·专题综述·

帕金森病疾病修饰治疗进展

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【摘要】 延缓或阻止帕金森病神经退行性变进程仍是帕金森病治疗领域的难题，而疾病修饰治疗是一种改变疾病自然病程的干预措施，目前一系列潜在的疾病修饰治疗药物正在研发。本文综述靶向α-突触核蛋白药物、靶向*LRRK2*基因变异药物、靶向*GBA*基因变异药物、靶向线粒体功能障碍药物、胰高血糖素样肽-1受体激动药、靶向炎症反应药物、钙拮抗药和铁螯合剂等方面对帕金森病疾病修饰治疗的最新研究进展。

【关键词】 帕金森病； 神经保护； 药物疗法； 综述

New advance for disease modification therapy in Parkinson´s disease

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【Abstract】 Therapy to halt or slow down the progression of neurodegeneration in Parkinson′s disease (PD) is urgently demand. Disease modification therapy can modify the natural history of the disease and show neuroprotective effect in PD. Currently, many potential neuroprotective therapies are emerging. The review aims to summarize the new advances for disease modification therapies in PD including targeting drugs α-synuclein, *LRRK2* gene, *GBA* gene, mitochondrial function, glucagon-like peptide-1 (GLP-1), neuroinflammation, calcium antagonist and iron chelating agent.

【Key words】 Parkinson disease; Neuroprotection; Drug therapy; Review

This study was supported by the Science and Technology Foundation of Chengdu Science and Technology Bureau (No. 2019-YF05-00307-SN) and the 1·3·5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (No. ZYJC18038).

Conflicts of interest: none declared

目前尚无法满足的帕金森病治疗需求之一为延缓或阻止神经退行性变进展。疾病修饰治疗是一种改变自然病程的干预措施，可以影响神经元变性的初始触发因素，并促使神经元代偿反应或减少病理传播和进展[1]。帕金森病疾病修饰治疗的首要目的是神经保护。尽管迄今已完成的疾病修饰治疗试验均以失败告终[2]，但仍无法阻止一系列有潜在希望的疾病修饰治疗药物的研发。本文拟从靶向α-突触核蛋白(α-Syn)药物、靶向*LRRK2*基因变异药物、靶向*GBA*基因变异药物、靶向线粒体功能障碍药物、胰高血糖素样肽-1(GLP-1)受体激动药、靶向炎症反应药物、钙拮抗药和铁螯合剂等方面对帕金森病疾病修饰治疗最新进展进行概述，以为临床治疗提供新的思路。

一、靶向α-突触核蛋白药物

路易小体(LB)内α-Syn聚集在帕金森病的发病机制中具有核心作用[3]。业已证实，内溶酶体系统形成错误折叠α-Syn聚集物和α-Syn自我清除障碍是形成路易小体的重要原因[4]，通过小干扰RNA(siRNA)或反义寡核苷酸(ASO)的基因干扰方法以减少α-Syn聚集是帕金森病的潜在治疗方法。目前，首个抗α-Syn反义寡核苷酸的Ⅰ期临床试验(试验编号：NCT04165486)已经启动。另一种可以抑制α-Syn聚集的新型寡聚体调节剂为Anle138b[5]，其动物实验显示具有阻止帕金森病模型小鼠多巴胺能神经元死亡，并改善步态之功效[6]。目前关于

doi：10.3969/j.issn.1672-6731.2022.03.005

基金资助：四川省成都市科学技术局科技项目(项目编号：2019-YF05-00307-SN)；四川大学华西医院学科卓越发展1·3·5工程(项目编号：ZYJC18038)

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Anle138b的Ⅰ期临床试验(试验编号:NCT04208152)正在进行中。其他新型小分子抑制剂如NPT200-11,业已在帕金森病模型小鼠中证实其可靶向α-Syn特殊区域,而该区域是形成错误折叠α-Syn聚集物的关键区域[7],但尚未进入临床试验阶段。

