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轴突损伤及修复在神经退行性疾病中的研究进展

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摘　要：随着老龄化社会快速到来，衰老相关的神经退行性疾病如阿尔茨海默病 (Alzheimer's disease, AD)、帕金森病 (Parkinson's disease, PD)、肌萎缩侧索硬化症 (amyotrophic lateral sclerosis, ALS) 等发病率日益升高，给社会和家庭带来巨大经济负担。轴突损伤是 AD、PD 和 ALS 的共有病理特征，不同疾病轴突损伤机制虽各不相同却又相互联系，修复轴突损伤已成为治疗衰老相关的神经退行性疾病的重要路径之一。本文总结和归纳了 AD、PD 和 ALS 中神经元轴突损伤机制及修复方法相关研究进展，以期为早期防治衰老相关的神经退行性疾病提供新的靶点和思路。

关键词：阿尔茨海默病；帕金森病；肌萎缩侧索硬化症；轴突
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Progress in the study of axonal damage and repairment in neurodegenerative diseases

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Abstract: With the rapid arrival of the aging society, increasing incidence of Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) has brought great economic burden to the society and families. Axonal damage is a common pathological feature of AD, PD and ALS. Though the mechanisms of axonal damage are different, evidences indicate that pathomechanism of these diseases are interrelated, thus repairing axonal damage has become one of the important pathways for the treatment of age-related neurodegenerative diseases. In this paper, we summarize the research progress in the mechanisms of axonal damage and the related repairment in AD, PD and ALS, aiming to provide new targets and ideas for the prevention and treatment of aging-related neurodegenerative diseases in the early stage.

Key words: Alzheimer's disease; Parkinson's disease; amyotrophic lateral sclerosis; axon

随着我国快速进入老龄化社会，与衰老相关的神经退行性疾病如阿尔茨海默病 (Alzheimer's disease, AD)、帕金森病 (Parkinson's disease, PD)、肌萎缩侧索硬化症 (amyotrophic lateral sclerosis, ALS) 等患者人数正快速增加。据统计，中国 60 岁及以上人群中 AD 患者超过 1 507 万 [1]，PD 患者预计至 2030 年将增至 494 万，占全球 PD 患者人数的一半 [2]，而 ALS 患病率约为 2.91/10 万 [3]。衰老相关的神经退行性疾病不仅严重影响患者生活质量，还给社会及家庭带来沉重负担。

轴突损伤和退变是衰老相关的神经退行性疾病共有的病理特征。例如，AD 患者和模型小鼠海马神经元轴突中髓鞘碱性蛋白显著减少，造成髓鞘丢失和降解 [4]；PD 模型大鼠神经元轴突长度下降，囊泡运输减少，轴突变性增加 [5]；ALS 患者外周运

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动神经元轴突生长及运输功能异常并发展为运动神经元退化[6-7]。轴突损伤和退变与神经退行性疾病发生发展密切相关，但潜在病理机制仍不清晰。本文针对领域内最新研究进展进行综述，总结AD、PD和ALS等衰老相关神经退行性疾病中神经元轴突损伤的机制及修复方法，旨在解析轴突损伤在神经退行性疾病发生发展中的作用，为治疗衰老相关的神经退行性疾病提供新靶点和新思路。

1 AD

AD是老年人群中最常见的神经退行性疾病，也是痴呆最主要的类型[8]。全世界有超过5 000万人患有AD，预计到21世纪中叶，患病人数将增至1.15亿人并影响近一半的85岁以上老人[9]。AD的典型病理特征为β-淀粉样蛋白(amyloid beta, Aβ)沉积、Tau蛋白异常磷酸化形成的神经原纤维缠结(neurofibrillary tangles, NFTs)、炎症小体、神经血管损伤等[10]。已有大量研究表明，AD病理特征和发生发展过程与轴突结构和功能障碍等密切相关。

1.1 Aβ

Aβ由β-分泌酶[如β位点淀粉样前体蛋白裂解酶1 (β-site APP cleaving enzyme 1, BACE1)]和γ-分泌酶依次裂解淀粉样前体蛋白(amyloid precursor protein, APP)产生[11]。Aβ易聚集形成淀粉样斑块，淀粉样斑块周围的轴突表现为营养不良且BACE1表达水平升高[12]。轴突在Aβ作用下出现弥漫性损伤时，由于细胞骨架被破坏，轴突运输中断，进而导致大量蛋白质包括APP积聚于轴突内[13]。其次，淀粉样斑块周围的轴突形态结构发生改变，在轴突内有大量溶酶体聚集形成的囊泡，且囊泡直径越大，轴突动作电位传导的速度越慢，这表明Aβ可通过影响轴突形态结构进而影响动作电位传导和神经网络兴奋性[14]。

Aβ还可通过损伤线粒体影响轴突形态结构和功能。Aβ诱导的线粒体病变表现为结构和功能异常。在AD病理早期阶段，APP转基因小鼠突触内线粒体氧化应激增加，ATP产生减少，且海马神经元轴突线粒体密度降低[15]。此外，Wang等[16]研究发现，Aβ可降低驱动蛋白家族成员5A (kinesin family member 5A, KIF5A)的表达量，并导致5×FAD (familial Alzheimer's disease, FAD)小鼠线粒体轴突顺行运输缺陷。Aβ还可引起动力蛋白和snapin蛋白解耦联，使自噬内涵体在轴突末端聚集，导致APP转基因小鼠线粒体轴突逆行转运受损[17]。更严重的是，对AD患者和APP小鼠脑组织进行免疫共沉淀检测发现，Aβ与动力相关蛋白相互作用诱导线粒体肿胀、破碎，进而引起轴突变性[18]。

Aβ可减弱少突胶质细胞和小胶质细胞对轴突的保护作用，使轴突形态发生改变、功能受损。少突胶质细胞以髓鞘包裹轴突并促进动作电位的快速传播，髓鞘形成缺陷将影响神经传导和运动功能[19]。针对5×FAD小鼠和AD患者脑组织的蛋白质空间定位分析结果表明，少突胶质细胞富集于Aβ斑块周围，Aβ和炎症因子协同作用导致少突胶质细胞功能异常[20]。髓鞘障碍可加速轴突病变处淀粉样斑块形成，而本应清除淀粉样斑块的小胶质细胞被大量转移至髓鞘损伤处干扰Aβ斑块清除[21]。其次，小胶质细胞可保留髓磷脂结构完整性，并限制髓鞘过度形成和防止脱髓鞘[22]。Depp等[21]研究发现，5×FAD小鼠在敲除髓鞘蛋白基因或髓磷脂髓鞘蛋白基因后，脑内出现大量轴突膨胀，在轴突性膨胀区域富集表达BACE1和APP。老化的髓鞘由于失去轴突支持功能，导致轴突窘迫，这反过来提高了神经元BACE1和APP的水平，增加了Aβ产生[23]。综上，Aβ沉积不仅会导致轴突形态异常和线粒体病变，降低轴突运输速度，还损伤了少突胶质细胞和小胶质细胞对轴突的保护作用，而轴突损伤又可通过促进BACE1和APP的生成使Aβ产生增加，最终形成恶性循环，加快AD进展。

1.2 Tau

AD的另一个标志性病变为NFTs，由过度磷酸化的微管相关蛋白Tau组成[24]。Tau蛋白的主要功能是稳定轴突微管结构，促进神经元轴突生长及辅助轴突内物质运输[25]。磷酸化Tau (phosphorylated tau, p-Tau)更易聚集，且由于失去了Tau蛋白原有稳定微管的能力而使轴突物质运输更易受损[26]。

AD患者脑脊液总Tau和p-tau浓度升高与认知功能损伤呈正相关[27-28]。在三转基因(triple-transgenic, 3×Tg) AD小鼠大脑中受损的神经元通过释放载脂蛋白E4 (apolipoprotein E4, ApoE4)使Tau聚集于轴突中[29]；而在弥漫性脑白质轴突损伤时，神经元核周也可以观察到Tau和神经丝包涵体的富集[30]。因而，神经元损伤会导致Tau分布异常，而Tau分布改变又影响微管的稳定性，使轴突运输紊乱甚至改变轴突结构，加快AD发生发展[31]。对过表达人源Tau (pathological human tau, ph-Tau)蛋白小鼠模型的研究发现，高浓度的ph-Tau可破坏轴突细胞骨架从而损伤认知能力[32]。Tau还可通过激

