靶向蛋白降解策略用于神经退行性疾病精准治疗前沿进展

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摘要: 神经退行性疾病 (neurodegenerative diseases, NDDs) 普遍伴随蛋白质稳态失衡, 包括致病蛋白的异常合成、错误折叠、聚集沉积与降解障碍, 进而诱发神经毒性反应。近年来, 围绕蛋白稳态调控的多层次干预策略不断发展, 包括转录与翻译水平的表达调控、构象维持与聚集抑制, 以及以靶向蛋白降解 (targeted protein degradation, TPD) 为代表的降解清除技术。鉴于NDDs病灶主要位于中枢神经系统, 有效干预依赖治疗分子穿越血脑屏障并精准递送至脑内病变区域。本文围绕NDDs中蛋白稳态失衡的发病机制, 系统综述了当前主要的干预策略, 重点讨论了TPD策略的技术进展与治疗潜力。此外, 本文进一步总结了多种脑部纳米递送系统的设计策略, 包括微环境响应、细胞特异性靶向与亚细胞器定向等, 以实现跨越血脑屏障后对特定靶点的精准递送, 实现基于蛋白稳态调控策略的神经退行性疾病精准治疗。本综述有望为开发脑靶向蛋白降解技术及其高效递送策略提供参考。

关键词: 神经退行性疾病; 蛋白质稳态; 靶向蛋白质降解; 靶向脑内药物递送

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Advances of targeted protein degradation strategies for precision therapy of neurodegenerative diseases

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Abstract: Neurodegenerative diseases (NDDs) are marked by disruptions in protein homeostasis, including abnormal synthesis, misfolding, aggregation, and defective degradation of pathogenic proteins, leading to neurotoxicity. In recent years, multilayered therapeutic strategies targeting protein homeostasis have been developed, such as transcriptional and translational regulation, conformational stabilization, aggregation inhibition, and protein clearance approaches represented by targeted protein degradation (TPD). Since the pathological lesions of NDDs are primarily located in the central nervous system, effective interventions require that therapeutic agents cross the blood-brain barrier (BBB) and be precisely delivered to diseased brain regions. This review systematically summarizes the pathogenic mechanisms underlying protein homeostasis imbalance in NDDs and highlights current therapeutic strategies, with an emphasis on recent advances and therapeutic potential of TPD approaches. We further overview various brain-targeted nanodelivery systems, including those responsive to the brain microenvironment

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and capable of targeting specific cells and subcellular organelles, which collectively enable precise trans-BBB delivery and intracellular targeting. These advances support the development of precision therapies aimed at restoring protein homeostasis. This review provides insights into the progress of brain-targeted TPD technologies and their supporting nanodelivery strategies.

Key words: neurodegenerative disorder; protein homeostasis; targeted protein degradation; brain-targeted drug delivery

蛋白质稳态 (protein homeostasis, proteostasis) 是维持细胞正常生理功能的核心机制, 涵盖蛋白质的合成、折叠、修饰与降解等动态调控过程[1]。在神经退行性疾病 (neurodegenerative diseases, NDDs) 中, 这一平衡状态往往被打破, 导致致病蛋白的异常积累、错误折叠、聚集沉积及降解障碍等一系列病理改变, 从而诱发突触功能损伤、炎症激活与细胞凋亡等神经毒性反应。因此, 靶向修复蛋白稳态紊乱被认为是干预NDDs进程的关键策略之一。

随着分子生物学、基因编辑与纳米技术等多学科领域的飞速发展, 多层次蛋白质稳态干预手段不断涌现。在蛋白合成调控方面, 通过干预转录或翻译过程, 不仅可抑制病理蛋白的过度表达, 也可补充关键保护蛋白以恢复稳态。在蛋白构象与聚集干预层面, 策略主要包括激活分子伴侣系统、稳定功能构象、抑制有害聚集及调控翻译后修饰, 从而延缓聚集体形成并阻断下游毒性反应链条。在蛋白降解与清除方面, 近年来兴起的靶向蛋白降解 (targeted protein degradation, TPD) 技术逐渐成为该策略的研究重点。TPD通过诱导致病蛋白进入细胞自身的降解通路, 打破了传统药物“抑制而不清除”的局限, 具有显著的靶点拓展潜力与功能剥夺优势。当前, TPD策略已覆盖从泛素–蛋白酶体系统 (ubiquitin-proteasome system, UPS) 拓展至自噬–溶酶体系统 (autophagy-lysosome pathway, ALP) 等多种降解路径。代表性平台包括蛋白降解靶向嵌合体 (proteolysis targeting chimera, PROTAC)、分子胶 (molecular glue)、溶酶体靶向嵌合体 (lysosome targeting chimeras, LYTACs)、自噬拴系化合物 (autophagy tethering compounds, ATTECs)、自噬靶向嵌合体 (autophagy targeting chimeras, AUTOTACs)、分子伴侣介导自噬 (chaperone mediated autophagy, CMA) 和疏水标签 (hydrophobic tag, HyT) 等多个策略。这些策略通过精准招募E3连接酶、自噬受体或膜转运通路, 诱导特定蛋白降解, 已在阿尔茨海默症 (Alzheimer's disease, AD)、帕金森病 (Parkinson's disease, PD) 等多种神经退行性疾病模型中展现出靶蛋白水平降低、神经毒性缓解与认知功能改善等显著效果。

由于NDDs的病变主要位于中枢神经系统, TPD等稳态干预策略的有效性高度依赖于治疗性效应分子在脑组织的精准递送。然而, 血脑屏障 (blood-brain barrier, BBB) 作为一种高度选择性的生理屏障, 显著限制了大多数TPD药物进入脑实质。此外, 即使成功入脑, TPD药物在脑组织中仍可能面临靶向性不足的问题, 难以精准作用于特定病灶或细胞, 进一步限制了其治疗效果并增加脱靶风险。近年来发展迅速的纳米递送系统在穿越BBB、定位脑内病灶及实现胞内递送方面展现出独特优势。通过构建具备受体介导穿越能力、病灶微环境响应释放机制及细胞和亚细胞靶向功能的智能纳米平台, 可实现TPD药物从外周到胞内靶点的连续递送过程。

本文围绕蛋白稳态失衡在神经退行性疾病中的关键作用, 综述其在合成调控、构象调节与降解清除等层面的干预路径, 重点以TPD为核心, 探讨其策略创新与治疗潜力, 并系统评述纳米递送平台在促进其脑部精准递送与效应释放中的支撑价值 (图1)。本综述有助于推动蛋白降解策略在脑靶向递送与精准治疗中的应用。

1 神经退行性疾病中蛋白质稳态失衡的机制与干预策略

1.1 蛋白稳态失衡的病理学基础

NDDs是一类以中枢神经系统进行性退化为特征的复杂疾病, 典型代表包括AD、PD、亨廷顿舞蹈病 (Huntington's disease, HD)、肌萎缩侧索硬化症 (amyotrophic lateral sclerosis, ALS) 及额颞叶痴呆 (frontotemporal dementia, FTD) 等。这些疾病的共同病理特征是蛋白质稳态失衡, 表现为致病蛋白的异常表达、错误折叠、聚集沉积与降解障碍。以AD为例, β-淀粉样蛋白 (amyloid-β, Aβ) 和过度磷酸化tau蛋白 (p-tau) 的异常聚集可引发细胞毒性、突触损伤及神经炎症反应[2]; PD中, α-突触核蛋白 (α-synuclein, α-syn) 异常聚集形成Lewy小体, 损伤多巴胺能神经元[3]。HD由突变Huntingtin蛋白 (mutant Huntingtin protein, mHTT) 聚集引起, 诱发细胞毒性应激[4]。ALS则与TAR DNA结合蛋白43 (TAR DNA-binding protein 43, TDP-43)