朊蛋白样繁殖与细胞间传递的错误折叠α-Syn聚集物在帕金森病进展中发挥关键作用[8],针对这一机制而研发的抗α-Syn抗体是一种潜在的治疗药物[9]。研究显示,特异性抗α-Syn单克隆抗体可以促进α-Syn聚集物降解,保护多巴胺能神经元[10],并阻止其在多巴胺能神经元之间的传播[11]。抗α-Syn抗体治疗有主动免疫(疫苗:PD01A和PD03A)和被动免疫[抗体:BIIB054(RO7046015)、BAN0805(MEDI1341)、PRX002(AF82422)]两种方法[12]。尽管Jankovic等[13]和Brys等[14]均发现,帕金森病患者经抗α-Syn抗体治疗后血清α-Syn水平下降,提示抗α-Syn抗体对靶点有效。但这两项抗α-Syn抗体治疗帕金森病的随机对照Ⅱ期临床试验(试验编号:NCT03318523,NCT03100149)均显示,其主要终点结局指标——国际运动障碍协会(MDS)统一帕金森病评价量表(UPDRS)运动评分在治疗前后并无显著变化[15-16]。

激活α-Syn自噬是帕金森病疾病修饰治疗的另一种潜在策略[17],主要药物为尼洛替尼,是一种治疗慢性髓细胞性白血病(CML)的*ABL*基因非受体酪氨酸激酶(RTK)抑制剂[18]。*ABL*基因参与包括自噬在内的多种生理功能[19]。针对帕金森病小鼠模型的研究显示,尼洛替尼通过诱导自噬和清除α-Syn逆转多巴胺能神经元丢失[20];而且小样本临床研究亦证实尼洛替尼治疗帕金森病具有良好的安全性和耐受性[21-22]。然而两项Ⅱ期临床试验(试验编号:NCT02954978,NCT03205488)均显示,尼洛替尼的中枢神经系统渗透性较低,临床疗效较差,限制了其未来的开发潜力[23-24]。另一项针对尼洛替尼治疗帕金森病的Ⅱ期试验(试验编号:NCT03655236)正在进行中。此外,新研发的新型中枢神经系统渗透型*ABL*基因抑制剂K-0706(试验编号:NCT02970019)和ikt-148009(试验编号:NCT04350177)正在进行Ⅱ期和Ⅰ期临床试验。

应用上述靶向α-Syn药物时,应考虑到α-Syn反义寡核苷酸策略有可能干扰α-Syn参与突触结构的维持和多巴胺神经递质的释放。

二、靶向*LRRK2*基因变异药物

*LRRK2*基因的常见变异位点可增加帕金森病的发病风险[25]。*LRRK2*基因Gly2019Ser位点变异是最常见的常染色体显性遗传性帕金森病致病原因,可以导致富亮氨酸重复序列激酶2(LRRK2)活性增强和自噬中断[26]。*LRRK2*基因变异可以通过激活自噬-溶酶体系统和导致线粒体功能障碍等以促进α-Syn异常聚集[27]。与不携带*LRRK2*基因变异的帕金森病患者相比,携带*LRRK2*基因变异的患者发病年龄更早,运动症状进展更迅速[28];而携带*LRRK2*基因罕见或可能致病变异的早发型帕金森病患者与散发性早发型帕金森病患者的临床特征无显著差异[29]。LRRK2激酶抑制剂通过促进自噬以预防神经退行性变[26]。既往曾因LRRK2激酶抑制剂的肺毒性作用而限制其临床应用。目前,两种新型LRRK2激酶抑制剂——DNL201和DNL151的安全性和耐受性Ⅰb期临床试验(试验编号:NCT03710707和NCT04056689)正在进行中。不携带*LRRK2*基因变异的散发性帕金森病患者是否可从LRRK2激酶抑制剂中获益尚不清楚,因此该药物能否广泛应用尚待进一步研究证实。此外,针对帕金森病小鼠模型的研究显示,LRRK2反义寡核苷酸可以减少α-Syn的聚集[30-31]。经鞘内注射LRRK2反义寡核苷酸BIIB094治疗帕金森病安全性和耐受性的Ⅰ期临床试验(试验编号:NCT03976349)正在进行中。