活蛋白磷酸酶 1 (protein phosphatase 1, PP1) 和糖原合成酶激酶 3 (glycogen synthase kinase 3, GSK3) 抑制轴突顺行快速运输 [33]。Olesen 等 [34] 发现衰老 C57BL/6 小鼠高表达半胱氨酸 - 天冬氨酸蛋白酶 3 (caspase-3, CASP3)，CASP3 可以切割 Tau 并将其水解为有毒性的小片段，诱导线粒体能量产生缺陷和轴突运输障碍，导致神经元损伤和认知功能下降。综上，高浓度的 Tau 和 p-tau 也会导致神经元轴突损伤，加重 AD 的认知功能衰退 [35]。

1.3　炎症因子

由小胶质细胞产生的促炎因子如白细胞介素 -1β (interleukin-1β, IL-1β)、IL-6 和肿瘤坏死因子 α (tumor necrosis factor-α, TNF-α) 在 AD 患者和 5 × FAD 小鼠脑组织中显著升高 [36]。在轴突损伤的脑组织周围可发现高浓度的 IL-1β 表达 [37]，Carlos 等 [38] 指出 IL-1β 可抑制长时程增强进而损伤学习和记忆。在弥漫性轴突损伤后，AD 小鼠大脑中 IL-1β 表达量也显著增加且认知能力逐渐恶化 [39]。在 AD 患者脑组织中，异常激活的小胶质细胞和星形胶质细胞释放的促炎因子 TNF-α 会影响少突胶质细胞分化过程，促进线粒体功能障碍并导致神经元脱髓鞘 [40-41]。研究发现，活化的 M1 型小胶质细胞释放的 TNF-α 损伤血脑屏障，使外界毒性物质更容易进入，从而加剧中枢神经系统微环境紊乱，阻止轴突重塑和记忆功能恢复 [42-43]。

Aβ 原纤维可激活含 pyrin 结构域 NOD 样受体家族 3 (NOD-, LRR-, and pyrin domain-containing 3, NLRP3) 炎症小体，诱导 Tau 过度磷酸化和聚集；在 P301S Tau 转基因小鼠和 AD 患者大脑组织中发现聚集的 Tau 又反过来激活小胶质细胞中的 NLRP3 炎症小体，如此恶性循环导致小胶质细胞凋亡，髓磷脂减少，进而造成脱髓鞘和轴突变性 [44-47]。弥漫性轴突损伤激活核因子 κB (nuclear factor kappa B, NF-κB) 级联信号，损害长期记忆形成和记忆再巩固 [48]。其次，AD 患者大脑中 NF-κB 激活 BACE1 的转录而导致 Aβ 产生增多，从而破坏轴突结构，影响轴突运输 [49]。当然，以上多种炎性因子之间也存在协同作用。例如，Aβ 和 Tau 聚集导致溶酶体损伤，促进 NLRP3 炎症小体组装，诱导 IL-1β 释放和凋亡相关斑点样蛋白 (apoptosis-associated speck-like protein containing a CARD, ASC) 寡聚化并形成 ASC 斑块 [50]；轴突损伤后，淀粉样斑块周围表现出促炎细胞因子上调和小胶质细胞浸润，小胶质细胞吞噬细胞外 ASC 斑块导致 Aβ 清除减少，并通过 IL-1β 进一步促进神经炎症恶化，加速 AD 病理发生发展 [51]。综上，炎症因子、炎症小体及 NF-κB 级联信号等均可引起轴突损伤，同时炎症因子还可与 Aβ、Tau 相互促进，加速 AD 病理发展。

1.4　AD的轴突损伤修复策略

髓鞘修复已成为改善神经元轴突损伤的重要靶点。含免疫球蛋白样结构域的 nogo 受体相互作用蛋白 1 (leucine-rich repeat and immunoglobulin-like domain-containing nogo receptor-interacting protein 1, LINGO-1) 是调控少突胶质细胞分化和髓鞘形成的调节因子，在 AD 患者大脑中高表达；LINGO-1 抗体可促进轴突髓鞘形成，进而改善神经元轴突功能，减轻 AD 小鼠记忆障碍 [52]。此外，使用氯马斯汀也能抑制少突胶质细胞前体细胞 (oligodendrocytes precursor cells, OPC) 衰老进而增加髓鞘密度，挽救 APP/PS1 小鼠记忆缺陷 [53]。同时，AD 患者神经元轴突微管蛋白稳定性下降，影响了轴突的运输功能。靶向受损的微管蛋白恢复正常轴突运输是另一种重要的治疗方法。Onishi 等 [54] 使用 T-518 抑制组蛋白去乙酰化酶 6 (histone deacetylases 6, HDAC6)，提高了 Tau 病理小鼠轴突微管乙酰化程度，增加了微管蛋白稳定性，缓解了 Tau 病理对轴突运输的影响。此外，一些药物，如抗肿瘤药埃博霉素 D、紫杉醇、CNDR-51657 等，也可与微管蛋白结合增加其稳定性，维持轴突运输 [55-57]。热休克同源蛋白 70 (heat shock cognate protein 70, HSC70) 也是修复轴突损伤的重要靶点。HSC70 在 3 × Tg-AD 小鼠和 AD 患者大脑中高表达 [58]，使用薯蓣皂苷元或 VER-155008 抑制 HSC70 表达后，5 × FAD 模型小鼠变性轴突肿胀减轻，微管蛋白表达水平增加 [59-60]。表 1 对 AD 轴突修复方法进行了归纳总结。

2　PD

PD 也是常见的神经退行性疾病之一。PD 典型的病理特征是黑质致密部多巴胺能神经元内有路易体形成和路易神经炎，进而引起 PD 患者运动功能障碍。PD 致病基因包括 α 突触核蛋白 (α-synuclein, α-syn)、富含亮氨酸重复激酶 2 (leucine-rich repeat kinase 2, LRRK2)、磷酸酶和张力蛋白同源物诱导的激酶 1 (phosphatase and tension homolog-induced kinase 1, PINK1) 和帕金森蛋白 (Parkin) 等。这些致病基因可通过损伤轴突内物质运输和影响轴突线粒体质量控制等途径影响神经元轴突生长和连接，进而促进 PD 发生发展。

表1 AD轴突损伤修复方法

药品	作用机制	靶点	动物模型	剂量/给药时间	改善与否	参考文献
抗LINGO-1抗体	拮抗LINGO-1对髓鞘的负性调控	LINGO-1	APP/PS1	10 mg·kg^{-1}·w^{-1}，8 w	增加髓鞘密度，改善认知缺陷	[52]
氯马斯汀	防止OPC衰老	OPC	APP/PS1	10 mg·kg^{-1}·d^{-1}，8 w	髓鞘密度升高，退化减少	[53]
T-518	促进微管蛋白乙酰化	微管蛋白	P301S Tau Tg	0.3~300 mg·kg^{-1}，4 h	轴突运输改善	[54]
埃博霉素D	稳定微管蛋白	微管蛋白	APP/PS1	2 mg·kg^{-1}·w^{-1}，12 w	轴突运输改善，抑制Tau磷酸化和神经炎症	[55]
紫杉醇	稳定微管蛋白	微管蛋白	3×Tg-AD	0.6 mg·kg^{-1}，8 w	轴突运输和认知功能改善	[56]
CNDR-51657	改善微管功能	微管蛋白	5×FAD	3 mg·kg^{-1}，4 w	轴突营养不良改善	[57]
薯蓣皂苷元	降低HSC70表达，保护微管蛋白	HSC70	5×FAD	0.1 μmol·kg^{-1}·d^{-1}，2 w	轴突微管蛋白含量增加，认知功能改善	[59]
VER- 155008	抑制HSC70	HSC70	5×FAD	10 μmol·kg^{-1}·d^{-1}，15/18 d	轴突变性肿胀减少，认知功能改善	[60]

LINGO-1, leucine-rich repeat and immunoglobulin-like domain-containing nogo receptor-interacting protein 1; OPC, oligodendrocytes precursor cells; APP, amyloid precursor protein; PS1, β-site APP cleaving enzyme 1; 3×Tg, transgene; HSC70, heat shock cognate protein 70; 5×FAD, familial Alzheimer's disease; h, hour; d, day; w, week