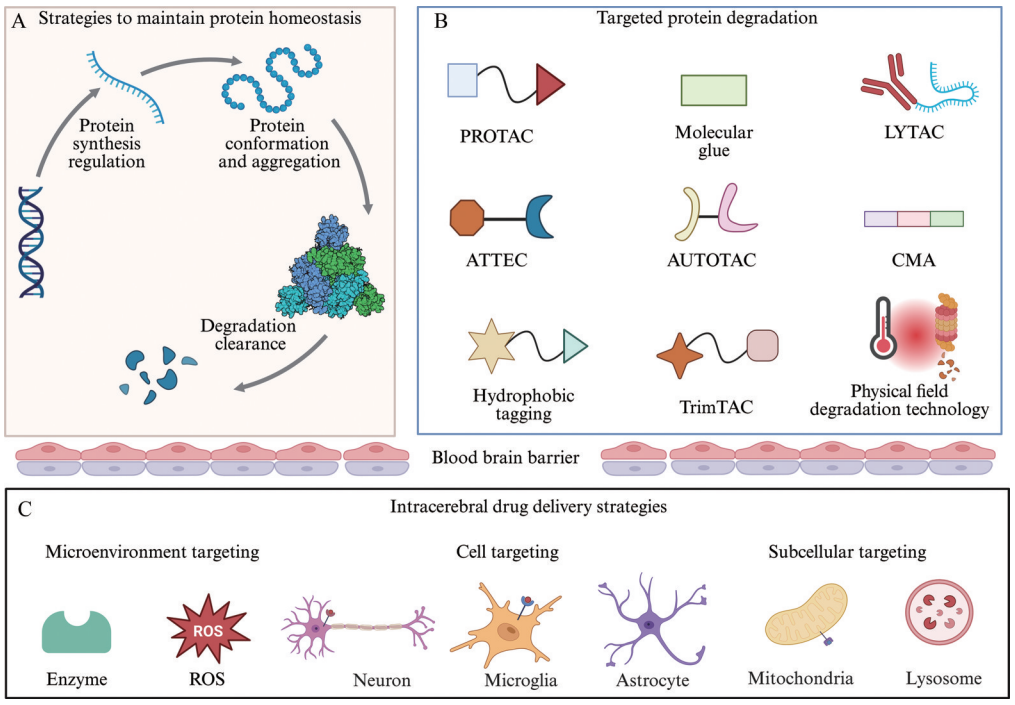


Figure 1 Schematic illustration of protein homeostasis strategies and brain-targeted delivery methods. A: Protein regulation encompasses strategies for protein synthesis regulation, conformation and aggregation intervention, as well as degradation and clearance strategies; B: Targeted protein degradation encompasses approaches such as PROTACs, molecular glues, LYTACs, among others; C: Intracerebral drug delivery strategies encompass microenvironment-responsive, cell-targeted, and subcellular-targeted delivery approaches. PROTAC: Proteolysis targeting chimera; LYTAC: Lysosome targeting chimeras; ATTEC: Autophagy tethering compounds; AUTOTAC: Autophagy targeting chimeras; CMA: Chaperone mediated autophagy; ROS: Reactive oxygen species

或超氧化物歧化酶 1 (superoxide dismutase 1, SOD1)蛋白异常聚集相关, 造成运动神经元退行性病变[5]。FTD 中, 也可观察到 tau 或 TDP-43 聚集的显著表现[6]。

上述病理蛋白的积聚不仅源于蛋白质合成、折叠、修饰与降解等过程的稳态紊乱, 也进一步加剧细胞器功能障碍、代谢紊乱与神经炎症反应, 构成了恶性正反馈环路, 推动疾病持续进展。因此, 恢复蛋白稳态被认为是干预神经退行性疾病的关键策略之一。不同 NDDs 的核心致病蛋白、降解障碍机制及干预策略如表 1[7-23]所示。

Table 1 Comparison of pathogenic proteins, degradation impairment, and targeted protein degradation (TPD) strategies in major neurodegenerative diseases. AD: Alzheimer's disease; GSK-3β: Glycogen synthase kinase-3β; PD: Parkinson's disease; ASO: Antisense oligonucleotides

Disease	Therapy	Technology	Target	Ref.
AD	C004019	PROTAC	Tau	[7]
	TH006	PROTAC	Tau	[8]
	QC-01-175	PROTAC	Tau	[9]
	PG21	PROTAC	GSK-3β	[10]
	BIIB080	ASO	Tau	[11]
	Lecanemab	Antibody	Aβ oligomers	[12]
	Donanemab	Antibody	Aβ plagues	[13]
	AADvac1	Antibody	Aβ oligomers/plagues	[14]
	E2814	Antibody	Aβ oligomers/plagues	[15]
PD	XL01126	PROTAC	α-Synuclein	[16]
	ATC161	AUTOTAC	α-Synuclein	[17]
	Tat-βsyn-degron	Targeted peptide	α-Synuclein	[18]
	PRX-002	Antibody	α-Synuclein	[19]
	SynO4	Antibody	α-Synuclein	[20]
	BIIB054	Antibody	α-Synuclein	[21]
	BIIB094	ASO	LRRK2	[22]
	DNL201	Small molecular	LRRK2	[23]

1.2 蛋白质稳态的多层次干预策略

蛋白质稳态依赖于其合成、构象维持与降解过程的动态平衡。NDDs中, 致病蛋白的异常合成、错误折叠与聚集沉积, 以及降解系统功能障碍, 共同推动了毒性蛋白的积累与神经元功能衰退。因此, 围绕蛋白质全生命周期提出干预策略, 已成为逆转病理进程的重要方向。当前研究可按机制划分为3类主要策略: 蛋白合成调控、构象与聚集干预, 以及降解与清除促进(图1A)。

1.2.1 蛋白合成调控策略 蛋白合成调控主要通过干预转录或翻译过程, 降低病理蛋白的表达水平, 或增强维持稳态所需蛋白的合成能力 (图1A)。蛋白表达的增强主要依赖于外源基因的导入与表达系统的激活, 常见方式包括腺相关病毒 (adeno-associated virus, AAV) 介导的基因导入及信使核糖核酸 (mRNA) 药物的递送。AAV载体可实现缺失或保护性蛋白的长期表达。例如, 2022年3月3日, Lexeo Therapeutics公司宣布, AAV基因疗法LX1001在治疗载脂蛋白E4 (apolipoprotein E4, APOE4) 纯合AD患者的临床Ⅰ/Ⅱ期试验中获得积极数据。该疗法将表达保护性载脂蛋白E2 (apolipoprotein E2, APOE2) 的基因递送到携带两个APOE4等位基因的AD患者的中枢神经系统, 在神经系统中持续稳定表达APOE2, 以达到阻止和减缓疾病进展的作用[24,25]。此外, mRNA药物也可用于补充因突变、缺失或功能障碍导致的特定蛋白不足, 从而恢复细胞稳态调节能力。例如, 有研究利用纳米系统将白介素-10 (interleukin-10, IL-10) 的mRNA递送至脑内小胶质细胞, 诱导其表达IL-10并向M2型神经保护表型转化, 从而抑制神经炎症、发挥神经元保护作用[26]。Wongsodirdjo等[27]还利用mRNA表达tau蛋白特异性抗体 (包括scFv和全长抗体), 实现其在神经细胞内的表达并结合胞内tau蛋白, 显示出mRNA药物在细胞内抗体治疗中的应用潜力。

