	[118]
Clear cell renal cell carcinoma	PRR11 protein induces the degradation of E2F1 protein through interaction with E2F1, affecting the cell cycle progression	PRR11 inhibitor	PRR11-E2F1 interaction, c-Myc regulation	[119]
Acute myeloid leukemia	ADGRE2 drives protein homeostasis imbalance	ADGRE2 inhibitor	ADGRE2, PLCβ/PKC/MEK/ERK signaling axis, AP1, DUSP1, DNAJB1-HSP70 interaction	[120]
	FLT3 mutation leads to abnormal protein synthesis and dysregulation of the ubiquitination system	FLT3 inhibitor, proteasome inhibitor	UPS	[121]
Chronic lymphocytic leukemia	Abnormal activation of B-cell receptor signaling; overexpression of BCL-2 inhibits apoptosis	BCL-2 inhibitor, BH3 mimetic drug venetoclax	NF-κB signaling, cytokine-cytokine receptor interaction, BAFF-BAFF-R pathway	[122]

($r = -0.72$, $P < 0.001$), 为深入理解该癌症的发病机制提供了新线索。另外, 靶向RET/PTC致癌融合蛋白的PROTAC能高效诱导其降解, 并阻断MAPK信号通路, 对放疗产生的耐药性也具有一定的减轻效果[130] (表3)。

3 展望与挑战

本文系统综述了TPD通过重塑蛋白质稳态网络突破“不可成药”靶点的药学机制及其在跨疾病谱系治疗中的前沿应用。从技术分类、分子机制及疾病干预3个层面展开, 深入解析了以PROTAC、分子胶为核心的UPS介导降解技术, 以及LYTAC、AUTAC等新兴技术如何通过诱导蛋白质泛素化或模拟自噬标签实现靶向清除, 并结合蛋白质稳态失衡的病理共性, 阐述了TPD在神经退行性疾病、肿瘤、自身免疫病及中枢神经系统脱髓鞘疾病中的干预策略, 最后通过具体案例揭示了TPD技术通过降解致病蛋白或修复蛋白稳态系统实现疾病修饰的分子基础。然而, TPD技术的临床转化仍面临多重挑战。首先, 在递送系统方面, 现有载体存在靶器官富集效率低、组织穿透性差等问题, 需开发组织特异性纳米递送平台或利用生物正交反应实现精准释放; 其次, 耐药性监测需关注靶蛋白突变、E3连接酶适应性改变及替代性降解途径激活等机制, 可通过多靶点降解剂联用或动态监测降解动力学加以应对; 再者, 个体化治疗需建立降解效能生物标志物体系, 整合患者基因组学、蛋白质组学数据构建预测模型。未来, TPD技术需向精准医疗模式转型, 通过结构生物学指导降解剂理性设计, 结合AI算法优化双功能分子构效关系。同时, 跨学科合作将推动递送系统、生物标志物及耐药机制研究, 最终实现从“蛋白清除”到“稳态调控”的治疗理念升级, 为复杂疾病的治疗提供全新思路。

作者贡献: 孟鼎伦负责组织文章框架、文章撰写及修改; 李舒弘负责审阅、修改和完善; 刘星雨、陆晨曦负责图表的制作; 靳雅惠负责选题、审校。

利益冲突: 本文所有作者声明不存在利益冲突关系。

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