2.1 α-syn

病理性 α-syn 的异常聚集体是路易氏体的主要成分。研究表明病理性 α-syn 可与磷酸肌醇 -3 激酶增强子 (phosphoinositide-3 kinase enhancer, PIKE) 结合来减弱其抑制作用，使 AMP 活化蛋白激酶 (AMP-activated protein kinase, AMPK) 过度激活，最终导致驱动蛋白表达下调，影响轴突顺行运输效率 [61-62]。PIKE 也是形成自噬体的重要因子，α-syn 抑制 PIKE 导致其产物介导的内质网表面自噬体以及自噬前膜形成受阻，无法吞噬受损细胞 [63]。在过表达 α-syn 的大鼠中，动力蛋白表达水平在 PD 运动功能障碍出现前曾短暂上调，而在 PD 晚期则明显下降 [64]。动力蛋白表达上调有助于自噬清除病理性 α-syn[65]。同时，由于病理性 α-syn 的存在，轴突中以通道微管为载体的逆行运输亦受到影响。突变型 α-syn 蛋白导致乙酰化微管减少，而微管蛋白乙酰化有助于保护微管抵抗机械性衰老 [66-67]。另外，Stykel 等 [68] 揭示在 PD 神经元模型中，微管蛋白被一氧化氮硝基化，从而阻碍了线粒体的顺行轴突运输。α-syn 聚集体通过活化的蛋白激酶 A (protein kinase A, PKA) 和糖原合成酶激酶 3β (glycogen synthase kinase 3β, GSK3β) 促进 Tau 蛋白磷酸化，最终导致微管解聚，轴突物质运输减少，进而加速轴突内 α-syn 聚集体积累，引发恶性循环 [69]。综上，α-syn 可通过影响微管蛋白以及运输相关蛋白损害轴突的运输功能。

2.2 LRRK2

LRRK2 突变基因在家族性 PD 中比较常见。冷冻电镜观察显示，LRRK2 激酶结构域包括开放构象和封闭构象，其封闭构象会导致微管低聚化 [70]。无论是 LRRK2 功能缺失还是 LRRK2 G2019S 位点突变均会引起轴突导向性缺陷 [71]。在小鼠中过表达突变体 LRRK2 发现，LRRK2 突变促进微管去乙酰化，进而抑制神经元轴突运输 [72]。LRRK2 还可促进精子相关抗原 9 (sperm-associated antigen 9, SPAG9)/C-Jun 氨基末端激酶相互作用蛋白 4 (C-Jun NH2-terminal kinase (JNK)-interacting protein 4, JIP4) 在自噬体膜积累，造成驱动蛋白 1 (kinesin-1) 异常募集，进而导致自噬体运输紊乱，并在 PD 模型小鼠轴突中引发自噬及运输缺陷 [73-74]。综上，LRRK2 突变会损害轴突的运输并引发自噬缺陷。

2.3 PINK1/Parkin

PINK1/Parkin 是引起青少年 PD 的最常见病因，两者共同介导泛素依赖的线粒体自噬过程，其中线

粒体跨膜蛋白 Miro 处于核心地位。多巴胺能神经元轴突长而高度分支，极度依赖线粒体顺向运输以维持正常生理功能[75]。在正常情况下，Miro 负责介导线粒体轴突运输，未激活的 Parkin 蛋白与之关联[76]；而在线粒体受损后，Miro 会被 LRRK2 磷酸化，导致受损线粒体选择性自噬[77]。无论是 α-syn、LRRK2 还是 PINK1/Parkin 的突变均会干扰这一过程，导致轴突线粒体质量控制异常，进而引发轴突转运能量不足[77-79]。此外，Parkin 蛋白还与轴突微管共定位，Parkin 基因突变会导致微管稳定性下降，损害轴突运输功能[80]。综上，PINK1/Parkin 突变可引发泛素依赖的线粒体自噬障碍，导致轴突供能不足。

2.4　PD的轴突损伤修复策略

目前虽已开发多种 PD 靶向性药物，但这些药物只能暂时改善运动症状，无法改善 PD 的病理学特征[81]。既往研究表明，调控微管蛋白乙酰化水平可能是修复 PD 轴突运输功能的有效途径。抑制沉默信息调节因子 2 (sirtuin 2, SIRT2) 和 HDAC6 等靶向微管蛋白的脱乙酰酶可增加微管蛋白乙酰化，常用的 HDAC6 抑制剂有曲霉菌素 A 和文拉法辛，SIRT2 抑制剂有 AK7、新型肽 YKK(ε-thioAc)AM[72, 82-84]。其他增加微管蛋白稳定性的方法在挽救轴突运输方面也展现出一定潜力。例如，EpoD 与微管蛋白结合形成更稳定的横向作用，同时提高了微管蛋白表达水平[85]；此外，α-syn 特异性抗体如 MEDI1341 和 1H7 可减少 α-syn 在轴突内的积累和传播[86-87]。表 2 对 PD 轴突修复方法进行了归纳总结。

表2 PD轴突损伤修复方法

药品	作用机制	靶点	动物模型	剂量/给药时间	改善与否	参考文献
曲霉菌素A	抑制HDAC6活性	HDAC6	LRRK2果蝇	10 μmol·L^{-1}，5 d	恢复轴突运输	[72]
			α-syn大鼠	15 mg·kg^{-1}，2 w	微管乙酰化水平增加	[88]
文拉法辛	抑制HDAC6活性	HDAC6	鱼藤酮诱导PD大鼠	1 mg·kg^{-1}	Parkin升高，α-syn减少，自噬增强	[82]
AK7	选择性抑制SIRT2	SIRT2	MPTP小鼠	30 mg·kg^{-1}，2次	纹状体乙酰化微管含量增加	[83]
埃博霉素D	与微管形成稳定构象	微管蛋白	MPTP小鼠	1或3 mg·kg^{-1}，4 d	黑质微管蛋白密度升高	[89]
MEDI1341	特异性结合α-syn	α-syn的C末端	α-syn小鼠	20 mg·kg^{-1}·w^{-1}，13 w	减少α-syn经轴突向对侧传递	[86]
1H7	特异性结合α-syn	α-syn的C末端	α-syn小鼠	30 mg·kg^{-1}·w^{-1}，12 w	α-syn在轴突积累减少，行为缺陷和轴突完整性改善	[87]

HDAC6, histone deacetylases 6; LRRK2, leucine-rich repeat kinase 2; α-syn, α-synuclein; PD, Parkinson's disease; SIRT2, sirtuin 2; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; d, day; w, week

3　ALS

ALS 是最常见的运动神经元疾病，ALS 病理特征表现为患者大脑和脊髓中运动神经元逐渐丧失，进而产生肌肉无力和萎缩等症状[90]，通常在发病 3~5 年后因呼吸衰竭而死亡[91]。ALS 患者群体中约 90% 为散发性 ALS，10% 为家族性 ALS[92]。目前 ALS 的病理机制仍不明确，研究表明 TAR DNA 结合蛋白 43 (transactive response DNA binding protein 43, TDP-43)、肉瘤融合蛋白 (fused in sarcoma, FUS) 和无菌 α 和 Toll 白介素受体基序蛋白 1 (sterile alpha and Toll interleukin receptor motif-containing protein 1, SARM1) 等分子结构和功能改变会引起神经元轴突损伤，促进 ALS 发展[93-95]。