与此同时, 多种转录后水平干预工具也被用于抑制异常蛋白表达。反义寡核苷酸 (antisense oligonucleotides, ASO)、小干扰RNA (small interfering RNA, siRNA) 和CRISPR-Cas9干扰系统可通过靶向突变或异常高表达的mRNA, 抑制病理蛋白的翻译。以tau蛋白为例, ASO通过靶向人类微管相关tau蛋白 (microtubule associated protein tau, MAPT) mRNA可有效降低其表达。治疗性ASO药物BIIB080已在临床研究中表现出良好的安全性与总tau水平下降效果[11]。此外, Tong等[28]开发了一种针对α-syn编码基因SNCA mRNA的小分子抑制剂synucleozid-2.0 (图2A), 并在此基础上构建了核糖核酸酶靶向嵌合体Syn-RiboTAC (图2B), 能够特异性招募RNA酶降解SNCA mRNA, 有效下调α-syn的表达水平 (图2C), 并部分恢复因其异常积累而紊乱的基因表达谱 (图2D)。

1.2.2 蛋白构象与聚集干预策略 蛋白折叠与构象维持对其功能至关重要, 异常构象可引发神经毒性 (图1B)。相关策略通过稳定构象或抑制聚集, 减少有害寡聚体和纤维沉积, 从而在早期阻断错误折叠的连锁反应。

一类常用方法是激活分子伴侣系统, 如热休克蛋白 (heat shock proteins, HSPs) 可识别并稳定错误折叠蛋白, 促进其正确折叠或转运至降解通路。Arimoclomol作为一种可诱导HSP表达的药物, 已在ALS的临床研究中显示出延缓疾病进展和改善肌肉功能的潜力[29]。类似的策略也可用于激活HSP70、HSP90等关键分子伴侣, 从而在细胞层面提升整体折叠质量控制能力。

此外, 小分子抑制剂或功能性肽类可通过结合致病蛋白 (如Aβ、tau或α-syn), 阻断其聚集核化过程或稳定其无毒构象。例如, TRx0237是一种可干预tau聚集的分子, 已进入阿尔茨海默症患者的临床试验阶段, 并在早期研究中显示出对认知功能衰退的延缓效果[30]。金属离子螯合剂如clioquinol和PBT2则可通过调节铜、锌等离子浓度, 抑制Aβ-金属离子复合物形成, 进而减缓Aβ聚集与沉积[31-33]。近年来还发展出多肽类干预策略, 如针对α-syn寡聚体的抑制性多肽T02、T03、T05和T06[34], 均展现出聚集抑制或毒性缓解的能力。

除了直接阻断聚集过程外, 调控致病蛋白的翻译后修饰状态也是构象干预的重要切入点。以tau蛋白为例, 其过度磷酸化会诱导构象不稳定, 促进寡聚化并加速神经原纤维缠结形成, 是AD和其他tau蛋白病的核心致病机制之一。研究表明, 糖原合酶激酶3β (glycogen synthase kinase-3β, GSK-3β)、周期素依赖性激酶5 (cyclin-dependent kinase 5, CDK5) 等激酶在tau的异常磷酸化中发挥关键作用[35]。因此, 靶向这些激酶的小分子抑制剂被广泛用于阻断tau构象异常的形成。例如, GSK-3β抑制剂tideglusib在AD和FTD模型中显示出显著的tau磷酸化抑制与神经保护作用, 并已进入多项临床试验[36,37]。类似地, CDK5抑制剂roscovitine也被用于减轻tau磷酸化诱导的突触损伤与记忆障碍, 提示其在调控蛋白构象方面的干预潜力[38]。研究表明, c-Jun N端激酶 (c-Jun N-terminal kinase, JNK) 抑制剂SP600125能够降低tau蛋白的磷酸化水平, 并在AD模型中展现出神经保护作用[39]。此外, Hu等[40]开发了磷酸化靶向嵌合体 (PhosTACs), 能够将tau蛋白招募至其天然磷酸酶蛋白磷酸酶2A (protein phosphatase 2A, PP2A) (图2E), 从而实现tau蛋白的有效、快速和可

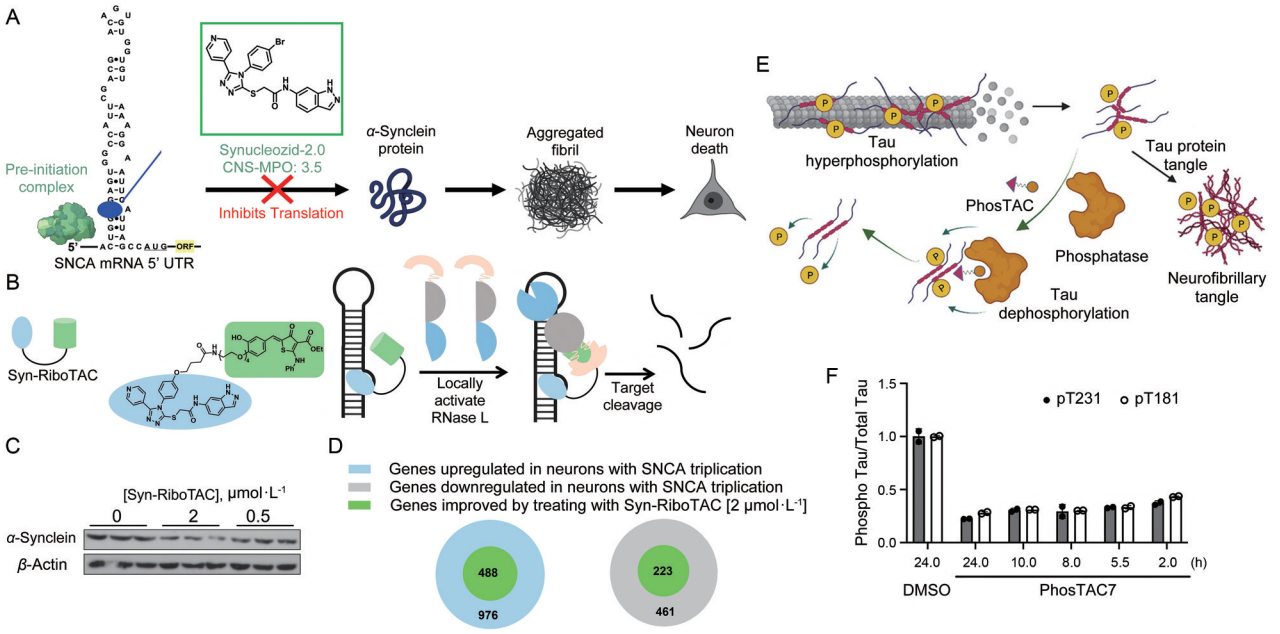


Figure 2 Strategies targeting pathological proteins in neurodegenerative diseases (NDDs). A: The iron-responsive element (IRE) in the 5′UTR of *SNCA* mRNA regulates α-syn translation, synucleozid-2.0 blocks this process by binding the IRE bulge; B, C: Syn-RiboTAC degrades *SNCA* mRNA and dose-dependently reduces α-syn protein levels in SH-SY5Y cells; D: In PD patient-derived dopaminergic neurons, Syn-RiboTAC partially restored gene expression profiles toward control levels after 48 h; E: Mechanism of PhosTAC-mediated tau dephosphorylation; F: PhosTAC7 rapidly induces tau dephosphorylation. Adapted from Ref. 28 and 40 with permission. Copyright © 2022 American Chemical Society

持续去磷酸化 (图2F)。

1.2.3 蛋白降解与清除促进策略 蛋白降解与清除策略通过激活细胞自身的蛋白降解系统, 如泛素−蛋白酶体系统和自噬−溶酶体通路, 实现对致病蛋白的有效去除 (图1A)。其中, TPD技术代表了新兴方向, 核心技术包括PROTAC、分子胶、LYTAC、ATTEC、AUTOTAC、CMA和HyT等 (图1B)。