三、靶向*GBA*基因变异药物

编码溶酶体酶β-葡萄糖脑苷酯酶的*GBA*基因变异与帕金森病有关联[29]。*GBA*基因变异可以导致β-葡萄糖脑苷酯酶在内质网降解,活性降低,从而导致溶酶体功能障碍和α-Syn聚集[32]。研究显示,携带*GBA*基因变异较不携带*GBA*基因变异的早发型帕金森病患者的发病年龄更早、认知功能下降速度更迅速[33]。体外研究显示,氨溴索可使携带*GBA*基因变异的纤维母细胞系β-葡萄糖脑苷酯酶活性增强,降低α-Syn水平[34]。一项采用氨溴索治疗携带或不携带*GBA*基因变异的帕金森病的Ⅱ期临床试验(试验编号:NCT02941822)显示,大剂量(1.26 g/d,约为推荐剂量的10倍)氨溴索口服安全性较高,并且具有中枢神经系统渗透性,可使脑脊液α-Syn水平降低和β-葡萄糖脑苷酯酶活性增强,提示氨溴索具有治疗的靶向作用[35]。目前一项更大规模的氨溴索治疗帕金森病的Ⅱ期前瞻性开放

标签临床试验(试验编号:NCT02914366)正在进行中[36]。此外,一种新型β-葡萄糖脑苷酯酶小分子激活物LTI-291正在进行Ⅰ期临床试验(试验编号:NTR6705和NTR7299)。其他新型药物包括β-葡萄糖脑苷酯酶激活物[37]和针对携带*GBA*基因变异帕金森病患者β-葡萄糖脑苷酯酶活性的转基因治疗(病毒载体PR001)正处于临床前研究阶段[38]。

葡萄糖神经酰胺(glucosylceramide)是β-葡萄糖脑苷酯酶底物,*GBA*基因变异使β-葡萄糖脑苷酯酶活性降低,从而导致底物堆积,影响神经元功能,提示抑制底物也有神经保护作用[39]。Venglustat、Ibiglustat(或GZ/SAR402671)和GZ667161(可透过血-脑屏障)是3种不同的葡萄糖神经酰胺合成酶抑制剂[40]。在携带或不携带*GBA*基因变异的帕金森病转基因小鼠模型中,葡萄糖神经酰胺合成酶抑制剂可以减少α-Syn聚集[41]。然而,Venglustat治疗帕金森病的Ⅱ期临床试验(试验编号:NCT02906020)的主要结局终点指标——UPDRS运动评分在治疗前后无显著变化[42]。由于不同*GBA*基因变异造成的β-葡萄糖脑苷脂酶活性降低程度不同,未来可能需要招募携带特定*GBA*基因变异的帕金森病患者以确保临床试验的成功[25]。

四、靶向线粒体功能障碍药物

线粒体是神经元的重要组成部分,对维持正常神经元功能具有重要作用,线粒体α-Syn聚集可损伤线粒体功能并导致细胞死亡[43]。*Parkin*、*DJ-1*和*PINK1*基因变异主要通过损伤线粒体功能导致常染色体隐性遗传性帕金森病;散发性帕金森病同样存在线粒体功能障碍[43]。尽管帕金森病动物模型显示针对线粒体的治疗效果令人鼓舞,但线粒体功能保护药如降糖药、尿酸盐、肌苷、辅酶Q10等的临床试验均告失败。例如,降糖药吡格列酮可以通过改善线粒体功能,阻止帕金森病模型小鼠的神经退行性变[44],但相关多中心随机双盲对照Ⅱ期临床试验(试验编号:NCT01280123)并未发现该药可以延缓帕金森病进展[45];尿酸盐(一种抗氧化剂)具有减少帕金森病模型大鼠多巴胺能神经元丢失的作用;而肌苷可以有效提高血清和脑脊液尿酸盐水平,但随机对照Ⅲ期临床试验(试验编号:NCT00833690)并未发现肌苷有神经保护作用[46];一项为期16个月的随机对照临床试验(试验编号:NCT00740714)亦未发现辅酶Q10具有神经保护作用[47],目前,来自德国的一项辅酶Q10治疗*parkin*基因变异的帕金森病的临床试验(试验编号:DRKS0001588)正在进行中[48],其结果值得期待。熊去氧胆酸具有良好的中枢神经系统渗透性,可以改善线粒体功能,具有改善散发性帕金森病患者周围组织线粒体功能的潜力[49]。两项评估熊去氧胆酸安全性和有效性的临床试验(试验编号:NCT02967250,NCT03840005)正在进行中[50-51],均采用^{31}P-MRS测量ATP含量以确定药物靶向作用,其中,Sathe等[50]采用7.0T MRI量化枕叶能量代谢产物,Payne等[51]采用3.0T MRI确定黑质中药物靶向作用。上述靶向线粒体功能障碍药物临床试验的失败,提示针对单一靶点进行干预对复杂神经系统疾病的疗效有限。