3.1　TDP-43

ALS 患者外周运动神经轴突内蓄积有大量磷酸

化 TDP-43 蛋白 (phosphorylated TAR DNA binding protein 43, pTDP-43)[96]。在生理情况下，TDP-43 主要位于细胞核；而在病理情况下，pTDP-43 异常聚集于运动神经元细胞质，即错误定位 [97-98]。pTDP-43 蛋白与核糖核酸蛋白 (ribonucleoprotein, RNP) 组分 Ras-GTP 酶激活蛋白 SH3 结构域结合蛋白 1 (Ras-GAP SH3 domain-binding protein 1, G3BP1) 相结合，在轴突内形成 RNP 凝聚物并隔离细胞核中编码线粒体基因的 mRNA，进而导致轴突中线粒体相关蛋白质合成减少，导致轴突生长受损 [98]。针对斑马鱼 ALS 模型的研究表明，短时光刺激可诱导脊髓运动神经元中 TDP-43 蛋白错误定位，抑制支配肌纤维相关的轴突生长 [99]。此外，TDP-43 缺失会破坏轴突转录组，使轴突中局部蛋白翻译受限，抑制轴突生长 [100]。在人源诱导多能干细胞 (induced pluripotent stem cells, iPSCs) 分化的运动神经元中敲低 TDP-43 蛋白，微管解聚蛋白 2 (stathmin-2, STMN2) 水平随之下降，运动神经元轴突生长被显著抑制 [7]。Sleigh 等 [101] 研究发现，TDP-43 突变体小鼠外周运动神经元轴突转运体缺陷起始于运动障碍前，这可能是导致 TDP-43 小鼠运动功能缺陷和神经肌肉受损的重要病因。综上，TDP-43 在神经元轴突内错误定位及聚集或低表达均会限制轴突的生长。

3.2 FUS

ALS 与 FUS 突变密切相关，针对过表达人源 FUS 突变型 iPSCs 的研究表明，FUS 基因突变增加了 iPSCs 分化的运动神经元轴突分支，并促使远端轴突肿胀并逐渐退化 [102-103]。Garone 等 [104] 针对 FUS 突变模型小鼠的研究揭示，FUS 突变通过影响 HuD/ELAVL4 和脆性 X 智力低下蛋白 (fragile X mental retardation protein, FMRP) 活性增加轴突分支。在含 FUS 突变的小鼠模型神经元轴突内，FMRP 蛋白表达量增加，且蛋白质翻译被抑制 [105]。此外，在含缬酪肽蛋白 (valosin-containing protein, VCP) 突变的 ALS 运动神经元内，FUS 在轴突内增加并发生错误定位，进而扰乱了蛋白质的翻译 [106-107]。综上，FUS 基因突变会引起轴突肿胀，分支增加，其在轴突内异常聚集还会干扰蛋白质翻译。

3.3 SARM1

SARM1 是含有 Toll- 白介素 1 受体 (Toll/interleukin-1 receptor, TIR) 结构域的蛋白质，其 TIR 结构域具有烟酰胺腺嘌呤二核苷酸 (nicotinamide adenine dinucleotide, NAD) 水解酶活性 [108]。轴突损伤可激活 SARM1 介导的程序性退变信号通路，引起沃勒变性及轴突节段性消融 [109]。ALS 患者神经元内含有大量突变型 SARM1 聚集体，加速了轴突丢失 [110]。烟酰胺单核苷酸腺苷酰转移酶 2 (nicotinamide mononucleotide adenylyl transferase 2, NMNAT2) 具有 NAD 合酶活性，能够合成 NAD 保护轴突，物理损伤或病理刺激均会降低 NMNAT2 表达水平，进而激活 SARM1 并导致轴突变性，促进 ALS 发生发展 [111]；NMNAT2 减少与激活的 SARM1 信号通路综合作用使 NAD 大幅减少，可能通过抑制 ATP 合成加速轴突变性 [95, 112]。SARM1 一方面可抑制受损轴突再生能力 [113]，另一方面可调节轴突损伤引起的细胞自主反应；当坐骨神经损伤后，神经元可快速产生细胞因子和趋化因子，阻断 SARM1 信号通路可抑制免疫细胞向受损伤神经组织聚集 [114]。SARM1 缺失可缓解 TDP-43 突变小鼠轴突变性 [115]，但在携带突变超氧化物歧化酶 1 (superoxide dismutase 1, SOD1) 的小鼠模型中 SARM1 缺失不会减缓 ALS 疾病进展和运动功能衰退 [116]，提示在不同的 ALS 模型小鼠中 SARM1 的作用有所差异。综上，SARM1 的激活可导致轴突沃勒变性，其突变则会加速轴突丢失，此外 SARM1 还可调节轴突损伤引起的细胞自主反应。

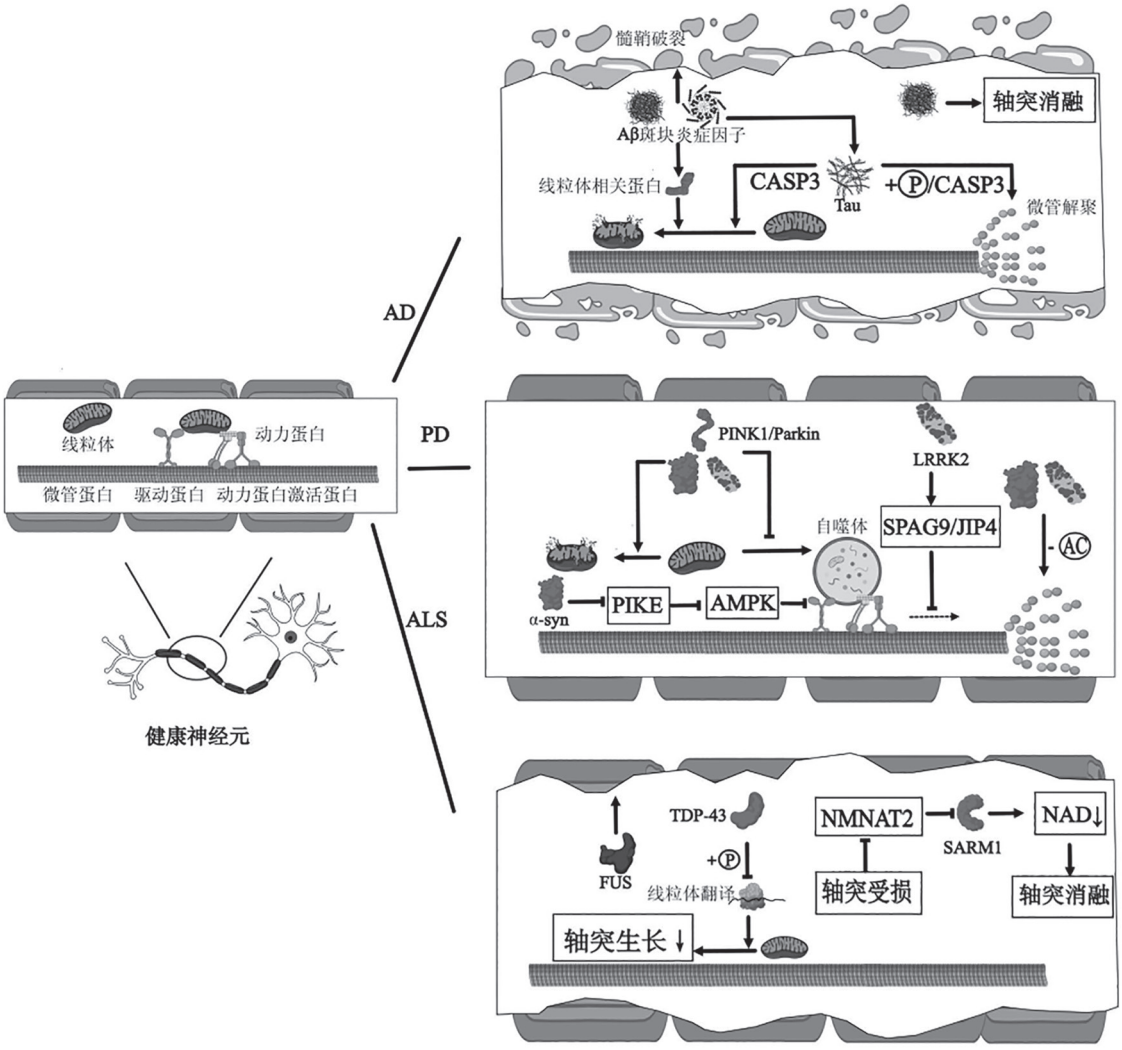
3.4 ALS的轴突损伤修复策略

改善运动神经元轴突生长和功能已成为评判 ALS 药物是否取得成功的重要指标。短期使用 SB-239063 抑制 p38 丝裂原活化蛋白激酶 (mitogen-activated protein kinases, MAPK) α 亚基成功恢复了 SOD1 小鼠的逆行轴突运输能力 [117]。MBi-9 通过抑制 BACE1，在 SOD1 小鼠中使轴突再生增加并改善肌肉神经再支配 [118]。同时，FG-3019 通过抑制结缔组织生长因子 (connective tissue growth factor, CTGF/CCN2) 活性，使坐骨神经中髓鞘变性减少，肌萎缩和运动功能改善 [119]。此外，已在临床上大规模应用的反义寡核苷酸 (antisense oligonucleotides, ASOs) 类药物也提供了新的治疗策略。利用 ASOs 降低 SARM1 水平可延缓 SARM1 单倍体不足小鼠 ($SARM1^{+/-}$) 轴突变性 [120]。针对 FUS 突变引起的 ALS，一些 ASOs 类药物临床前期试验正在进行中 [121]。不仅如此，已批准的临床一线药物在改善 ALS 轴突损伤方面也展现出良好的疗效。例如，依达拉奉作为一种自由基清除剂，可通过激活核因子 E2 相关因子 (nuclear factor-erythroid 2-related factor 2, Nrf2) 抗氧化信号通路有效防止线粒体功能受损，促进轴突转运 [122]。另外，干细胞移植在 ALS 治疗