PROTAC是一类双功能小分子, 一端结合目标蛋白 (protein of interest, POI), 另一端招募E3连接酶诱导其泛素化, 从而启动蛋白酶体降解 (图3A)[41,42]。该技术由Lai[43]于2001年提出, 近年来在神经退行性疾病中展现出巨大潜力。例如, 基于cereblon (CRBN) 和von hippel-lindau (VHL) E3连接酶设计的PROTAC分子C004019[7]和QC-01-175[9]可在AD模型中显著降低总tau及p-tau水平 (图3I)。基于此类结构, Kargbo[44]成功开发了专门靶向tau的小分子PROTAC。这些化合物利用CRBN和VHL E3连接酶设计, 并采用不同长度的连接子, 共产生了12种变体。PROTAC也被用于PD的治疗, Tong等[45]筛选得到了与α-syn高亲和性的分子sery308, 并以此为靶头开发了可靶向α-syn的PROTAC。此外, Zhu等[46]还开发了一类针对tau与α-syn的双靶向PROTAC。研究证实, 该化合物在促进tau和α-syn降解方面具有良好的有效性。这些化合物进一步拓展了PROTAC技术在神经退行性疾病治疗中的应用前景。

除PROTAC外, 分子胶作为另一类小分子降解工具, 通过稳定连接POI与E3连接酶形成复合物, 也可诱导靶蛋白降解 (图3B)[47]。例如, Bushman等[48]通过构建基于VHL配体的小分子库, 并以靶标不可知的方式进行筛选新型VHL分子胶。他们利用Picowell RNA-seq技术筛选发现了一种靶向GEMIN3解旋酶ATP结合域的分子胶dGEM3。由于GEMIN3在ALS中发挥重要作用, 这也提示了该分子胶可能对神经退行性疾病具备治疗意义。

其他基于自噬−溶酶体的降解策略如LYTAC、ATTEC、AUTOTAC与CMA等也被用于清除胞外蛋白如膜蛋白或聚集性蛋白。这些途径不依赖于泛素化过程。其中LYTAC通过连接抗体或配体与溶酶体靶向基团, 可诱导细胞外或膜蛋白进入内吞途径后降解 (图3E)[49,50]。对LYTAC结构的改造可以赋予其特殊功能。例如, 2023年报道cli-LYTAC体系[51]通过递送系统包载炔基修饰的Aβ结合模块与叠氮修饰的细胞表面溶酶体穿梭受体CD206结合模块, 并将其靶向递送至Aβ富集区域后释放。释放后两个模块通过生物正

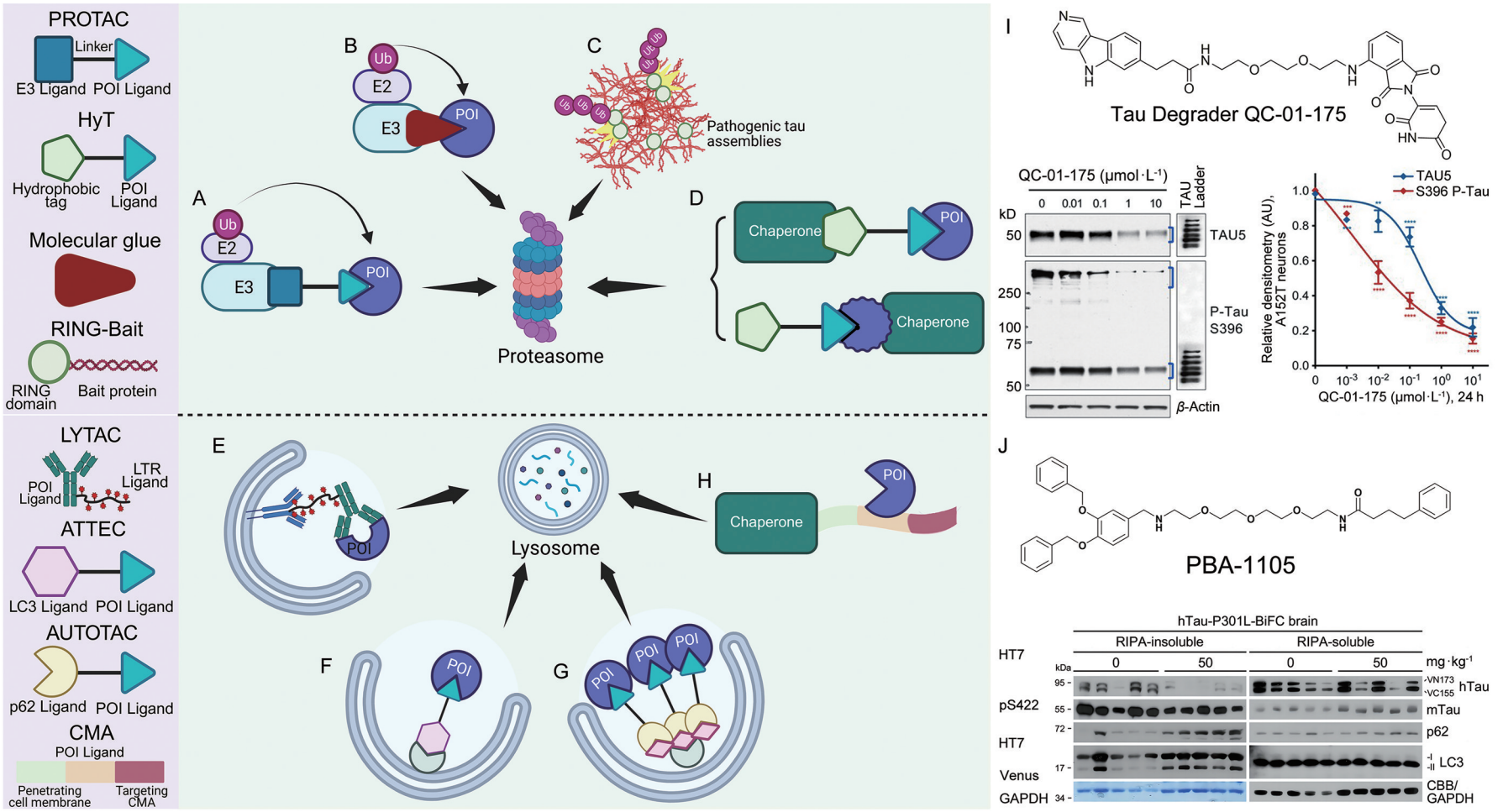


Figure 3 Representative TPD strategies for NDDs. A – H: Schematic illustration of major TPD approaches, including ubiquitin-proteasome-based strategies (PROTAC, HyT, molecular glue, RING-Bait) and lysosome/autophagy-based strategies (LYTAC, ATTEC, AUTOTAC, CMA); I: Structure of the tau degrader QC-01-175 and its activity in reducing total tau and p-tau; J: Structure of the AUTOTAC molecule PBA-1105 and its protein degradation effects[58]. Adapted from Ref. 9 and 58 with permission. Copyright © 2022 American Chemical Society

交反应结合, 并经由CD206介导的小胶质细胞内吞−溶酶体作用, 实现对Aβ的高效降解, 展现出治疗AD的潜力[51]。

ATTEC通过连接靶蛋白与自噬体形成关键蛋白LC3, 实现选择性自噬降解 (图3F)[52,53]。Li等[54]开发出一类可同时结合LC3和致病性mHTT的小分子, 能够依据polyQ序列长度差异, 特异性识别并通过自噬途径降解mHTT而不影响野生型HTT。在神经元细胞模型中, 该类ATTEC展现出良好的选择性与降解效率, 为治疗HD等聚集性蛋白病提供了新方向[54,55]。

AUTOTAC分子由两个模块组成: 一端结合自噬受体SQSTM1 (sequestosome-1)的ZZ结构域; 另一端识别特定靶蛋白, 并通过自噬途径促进其降解 (图3G)[56,57]。Ji等[58]构建的通用化学平台PBA-1105可在AD模型中有效清除不溶的异常p-tau蛋白, 对可溶的tau无显著影响 (图3J)。2023年, Lee等[17]进一步开发了靶向α-syn的新型AUTOTAC, 并对其实现了特异性清除, 为PD治疗开辟了新的有效方案。

此外, CMA通过热休克蛋白70 (heat shock protein 70, HSC70)识别含KFERQ基序的靶蛋白, 并通过与溶酶体膜蛋白LAMP2A结合后转运入溶酶体, 实现选择性降解 (图3H)[59]。Fan等[60]基于该机制开发了三功能嵌合肽, 融合CMA识别基序、细胞穿透肽与靶蛋白结合域, 实现对α-syn与PSD-95的选择性清除, 展示了CMA在调控NDDs相关蛋白稳态中的应用潜力。

除小分子手段外, 近年来也有研究聚焦于E3连接酶本身的工程化利用, 其中TRIM21作为RING型E3泛素连接酶受到了广泛研究。有研究利用TRIM21的RING结构, 构建了带有含有部分tau序列的RING-诱饵(RING-bait), 该诱饵利用了tau蛋白聚集的特性, 使得诱饵序列被整合在了tau聚集体上, 进而活化TRIM21, 通过蛋白酶体途径将tau聚集体降解 (图3C)[61]。还有研究通过共表达TRIM21与抗tau抗体, 或构建TRIM21融合的单链抗体 (scFv-TRIM21), 实现了tau蛋白的高效降解, 为无需传统小分子配体的TPD策略提供了新路径[62]。在此基础上, Lu等[63]进一步发现, 抗精神病药物乙酰丙嗪的代谢物 (*S*)-ACE-OH可作为分子胶, 诱导TRIM21介导核孔蛋白NUP98降解, 并识别出TRIM21中的配体结合位点, 开发了基于TRIM21的TrimTACs分子, 拓展了其在多聚体蛋白降解中的应用潜力。

在非典型UPS通路中, HyT策略通过引入疏水标签 (如金刚烷、苯、芘和碳硼烷), 诱导目标蛋白折叠异常并被蛋白酶体识别降解 (图3D)[64]。2017年, Gao等[65]开发的HYT-Tau-CPP融合体整合tau结合基序、疏水标签及细胞穿透肽, 能在剂量和时间依赖下有效降低tau蛋白水平。

除生物分子策略外, 近年来物理刺激诱导的蛋白降解手段也逐渐受到关注。光动力 (photodynamic therapy, PDT)与光热 (photothermal therapy, PTT)[66]等物理刺激手段, 利用外源性光源激活纳米材料, 实现Aβ等异常蛋白的定点降解或聚集体解聚。例如, PDT通过激发光敏剂产生单线态氧等活性氧物种, 从而氧化断裂Aβ聚集体, 进而降低其Aβ聚集体并减少细胞毒性。姜黄素等分子的近红外光敏化改造亦实现了在动物模型中的Aβ光降解 (如氟硼衍生物[67]、ADLumin-4联合化学发光实现深部Aβ氧化降解[68])。光热治疗则通过纳米材料吸收近红外光并转化为热量, 促进Aβ蛋白构象变化和聚集体解离, 如CeO_2包覆金纳米棒、碳点等材料在动物模型中证实可逆转Aβ相关病理损伤[69,70]。Lai等[71]亦构建了一种基于近红外响应共轭聚合物PDPP3T-O14的光热纳米颗粒系统, 通过包裹热敏脂质和协同递送抗Aβ聚集药物, 实现激光照射下的产热与药物协同释放, 有效清除Aβ沉积, 缓解细胞毒性, 并展现出阿尔茨海默症模型中良好的治疗前景。

与化学或生物降解策略相比, 物理刺激法具有明显的时空可控性和非侵入性, 可通过调节光照区域、时长和剂量实现蛋白降解过程的精准干预。化学/生物策略通常依赖于酶促降解或分子识别, 降解效率与靶向性受限于分子结构和生物环境, 而光控策略可与纳米递送平台联用, 进一步提升其治疗靶向性和安全性。

2 神经退行性疾病中的蛋白质稳态调节的纳米递送策略

近年来, 围绕蛋白质稳态调控的多层次干预策略, 尤其是以TPD为代表的新兴分子工具, 在NDDs的基础和转化研究中展现出显著潜力。然而, 这类分子策略在实际应用过程中普遍受到递送瓶颈的限制。首先, TPD分子如PROTAC、LYTAC、ATTEC等通常分子质量大、结构复杂、水溶性和稳定性较差, 不仅难以主动穿越高度选择性的BBB, 还易在外周循环中降解或被非特异性清除, 导致脑内生物利用度极低。数据显示, BBB可阻断超过98%的常规药物进入脑组织[72], 极大限制了AD、PD等NDDs的治疗效果。此外, 即便这类TPD分子及其他大分子干预工具能够成功到达脑组织, 其在脑内的分布仍缺乏特异性, 常常难以实现对特定病变区域、目标细胞甚至亚细胞结构的精准富集和定向释放, 因而治疗效果有限, 同时还可能引发脱靶效应和不良反应。

针对上述挑战, 纳米递送系统因其高度可调控的粒径、表面性质和功能化能力, 为TPD等大分子药物

的高效递送提供了切实可行的技术途径。一方面, 纳米载体能够将分子质量较大的TPD类药物进行有效包载, 通过物理包封、表面吸附或共价担载等方式, 保护其免受外周环境中的酶降解和非特异性清除, 从而显著提升其血液循环稳定性和生物利用度。同时, 纳米递药系统通过粒径调控和表面配体修饰, 使大分子药物以纳米颗粒等形式实现对BBB内皮细胞上特定受体 (如转铁蛋白受体、低密度脂蛋白受体相关蛋白1等) 的主动识别与结合, 借助受体介导的胞吞转运机制高效穿越BBB[73], 或者通过鼻腔递药等路径绕过BBB[74], 突破传统大分子被BBB阻隔的限制。另一方面, 部分脑靶向纳米递送载体在成功跨越BBB后, 能进一步实现对病变区域、特定病变细胞及亚细胞结构的精准靶向。纳米粒表面修饰的配体可以进一步设计为特异性响应脑内病变区域微环境 (如炎症微环境)[75]或是特异性识别脑内病变细胞 (如异常神经元)[76]或亚细胞结构 (如异常线粒体)[77](图1C)。这种“多重靶向”的特性使药物能够高度富集于病灶部位, 大幅减少药物的全身性毒副作用, 提高治疗的安全性。本节将系统介绍多种脑靶向纳米递送系统的设计原理、关键性能及其在蛋白稳态调节策略中的最新应用进展。

2.1 脑部微环境靶向递送策略

脑部微环境靶向递送策略在传统“入脑”基础上, 进一步聚焦于药物在脑内特定病灶区域的时空精准释放。该策略通常包括两个关键环节: 第一步是穿越/绕过BBB, 实现药物有效进入脑组织; 第二步, 基于病灶微环境特征 (如特异性酶表达或氧化还原状态)[78,79]设计响应性纳米载体, 实现药物在病灶区域的选择性释放。此类智能递送系统不仅提高了活性分子在靶区的有效浓度, 也有助于降低对非靶组织的毒副作用, 从而整体提升治疗的安全性与有效性。