表3 ALS轴突损伤修复方法

药品	作用机制	靶点	动物模型	剂量/给药时间	改善与否	参考文献
SB-239063	抑制p38 MAPK α	p38 MAPK α	SOD1小鼠	100 mg·kg^{-1}，4 h	改善轴突逆行转运缺陷	[117]
MBi-9	抑制BACE1	BACE1	SOD1小鼠	30 mg·kg^{-1}，2 w	轴突再生缺陷改善	[118]
FG-3019	抑制 CTGF/CCN2活性	CTGF/CCN2	SOD1小鼠	25 mg·kg^{-1}，8 w	坐骨神经中髓鞘变性减少	[119]
ASOs	降低SARM1水平	SARM1	SARM$^{+/-}$小鼠	2.3 μmol·L^{-1}，7 d	轴突变性延缓	[120]
依达拉奉	通过 Nrf2 信号通路抗氧化	Nrf2	SOD1小鼠	15 mg·kg^{-1}，6 w	恢复线粒体功能，保护轴突转运	[122, 125]

MAPK, mitogen-activated protein kinases; SOD1, superoxide dismutase 1; BACE1, β-site APP cleaving enzyme 1; CTGF/CCN2, connective tissue growth factor; ASO, antisense oligonucleotides; SARM1, sterile alpha and Toll interleukin receptor motif-containing protein 1; Nrf2, nuclear factor-erythroid 2-related factor 2; h, hour; d, day; w, week



CASP3：胱氨酸-天冬氨酸蛋白酶3 (caspase-3)；α-syn：α突触核蛋白(α-synuclein)；LRRK2：富含亮氨酸重复激酶2 (leucine-rich repeat kinase 2)；PINK1：磷酸酶和张力蛋白同源物诱导的激酶1 (phosphatase and tension homolog-induced kinase 1)；Parkin：帕金森蛋白(Parkin)；PIKE：磷酸肌醇-3激酶增强子(phosphoinositide-3 kinase enhancer)；AMPK：AMP活化蛋白激酶(AMP-activated protein kinase)；SPAG9：精子相关抗原9 (sperm-associated antigen 9)；JIP4：C-Jun氨基末端激酶相互作用蛋白4 (C-Jun NH2-terminal kinase (JNK)-interacting protein 4)；TDP-43：TAR DNA结合蛋白43 (transactive response DNA binding protein 43)；FUS：肉瘤融合蛋白(fused in sarcoma)；SARM1：无菌α和Toll白介素受体基序蛋白1 (sterile alpha and Toll interleukin receptor motif-containing protein 1)；NAD：烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide)；NMNAT2：烟酰胺单核苷酸腺苷酰转移酶2 (nicotinamide mononucleotide adenylyl transferase 2)。

图1 神经退行性疾病与轴突损伤的分子机制

方面也具有巨大潜力[123]，将人源 iPSCs 分化的脊髓运动神经元移植到靶神经中，为修复轴突损伤提供了可能[124]。表 3 对 ALS 轴突修复方法进行了归纳总结。

4 小结

综上所述，虽然 AD、PD 和 ALS 等神经退行性疾病的病理特征和临床表现各不相同，但这些疾病的共同特征是神经元轴突均受到损伤 (图 1)。轴突损伤与神经退行性疾病的致病因子大量产生密切相关，如 Aβ、α-syn 和 TDP-43 等突变蛋白[14, 99, 126]。神经元轴突损伤机制可归纳为以下三方面：(1) 损伤轴突的正常形态和结构，进而影响神经元兴奋性与电信号传导；(2) 损伤轴突的运输功能，进而影响神经元的物质传递；(3) 损伤轴突的线粒体，进而影响轴突能量供应。修复轴突损伤是治疗神经退行性疾病的重要途径之一，增加对轴突损伤机制的理解并以此为基础开展早期综合治疗，有助于减缓神经退行性疾病发生发展。

神经退行性疾病一直是热门的话题，对于其病理机制与治疗方法的探索从未停止。虽然近年来围绕特定神经元轴突损伤展开的讨论越来越多，但对其损伤机制和修复方法的研究仍处于起步阶段，现有的研究结论也存在争论[127-128]。大量研究证据表明轴突损伤与神经退行性疾病其他病理改变密切相关，如氧化应激、神经炎症、核质运输、自噬障碍等，但是对于上述病理机制之间的因果关系仍缺乏准确性描述[63, 129-130]。通过总结当前 AD、PD 和 ALS 神经元轴突受损机制和治疗方法相关研究进展，期望能为防治神经退行性疾病提供新的靶点和思考。

[参 考 文 献]

[1] Jia L, Du Y, Chu L, et al. Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60 years or older in China: a cross-sectional study. Lancet Public Health, 2020, 5: e661-71

[2] Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology, 2007, 68: 384-6

[3] Xu L, Chen L, Wang S, et al. Incidence and prevalence of amyotrophic lateral sclerosis in urban China: a national population-based study. J Neurol Neurosurg Psychiatry, 2020, 91: 520-5

[4] Huang Z, Jordan JD, Zhang Q. Myelin pathology in Alzheimer's disease: potential therapeutic opportunities. Aging Dis, 2024, 15: 698-713

[5] Koch JC, Bitow F, Haack J, et al. α-synuclein affects neurite morphology, autophagy, vesicle transport and axonal degeneration in CNS neurons. Cell Death Dis, 2015, 6: e1811

[6] Guo W, Stoklund Dittlau K, Van Den Bosch L. Axonal transport defects and neurodegeneration: molecular mechanisms and therapeutic implications. Semin Cell Dev Biol, 2020, 99: 133-50

[7] Klim JR, Williams LA, Limone F, et al. ALS-implicated protein TDP-43 sustains levels of STMN2, a mediator of motor neuron growth and repair. Nat Neurosci, 2019, 22: 167-79

[8] Liu X, Chen K, Wu T, et al. Use of multimodality imaging and artificial intelligence for diagnosis and prognosis of early stages of Alzheimer's disease. Transl Res, 2018, 194: 56-67

[9] Cheng J, North BJ, Zhang T, et al. The emerging roles of protein homeostasis-governing pathways in Alzheimer's disease. Aging Cell, 2018, 17: e12801

[10] Guo J, Cheng J, North BJ, et al. Functional analyses of major cancer-related signaling pathways in Alzheimer's disease etiology. Biochim Biophys Acta Rev Cancer, 2017, 1868: 341-58

[11] Singh N, Das B, Zhou J, et al. Targeted BACE-1 inhibition in microglia enhances amyloid clearance and improved cognitive performance. Sci Adv, 2022, 8: eabo3610

[12] Cai Y, Zhang XM, Macklin LN, et al. BACE1 elevation is involved in amyloid plaque development in the triple transgenic model of Alzheimer's disease: differential Aβ antibody labeling of early-onset axon terminal pathology. Neurotox Res, 2012, 21: 160-74

[13] Johnson VE, Stewart W, Smith DH. Traumatic brain injury and amyloid-β pathology: a link to Alzheimer's disease? Nat Rev Neurosci, 2010, 11: 361-70

[14] Yuan P, Zhang M, Tong L, et al. PLD3 affects axonal spheroids and network defects in Alzheimer's disease. Nature, 2022, 612: 328-37

[15] Du H, Guo L, Yan S, et al. Early deficits in synaptic mitochondria in an Alzheimer's disease mouse model. Proc Natl Acad Sci U S A, 2010, 107: 18670-5

[16] Wang Q, Tian J, Chen H, et al. Amyloid β-mediated KIF5A deficiency disrupts anterograde axonal mitochondrial movement. Neurobiol Dis, 2019, 127: 410-8

[17] Tammineni P, Ye X, Feng T, et al. Impaired retrograde transport of axonal autophagosomes contributes to autophagic stress in Alzheimer's disease neurons. Elife, 2017, 6: e21776

[18] Reddy PH, Oliver DM. Amyloid β and phosphorylated Tau-induced defective autophagy and mitophagy in Alzheimer's disease. Cells, 2019, 8: 488

[19] Liu Z, Yan M, Liang Y, et al. Nucleoporin Seh1 interacts with Olig2/Brd7 to promote oligodendrocyte differentiation and myelination. Neuron, 2019, 102: 587-601.e7

[20] Kenigsbuch M, Bost P, Halevi S, et al. A shared disease-associated oligodendrocyte signature among multiple CNS pathologies. Nat Neurosci, 2022, 25: 876-86

[21] Depp C, Sun T, Sasmita AO, et al. Myelin dysfunction

drives amyloid-β deposition in models of Alzheimer's disease. Nature, 2023, 618: 349-57
[22] McNamara NB, Munro DAD, Bestard-Cuche N, et al. Microglia regulate central nervous system myelin growth and integrity. Nature, 2023, 613: 120-9
[23] Peters F, Salihoglu H, Pratsch K, et al. Tau deletion reduces plaque-associated BACE1 accumulation and decelerates plaque formation in a mouse model of Alzheimer's disease. EMBO J, 2019, 38: e102345
[24] Dunckley T, Beach TG, Ramsey KE, et al. Gene expression correlates of neurofibrillary tangles in Alzheimer's disease. Neurobiol Aging, 2006, 27: 1359-71
[25] Iijima-Ando K, Sekiya M, Maruko-Otake A, et al. Loss of axonal mitochondria promotes Tau-mediated neurodegeneration and Alzheimer's disease-related Tau phosphorylation via PAR-1. PLoS Genet, 2012, 8: e1002918
[26] Wang R, Lu KP, Zhou XZ. Function and regulation of cis p-Tau in the pathogenesis and treatment of conventional and nonconventional Tauopathies. J Neurochem, 2023, 166: 904-14
[27] Zetterberg H. Review: Tau in biofluids - relation to pathology, imaging and clinical features. Neuropathol Appl Neurobiol, 2017, 43: 194-9
[28] VanItallie TB. Traumatic brain injury (TBI) in collision sports: possible mechanisms of transformation into chronic traumatic encephalopathy (CTE). Metabolism, 2019, 100s: 153943
[29] Bennett RE, Esparza TJ, Lewis HA, et al. Human apolipoprotein E4 worsens acute axonal pathology but not amyloid-β immunoreactivity after traumatic brain injury in 3xTg-AD mice. J Neuropathol Exp Neurol, 2013, 72: 396-403
[30] Smith DH, Chen XH, Nonaka M, et al. Accumulation of amyloid β and Tau and the formation of neurofilament inclusions following diffuse brain injury in the pig. J Neuropathol Exp Neurol, 1999, 58: 982-92
[31] Fujii H, Takahashi T, Mukai T, et al. Modifications of Tau protein after cerebral ischemia and reperfusion in rats are similar to those occurring in Alzheimer's disease - hyperphosphorylation and cleavage of 4- and 3-repeat Tau. J Cereb Blood Flow Metab, 2017, 37: 2441-57
[32] Alonso AD, Cohen LS, Corbo C, et al. Hyperphosphorylation of Tau associates with changes in its function beyond microtubule stability. Front Cell Neurosci, 2018, 12: 338
[33] LaPointe NE, Morfini G, Pigino G, et al. The amino terminus of Tau inhibits kinesin-dependent axonal transport: implications for filament toxicity. J Neurosci Res, 2009, 87: 440-51
[34] Olesen MA, Quintanilla RA. Pathological impact of Tau proteolytical process on neuronal and mitochondrial function: a crucial role in Alzheimer's disease. Mol Neurobiol, 2023, 60: 5691-707
[35] Leoni V. The effect of apolipoprotein e (ApoE) genotype on biomarkers of amyloidogenesis, Tau pathology and neurodegeneration in Alzheimer's disease. Clin Chem Lab Med, 2011, 49: 375-83
[36] Marsh SE, Abud EM, Lakatos A, et al. The adaptive immune system restrains Alzheimer's disease pathogenesis by modulating microglial function. Proc Natl Acad Sci U S A, 2016, 113: E1316-25
[37] Lin Y, Wen L. Inflammatory response following diffuse axonal injury. Int J Med Sci, 2013, 10: 515-21
[38] Carlos AJ, Tong L, Prieto GA, et al. IL-1β impairs retrograde flow of BDNF signaling by attenuating endosome trafficking. J Neuroinflammation, 2017, 14: 29
[39] Johnson NH, de Rivero Vaccari JP, Bramlett HM, et al. Inflammasome activation in traumatic brain injury and Alzheimer's disease. Transl Res, 2023, 254: 1-12
[40] Lue LF, Walker DG, Rogers J. Modeling microglial activation in Alzheimer's disease with human postmortem microglial cultures. Neurobiol Aging, 2001, 22: 945-56
[41] Winstone JK, Pathak KV, Winslow W, et al. Glyphosate infiltrates the brain and increases pro-inflammatory cytokine TNFα: implications for neurodegenerative disorders. J Neuroinflammation, 2022, 19: 193
[42] Perry VH, Nicoll JA, Holmes C. Microglia in neurodegenerative disease. Nat Rev Neurol, 2010, 6: 193-201
[43] Jaworski T, Lechat B, Demedts D, et al. Dendritic degeneration, neurovascular defects, and inflammation precede neuronal loss in a mouse model for Tau-mediated neurodegeneration. Am J Pathol, 2011, 179: 2001-15
[44] Ising C, Venegas C, Zhang S, et al. NLRP3 inflammasome activation drives Tau pathology. Nature, 2019, 575: 669-73
[45] Stancu IC, Cremers N, Vanrusselt H, et al. Aggregated Tau activates NLRP3-ASC inflammasome exacerbating exogenously seeded and non-exogenously seeded Tau pathology *in vivo*. Acta Neuropathol, 2019, 137: 599-617
[46] Zhang X, Wang R, Hu D, et al. Oligodendroglial glycolytic stress triggers inflammasome activation and neuropathology in Alzheimer's disease. Sci Adv, 2020, 6: eabb8680
[47] Heneka MT, McManus RM, Latz E. Inflammasome signalling in brain function and neurodegenerative disease. Nat Rev Neurosci, 2018, 19: 610-21
[48] Djordjevic J, Sabbir MG, Albensi BC. Traumatic brain injury as a risk factor for Alzheimer's disease: is inflammatory signaling a key player? Curr Alzheimer Res, 2016, 13: 730-8
[49] Chen CH, Zhou W, Liu S, et al. Increased NF-κB signalling up-regulates BACE1 expression and its therapeutic potential in Alzheimer's disease. Int J Neuropsychopharmacol, 2012, 15: 77-90
[50] Rajesh Y, Kanneganti TD. Innate immune cell death in neuroinflammation and Alzheimer's disease. Cells, 2022, 11: 1885
[51] González H, Pacheco R. T-cell-mediated regulation of neuroinflammation involved in neurodegenerative diseases. J Neuroinflammation, 2014, 11: 201
[52] Yang H, Jiang L, Zhang Y, et al. Anti-LINGO-1 antibody treatment alleviates cognitive deficits and promotes maturation of oligodendrocytes in the hippocampus of APP/PS1 mice. J Comp Neurol, 2022, 530: 1606-21
[53] Xie YY, Pan TT, Xu DE, et al. Clemastine ameliorates

myelin deficits via preventing senescence of oligodendrocytes precursor cells in Alzheimer's disease model mouse. Front Cell Dev Biol, 2021, 9: 733945