在NDDs中, 这一策略可用于特异性清除异常蛋白聚集体 (如Aβ) 或递送神经营养因子, 以重建蛋白质稳态和神经功能。例如, Zhang等[80]构建了一种基于工程化细胞外囊泡的纳米制剂用于靶向PD中过度激活的免疫微环境。这种纳米制剂由富含趋化因子受体2的间充质干细胞来源的细胞外囊泡作为外壳, 包裹二氢丹参酮I负载的介孔硅纳米载体作为核心。能够靶向结合黑质区域高表达的趋化因子配体2, 从而阻断外周炎症细胞的浸润; 同时, 介孔硅纳米载体可以调控促进Nrf2-GPX4通路中核因子E2相关因子2 (nuclear factor erythroid 2-related factor 2, Nrf2) 在细胞质中的释放, 从而上调谷胱甘肽过氧化物酶4 (gutathione peroxidase 4, GPX4) 催化还原型谷胱甘肽还原过氧化物, 自身氧化为氧化型谷胱甘肽, 从而减少过氧化物的积累, 抑制小胶质细胞中的铁死亡, 协同抑制神经炎症。另一项研究中, Feng等[74]开发了一种鼻腔递送的心磷脂脂质体系统, 负载姜黄素纳米颗粒 (curcumin nanoparticles, CNPs), 用于绕过BBB并响应AD病灶的氧化微环境, 实现对小胶质细胞的高效极化调控。鼻内给药后, 脂质体响应AD的氧化微环境崩解, 释放CNPs和心磷脂 (图4A)。前者抑制Aβ聚集并促进小胶质细胞对Aβ的吞噬或清除; 后者则有助于恢复小胶质细胞的正常极化状态, 减少促炎因子的释放 (图4B)。RCLs@CNPs的递送策略在AD转基因小鼠模型中显著缓解了Aβ沉积 (图4C)、神经炎症 (图4D)。Saling处理组小鼠脑内可见大量Aβ斑块 (图4C), 相比之下, RCLs@CNPs显著减少了Aβ沉积。图4D显示, 绿色标记的Aβ病灶区域与红色标记的活化小胶质细胞形成共定位, 而且RCLs@CNPs的治疗使斑块面积明显缩小。

2.2 脑部细胞靶向递送策略

为实现对中枢神经系统中特定细胞类型的精准干预, 脑部细胞靶向递送策略通过对纳米载体进行精细化设计, 在穿越/绕过BBB后, 进一步将药物选择性递送至神经元、小胶质细胞、星形胶质细胞等特定靶细胞。常见的策略包括“双重靶向”设计, 即在纳米载体表面同时修饰具备BBB穿透能力的配体 (如转铁蛋白、乳糖蛋白受体配体等)[81]及与目标细胞表面受体 (如*N*-甲酰肽受体、TREM2等)[82,83]特异结合的功能分子 (如肽段、抗体、适配体等)。此外, 利用具有脑部归巢特性的细胞载体 (如神经干细胞、间充质干细胞或工程化免疫细胞)[84-86]亦是一种有效策略, 可实现跨屏障递送与细胞定向靶向的协同。

脑部细胞靶向的递送方式能够让蛋白调控策略精准调控特定细胞中的蛋白稳态失衡。例如, Meng等[87]开发了一种神经元靶向纳米递送系统T-LIP@PL-LA/siRC, 以脂质纳米粒为载体共递送丹参酚B和小干扰RNA siROCK2, 并通过TPL肽修饰实现神经元特异识别。该系统通过siROCK2诱导自噬、清除Aβ与p-tau并促进轴突再生, 同时由丹参酚B缓解氧化应激、支持能量代谢并抑制tau异常磷酸化 (图5A)。在11月龄3×Tg-AD小鼠中, 该递送系统显著恢复树突分支复杂度和棘密度, 效果优于多种对照干预, 显示出在AD治疗中的突出潜力 (图5B、C)。此外, Wang等[88]开发了仿膜芽机制的脂蛋白生物模拟纳米载体 (RAP-BHP-rHDL) 用于高效递送脑源性神经营养因子 (brain-derived neurotrophic factor, BDNF) 至AD小鼠脑内血管内皮细胞, 从而改善认知功能。研究发现, RAP-BHP-rHDL能有效封装BDNF, 保护其生物活性, 并通

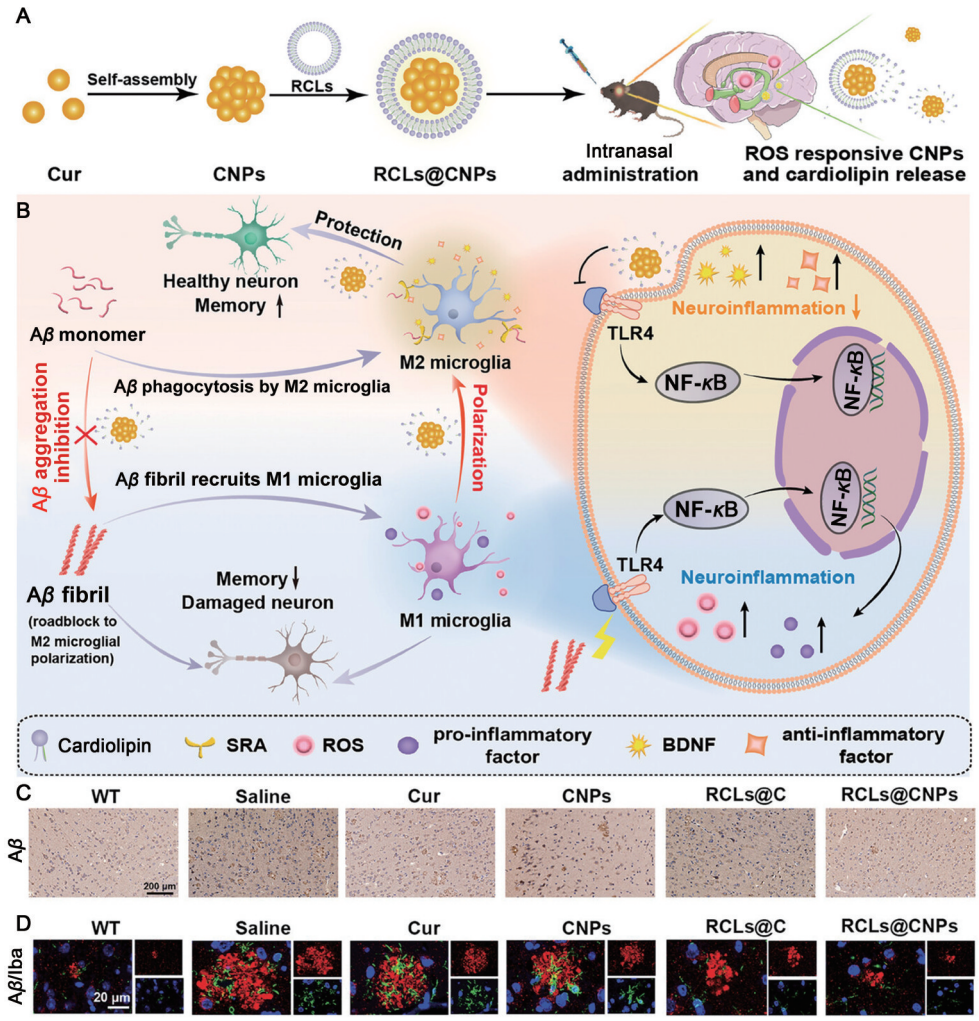


Figure 4 Schematic illustration of RCLs@CNPs and microglial polarization regulation. A: Formation of RCLs@CNPs and their ROS-responsive release of curcumin nanoparticles (CNPs) and cardiolipin; B: Strategy for inducing M2 microglial polarization; C: Representative Aβ immunohistochemistry images in brain; D: Confocal images of Aβ plaques (green) and activated microglia (red, Iba1 positive). Reprinted with permission from reference. Adapted from Ref. 74 with permission. Copyright © 2022 American Chemical Society