[54] Onishi T, Maeda R, Terada M, et al. A novel orally active HDAC6 inhibitor T-518 shows a therapeutic potential for Alzheimer's disease and Tauopathy in mice. Sci Rep, 2021, 11: 15423

[55] Fernandez-Valenzuela JJ, Sanchez-Varo R, Munoz-Castro C, et al. Enhancing microtubule stabilization rescues cognitive deficits and ameliorates pathological phenotype in an amyloidogenic Alzheimer's disease model. Sci Rep, 2020, 10: 14776

[56] Cross DJ, Huber BR, Silverman MA, et al. Intranasal paclitaxel alters Alzheimer's disease phenotypic features in 3xTg-AD mice. J Alzheimers Dis, 2021, 83: 379-94

[57] Yao Y, Nzou G, Alle T, et al. Correction of microtubule defects within Aβ plaque-associated dystrophic axons results in lowered Aβ release and plaque deposition. Alzheimers Dement, 2020, 16: 1345-57

[58] Piedrahita D, Castro-Alvarez JF, Boudreau RL, et al. β-secretase 1's targeting reduces hyperphosphorilated Tau, implying autophagy actors in 3xTg-AD mice. Front Cell Neurosci, 2015, 9: 498

[59] Yang X, Tohda C. Diosgenin restores Aβ-induced axonal degeneration by reducing the expression of heat shock cognate 70 (HSC70). Sci Rep, 2018, 8: 11707

[60] Yang X, Tohda C. Heat shock cognate 70 inhibitor, VER-155008, reduces memory deficits and axonal degeneration in a mouse model of Alzheimer's disease. Front Pharmacol, 2018, 9: 48

[61] Kang SS, Zhang Z, Liu X, et al. α-synuclein binds and sequesters PIKE-L into lewy bodies, triggering dopaminergic cell death via AMPK hyperactivation. Proc Natl Acad Sci U S A, 2017, 114: 1183-8

[62] Oliveras-Ferraros C, Vazquez-Martin A, Menendez JA. Genome-wide inhibitory impact of the AMPK activator metformin on [kinesins, tubulins, histones, auroras and polo-like kinases] M-phase cell cycle genes in human breast cancer cells. Cell Cycle, 2009, 8: 1633-6

[63] Cai Q, Ganesan D. Regulation of neuronal autophagy and the implications in neurodegenerative diseases. Neurobiol Dis, 2022, 162: 105582

[64] Yang X, Wang J, Zeng W, et al. Time-dependent alterations in the rat nigrostriatal system after intrastriatal injection of fibrils formed by α-syn and Tau fragments. Front Aging Neurosci, 2022, 14: 1049418

[65] Ripon MKH, Lee H, Dash R, et al. N-acetyl-D-glucosamine kinase binds dynein light chain roadblock 1 and promotes protein aggregate clearance. Cell Death Dis, 2020, 11: 619

[66] Prots I, Veber V, Brey S, et al. α-synuclein oligomers impair neuronal microtubule-kinesin interplay. J Biol Chem, 2013, 288: 21742-54

[67] Portran D, Schaedel L, Xu Z, et al. Tubulin acetylation protects long-lived microtubules against mechanical ageing. Nat Cell Biol, 2017, 19: 391-8

[68] Stykel MG, Humphries K, Kirby MP, et al. Nitration of microtubules blocks axonal mitochondrial transport in a human pluripotent stem cell model of Parkinson's disease. FASEB J, 2018, 32: 5350-64

[69] Grassi D, Diaz-Perez N, Volpicelli-Daley LA, et al. Pα-syn* mitotoxicity is linked to MAPK activation and involves Tau phosphorylation and aggregation at the mitochondria. Neurobiol Dis, 2019, 124: 248-62

[70] Deniston CK, Salogiannis J, Mathea S, et al. Structure of LRRK2 in Parkinson's disease and model for microtubule interaction. Nature, 2020, 588: 344-9

[71] Onishi K, Tian R, Feng B, et al. LRRK2 mediates axon development by regulating frizzled3 phosphorylation and growth cone-growth cone communication. Proc Natl Acad Sci U S A, 2020, 117: 18037-48

[72] Godena VK, Brookes-Hocking N, Moller A, et al. Increasing microtubule acetylation rescues axonal transport and locomotor deficits caused by LRRK2 Roc-COR domain mutations. Nat Commun, 2014, 5: 5245

[73] Boecker CA, Holzbaur ELF. Hyperactive LRRK2 kinase impairs the trafficking of axonal autophagosomes. Autophagy, 2021, 17: 2043-5

[74] Boecker CA, Goldsmith J, Dou D, et al. Increased LRRK2 kinase activity alters neuronal autophagy by disrupting the axonal transport of autophagosomes. Curr Biol, 2021, 31: 2140-54.e6

[75] Pozo Devoto VM, Onyango IG, Stokin GB. Mitochondrial behavior when things go wrong in the axon. Front Cell Neurosci, 2022, 16: 959598

[76] Safiulina D, Kuum M, Choubey V, et al. Miro proteins prime mitochondria for parkin translocation and mitophagy. EMBO J, 2019, 38: e99384

[77] Eberhardt EL, Ludlam AV, Tan Z, et al. Miro: a molecular switch at the center of mitochondrial regulation. Protein Sci, 2020, 29: 1269-84

[78] Prots I, Grosch J, Brazdis RM, et al. α-synuclein oligomers induce early axonal dysfunction in human iPSC-based models of synucleinopathies. Proc Natl Acad Sci U S A, 2018, 115: 7813-8

[79] Hsieh CH, Shaltouki A, Gonzalez AE, et al. Functional impairment in Miro degradation and mitophagy is a shared feature in familial and sporadic Parkinson's disease. Cell Stem Cell, 2016, 19: 709-24

[80] Sferra A, Nicita F, Bertini E. Microtubule dysfunction: a common feature of neurodegenerative diseases. Int J Mol Sci, 2020, 21: 7354

[81] Tan LY, Tang KH, Lim LYY, et al. α-synuclein at the presynaptic axon terminal as a double-edged sword. Biomolecules, 2022, 12: 507

[82] El-Saiy KA, Sayed RH, El-Sahar AE, et al. Modulation of histone deacetylase, the ubiquitin proteasome system, and autophagy underlies the neuroprotective effects of venlafaxine in a rotenone-induced Parkinson's disease model in rats. Chem Biol Interact, 2022, 354: 109841

[83] Chen X, Wales P, Quinti L, et al. The sirtuin-2 inhibitor AK7 is neuroprotective in models of Parkinson's disease but not amyotrophic lateral sclerosis and cerebral ischemia. PLoS One, 2015, 10: e0116919