过修饰的载脂蛋白E3 (apolipoprotein E3, ApoE3) 和αRAP肽穿越BBB, 靶向受损脑血管。递送的BDNF不仅促进神经干细胞分化、增强神经元存活, 还通过激活TrkB信号通路和改善脑血管功能发挥神经保护作用。在5×FAD小鼠中, RAP-BHP-rHDL显著缓解神经元损伤、恢复脑微血管结构, 并提升认知表现。

2.3 脑部细胞器靶向递送策略

脑部细胞器靶向递送策略旨在将治疗分子 (如药物、基因编辑工具等) 依次跨越三重生物屏障BBB、特定脑细胞膜及目标细胞器膜, 最终实现对神经元或胶质细胞内特定亚细胞结构 (如线粒体、细胞核或溶酶体) 的精准递送。这一过程常借助细胞器定位信号肽或功能性配体实现“分子邮政编码”式导航, 在递送载体上携带一段细胞器定位信号肽或功能性配体这样的引导分子, 为递送的治疗分子提供了细胞内的目的地信息, 而载体根据这些提供“目的地信息”的“邮政编码分子”将治疗分子准确的递送至目标细胞器。例如, 疏水性阳离子肽 (如TPP^+) 可引导载体富集于带负电的线粒体膜[89], 核定位信号肽则能通过核孔复合体将物质主动运输至细胞核[90], 甘露糖-6-磷酸 (mannose-6-phosphate, M6P) 则能靶向溶酶体受体[91]。

在NDDs中, 细胞内蛋白的稳态失衡影响着细胞正常功能的发挥, 而蛋白降解剂脑靶向递送策略可以有效调整细胞内蛋白稳态的失衡。例如, Ma等[92]报道了一种神经递质衍生脂类纳米颗粒 (neurotransmitter-derived lipidoids, NT-lipidoids) 递送tau靶向PROTAC的新策略。他们通过DNA插层自组装方式, 将阳离子肽类PROTAC负载于NT-lipidoid纳米粒, 构建了NT-lipidoid-PROTAC-DNA纳米复合体。该平台不仅具备优异的血清稳定性和血脑屏障穿透能力, 能够经静脉注

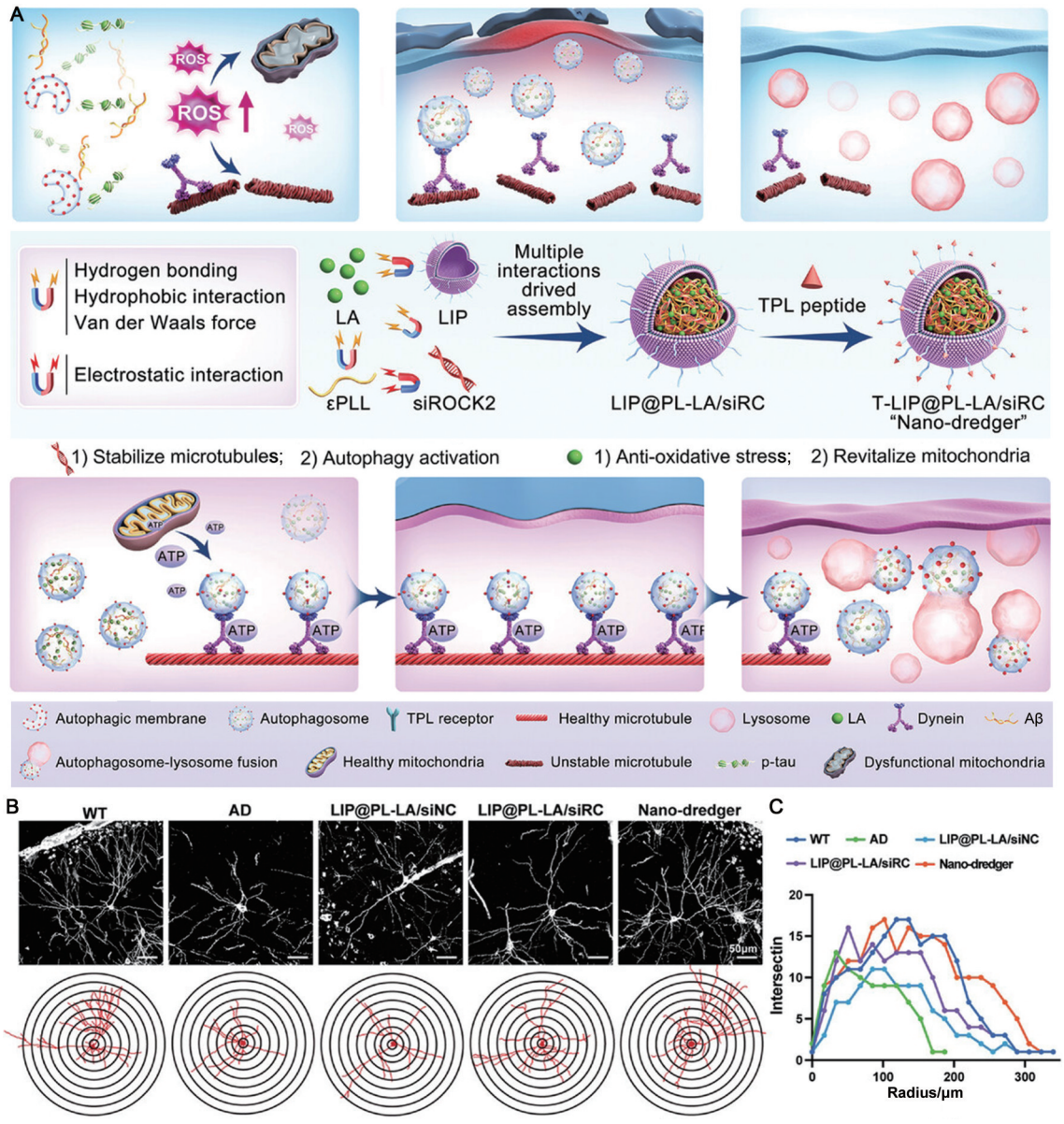


Figure 5 Schematic of the tailored Nano-dredger (T-LIP@PL-LA/siRC) for neuronal targeting and dendritic protection in AD. A: The nanocarrier co-delivers siROCK2 and LA *via* non-covalent assembly, crosses the blood–brain barrier (BBB) through TPL peptide, targets neurons, and releases therapeutics after lysosomal escape; B: 3D reconstruction of Golgi-stained cortical neurons from WT and 3×Tg-AD mice after different treatments; C: Sholl analysis of dendritic branching complexity and length. Reprinted with permission from reference. Adapted from Ref. 87 with permission. Copyright © 2022 American Chemical Society

射高效递送PROTAC进入脑内, 诱导tau蛋白高效降解, 并在阿尔茨海默症模型小鼠中显著改善认知功能, 同时表现出良好的生物安全性。然而, 仅跨越BBB进入脑细胞可能仍不足以实现精准治疗, 许多NDDs的致病蛋白需要被递送至特定细胞器 (如溶酶体或线粒体) 才能被有效清除或调控。例如, Wang等[93]构建了一种具多价受体结合能力的溶酶体穿梭纳米嵌合体 (SV@endoTAC), 用于增强晚期糖基化终产物受体 (receptor for advanced glycation end products, RAGE) 的降解效率并实现病灶特异性递药。RAGE在AD病理下于BBB异常高表达, 可促进Aβ跨屏障转运并激活炎症通路。SV@endoTAC通过RAP肽 (ELKVLMEKEL) 与RAGE多价结合, 提高其溶酶体转运和降解效率; 同时负载的辛伐他汀上调低密度脂蛋白受体相关蛋白1并协同下调RAGE, 恢复BBB功能, 减少Aβ沉积 (图6A)。实验表明, SV@endoTAC显著降低Aβ负荷 (图6B), 并在水迷宫测试中明显改善AD小鼠学习记忆能力 (图6C、D)。

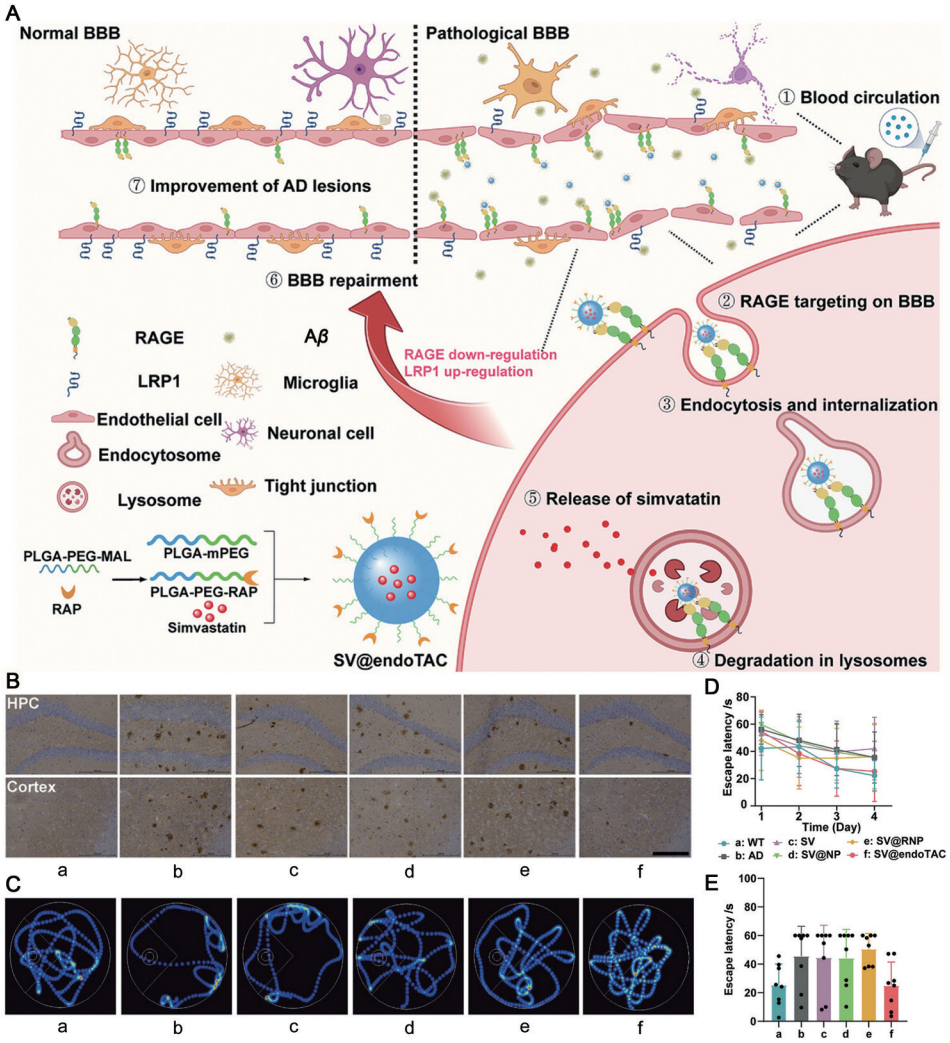


Figure 6 Therapeutic effects of SV@endoTAC on Aβ clearance and cognitive function in AD. A: Design of SV@endoTAC combining a lysosome-shuttle degrader with an efficient delivery system; B: Immunohistochemical staining of Aβ. Scale bar = 200 μm; C: Heat maps of searching paths in Morris water maze (MWM); D: Escape latencies during MWM training; E: Escape latencies in MWM test. Reprinted with permission from reference. Adapted from Ref. 93 with permission. Copyright © 2022 American Chemical Society

此外, Zhang 等[94]开发了一种靶向脑部细胞线粒体的人工纳米囊泡 (UDCA-NVs-TPP), 用于改善PD模型中的线粒体功能障碍。他们基于RAW264.7巨噬细胞制备人工纳米囊泡 (nanovesicles, NVs), 其能够在脑部炎症微环境的调控下穿越BBB。为实现线粒体特异性递送, 囊泡表面进一步修饰三苯基膦 (triphenylphosphine, TPP^+) 以增强线粒体靶向能力, 并负载具有抗氧化和线粒体保护作用的熊去氧胆酸 (ursodeoxycholic acid, UDCA), 构建成UDCA-NVs-TPP递送系统。该系统可高效富集于受损神经元的线粒体, 缓解氧化应激, 并提高ATP产量, 从而缓解由1-甲基-4-苯基吡啶 (1-methyl-4-phenylpyridine, MPP^+) 诱导的线粒体功能障碍和神经毒性。动物实验结果显示, UDCA-NVs-TPP在PD小鼠的纹状体区域有效聚集, 并显著改善其运动行为和神经病理表型, 展现出良好的治疗前景。

3 展望与挑战

蛋白质稳态的维持在NDDs的防治中具有关键意义。蛋白质稳态失衡被认为是NDDs的核心病理特征, 主要表现为致病蛋白的异常合成、错误折叠、聚集沉积及降解障碍等过程。针对上述机制, 目前已发展出多层次干预策略, 包括蛋白质合成调控、构象与聚集干预, 以及蛋白降解通路的激活。其中, TPD等新型蛋白降解技术凭借高度选择性和对传统“不可成药”靶点的适用性, 展现出广阔的研究和转化前景。本综述系统梳理了蛋白稳态干预策略在神经退行性疾病中的最新进展, 特别强调了血脑屏障高度选择性和脑内药物富集困难对有效治疗的限制。针对这些难题, 纳米递

送系统因其可调控的粒径、表面修饰和多级靶向能力, 为蛋白稳态调控分子实现高效跨BBB递送、脑内病灶区富集及细胞/亚细胞特异性定位提供了重要技术支撑, 极大拓展了蛋白稳态干预在NDDs防治中的应用前景。

尽管取得了诸多进展, 这些策略在临床转化过程中依然面临多重挑战。首先, 纳米递送系统自身在实现高效穿透BBB和脑部特异性富集方面仍需进一步优化; 其次, 复杂的纳米载体和蛋白调控分子可能带来脑内及外周组织的脱靶毒性和免疫原性风险, 影响长期安全性和临床可用性; 此外, 现有纳米递送平台在生产工艺复杂性、规模化制备、质量控制和批间一致性等方面尚存在瓶颈, 限制了其产业化和临床转化进程。同时, 蛋白稳态干预效果的实时动态监测与疗效评价手段有待完善, 这也影响了精准治疗和疗效反馈。

未来, 需持续推动递送系统在脑靶向性、递送效率、免疫相容性和工艺可控性等方面的创新, 并加快蛋白稳态调控分子与递送平台的协同优化。同时, 应加强对长期安全性和临床转化全过程的系统评估, 发展基于生物标志物和成像的新型动态监测手段, 为个体化精准治疗提供支撑。随着分子调控策略与纳米递送技术的不断完善, 蛋白稳态干预有望为NDDs治疗带来突破性进展。

作者贡献: 杨雯芳和赵倩对本研究贡献等同, 共同负责文章撰写、文献调研, 以及图表绘制及修改; 潘家兴、李卓亮和彭子睿负责文献收集; 来旖和于海军负责修改指导和审校; 来旖、于海军和徐志爱提供文章方向和思路。

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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