[84] Singh AP, Nigam L, Yadav Y, et al. Design and *in vitro*

analysis of SIRT2 inhibitor targeting Parkinson's disease. Mol Divers, 2021, 25: 2261-70
[85] Varidaki A, Hong Y, Coffey ET. Repositioning microtubule stabilizing drugs for brain disorders. Front Cell Neurosci, 2018, 12: 226
[86] Schofield DJ, Irving L, Calo L, et al. Preclinical development of a high affinity α-synuclein antibody, MEDI1341, that can enter the brain, sequester extracellular α-synuclein and attenuate α-synuclein spreading *in vivo*. Neurobiol Dis, 2019, 132: 104582
[87] Spencer B, Valera E, Rockenstein E, et al. Anti-α-synuclein immunotherapy reduces α-synuclein propagation in the axon and degeneration in a combined viral vector and transgenic model of synucleinopathy. Acta Neuropathol Commun, 2017, 5: 7
[88] Francelle L, Outeiro TF, Rappold GA. Inhibition of HDAC6 activity protects dopaminergic neurons from α-synuclein toxicity. Sci Rep, 2020, 10: 6064
[89] Cartelli D, Casagrande F, Busceti CL, et al. Microtubule alterations occur early in experimental parkinsonism and the microtubule stabilizer epothilone D is neuroprotective. Sci Rep, 2013, 3: 1837
[90] Shefner JM, Musaro A, Ngo ST, et al. Skeletal muscle in amyotrophic lateral sclerosis. Brain, 2023, 146: 4425-36
[91] Niedermeyer S, Murn M, Choi PJ. Respiratory failure in amyotrophic lateral sclerosis. Chest, 2019, 155: 401-8
[92] Mulder DW, Kurland LT, Offord KP, et al. Familial adult motor neuron disease: amyotrophic lateral sclerosis. Neurology, 1986, 36: 511-7
[93] Klim JR, Pintacuda G, Nash LA, et al. Connecting TDP-43 pathology with neuropathy. Trends Neurosci, 2021, 44: 424-40
[94] Humphrey J, Birsa N, Milioto C, et al. FUS ALS-causative mutations impair FUS autoregulation and splicing factor networks through intron retention. Nucleic Acids Res, 2020, 48: 6889-905
[95] Jiang Y, Liu T, Lee CH, et al. The NAD^+-mediated self-inhibition mechanism of pro-neurodegenerative SARM1. Nature, 2020, 588: 658-63
[96] Riva N, Gentile F, Cerri F, et al. Phosphorylated TDP-43 aggregates in peripheral motor nerves of patients with amyotrophic lateral sclerosis. Brain, 2022, 145: 276-84
[97] Ayala YM, Zago P, D'Ambrogio A, et al. Structural determinants of the cellular localization and shuttling of TDP-43. J Cell Sci, 2008, 121: 3778-85
[98] Altman T, Ionescu A, Ibraheem A, et al. Axonal TDP-43 condensates drive neuromuscular junction disruption through inhibition of local synthesis of nuclear encoded mitochondrial proteins. Nat Commun, 2021, 12: 6914
[99] Asakawa K, Handa H, Kawakami K. Optogenetic modulation of TDP-43 oligomerization accelerates ALS-related pathologies in the spinal motor neurons. Nat Commun, 2020, 11: 1004
[100] Briese M, Saal-Bauernschubert L, Lüningschrör P, et al. Loss of TDP-43 disrupts the axonal transcriptome of motoneurons accompanied by impaired axonal translation and mitochondria function. Acta Neuropathol Commun, 2020, 8: 116
[101] Sleigh JN, Tosolini AP, Gordon D, et al. Mice carrying ALS mutant TDP-43, but not mutant FUS, display *in vivo* defects in axonal transport of signaling endosomes. Cell Rep, 2020, 30: 3655-62.e2
[102] Naumann M, Pal A, Goswami A, et al. Impaired DNA damage response signaling by FUS-NLS mutations leads to neurodegeneration and FUS aggregate formation. Nat Commun, 2018, 9: 335
[103] Akiyama T, Suzuki N, Ishikawa M, et al. Aberrant axon branching via Fos-B dysregulation in FUS-ALS motor neurons. EBioMedicine, 2019, 45: 362-78
[104] Garone MG, Birsa N, Rosito M, et al. ALS-related FUS mutations alter axon growth in motoneurons and affect HuD/ELAVL4 and FMRP activity. Commun Biol, 2021, 4: 1025
[105] Birsa N, Ule AM, Garone MG, et al. FUS-ALS mutants alter FMRP phase separation equilibrium and impair protein translation. Sci Adv, 2021, 7: eabf8660
[106] Harley J, Hagemann C, Serio A, et al. FUS is lost from nuclei and gained in neurites of motor neurons in a human stem cell model of VCP-related ALS. Brain, 2020, 143: e103
[107] López-Erauskin J, Tadokoro T, Baughn MW, et al. ALS/FTD-linked mutation in FUS suppresses intra-axonal protein synthesis and drives disease without nuclear loss-of-function of FUS. Neuron, 2020, 106: 354
[108] Essuman K, Summers DW, Sasaki Y, et al. The SARM1 Toll/interleukin-1 receptor domain possesses intrinsic NAD^+ cleavage activity that promotes pathological axonal degeneration. Neuron, 2017, 93: 1334-43.e5
[109] Figley MD, DiAntonio A. The SARM1 axon degeneration pathway: control of the NAD^+ metabolome regulates axon survival in health and disease. Curr Opin Neurobiol, 2020, 63: 59-66
[110] Bloom AJ, Mao X, Strickland A, et al. Constitutively active SARM1 variants that induce neuropathy are enriched in ALS patients. Mol Neurodegener, 2022, 17: 1
[111] Li W, Gao M, Hu C, et al. Nmnat2: an important metabolic enzyme affecting the disease progression. Biomed Pharmacother, 2023, 158: 114143
[112] Coleman MP, Höke A. Programmed axon degeneration: from mouse to mechanism to medicine. Nat Rev Neurosci, 2020, 21: 183-96
[113] Czech VL, O'Connor LC, Philippon B, et al. TIR-1/SARM1 inhibits axon regeneration and promotes axon degeneration. Elife, 2023, 12: e80856
[114] Wang Q, Zhang S, Liu T, et al. SARM1/myd88-5 regulates neuronal intrinsic immune response to traumatic axonal injuries. Cell Rep, 2018, 23: 716-24
[115] White MA, Lin Z, Kim E, et al. SARM1 deletion suppresses TDP-43-linked motor neuron degeneration and cortical spine loss. Acta Neuropathol Commun, 2019, 7: 166
[116] Collins JM, Atkinson RAK, Matthews LM, et al. SARM1 knockout modifies biomarkers of neurodegeneration and spinal cord circuitry but not disease progression in the

mSOD1(G93A) mouse model of ALS. Neurobiol Dis, 2022, 172: 105821
[117] Gibbs KL, Kalmar B, Rhymes ER, et al. Inhibiting p38 MAPK α rescues axonal retrograde transport defects in a mouse model of ALS. Cell Death Dis, 2018, 9: 596
[118] Tallon C, Marshall KL, Kennedy ME, et al. Pharmacological BACE inhibition improves axonal regeneration in nerve injury and disease models. Neurotherapeutics, 2020, 17: 973-88
[119] Gonzalez D, Rebolledo DL, Correa LM, et al. The inhibition of CTgF/CCN2 activity improves muscle and locomotor function in a murine ALS model. Hum Mol Genet, 2018, 27: 2913-26
[120] Gould SA, Gilley J, Ling K, et al. SARM1 haploinsufficiency or low expression levels after antisense oligonucleotides delay programmed axon degeneration. Cell Rep, 2021, 37: 110108
[121] Cappella M, Pradat PF, Querin G, et al. Beyond the traditional clinical trials for amyotrophic lateral sclerosis and the future impact of gene therapy. J Neuromuscul Dis, 2021, 8: 25-38
[122] Cha SJ, Kim K. Effects of the edaravone, a drug approved for the treatment of amyotrophic lateral sclerosis, on mitochondrial function and neuroprotection. Antioxidants (Basel), 2022, 11: 195
[123] Baloh RH, Glass JD, Svendsen CN. Stem cell transplantation for amyotrophic lateral sclerosis. Curr Opin Neurol, 2018, 31: 655-61
[124] Bazarek S, Johnston BR, Sten M, et al. Spinal motor neuron transplantation to enhance nerve reconstruction strategies: towards a cell therapy. Exp Neurol, 2022, 353: 114054
[125] Shen Y, Zhang J, Xu Y, et al. Ultrasound-enhanced brain delivery of edaravone provides additive amelioration on disease progression in an ALS mouse model. Brain Stimul, 2023, 16: 628-41
[126] Murphy J, McKernan DP. The effect of aggregated alpha synuclein on synaptic and axonal proteins in Parkinson's disease-a systematic review. Biomolecules, 2022, 12: 1199
[127] Merlini E, Coleman MP, Loreto A. Mitochondrial dysfunction as a trigger of programmed axon death. Trends Neurosci, 2022, 45: 53-63
[128] Peters OM, Weiss A, Metterville J, et al. Genetic diversity of axon degenerative mechanisms in models of Parkinson's disease. Neurobiol Dis, 2021, 155: 105368
[129] Argueti-Ostrovsky S, Alfahel L, Kahn J, et al. All roads lead to rome: different molecular players converge to common toxic pathways in neurodegeneration. Cells, 2021, 10: 2438
[130] Tesco G, Lomoio S. Pathophysiology of neurodegenerative diseases: an interplay among axonal transport failure, oxidative stress, and Inflammation? Semin Immunol, 2022, 59: 101628