五、胰高血糖素样肽-1受体激动药

胰岛素抵抗可导致帕金森病特异性病理改变和多巴胺能神经元变性[52],而2型糖尿病可增加帕金森病的发病风险[53],提示胰岛素信号转导通路可以作为帕金森病疾病修饰治疗的新靶点。GLP-1受体激动药是其中最有希望的一类药物[54],通过减少神经炎症[55]和α-Syn聚集[56]等以发挥神经保护作用。艾塞那肽是最常用的GLP-1受体激动药。一项开放标签的Ⅱ期临床试验(试验编号:NCT01174810)显示,艾塞那肽可以改善帕金森病患者运动功能和认知功能[57],且停药12个月后仍维持疗效[58]。随后一项随机双盲安慰剂对照Ⅱ期临床试验(试验编号:NCT01971242)显示,与安慰剂相比,经艾塞那肽(2 mg/周)治疗48周的帕金森病患者"关"期UPDRS运动评分更低,且停药12周后组间仍有差异[59]。为进一步探究艾塞那肽的靶向作用,纵向采集上述两项临床试验患者的血液样本,分离源自神经元的外泌体,结果显示,帕金森病患者经艾塞那肽治疗后胰岛素信号转导、丝氨酸/苏氨酸激酶(AKT)和哺乳动物雷帕霉素靶蛋白(mTOR)信号转导通路活性增强,且总mTOR和磷酸化mTOR表达变化与UPDRS运动评分呈正相关[60]。目前,艾塞那肽Ⅲ期临床试验(试验编号:ISRCTN14552789)及其他艾塞那肽类似物的Ⅱ/Ⅲ期临床试验(试验编号:NCT04154072,NCT02953665,NCT03439943,NCT03659682)正在进行中[61]。艾塞那肽是唯一进入Ⅲ期临床试验的疾病修饰治疗药物。

六、靶向炎症反应药物

炎症反应是帕金森病患者相对出现较早的临床特征[62],可以作为潜在的疾病修饰治疗靶点。聚集的α-Syn通过激活小胶质细胞、$CD4^+$T细胞和巨噬

细胞以调节炎症反应[63],过度激活细胞因子可以促进神经退行性变[64]。

沙格司亭是一种重组人粒细胞-巨噬细胞集落刺激因子(rhGM-CSF),具有改善调节性T细胞(Treg)功能,并延缓帕金森病患者运动症状进展之功效[65]。

Verdiperstat(AZD3241)是一种选择性、不可逆性髓过氧化物酶(MPO)抑制剂,可以抑制小胶质细胞活化,保护多巴胺能神经元,在Ⅰ期/Ⅱ期临床试验中耐受性良好[66]。一项基于PET显像的随机对照Ⅱ期试验(试验编号:NCT01527695)显示,帕金森病患者经AZD3241治疗后脑组织^{11}C-PBR28与转位蛋白的结合减少,支持其对小胶质细胞具有靶向作用[66]。研究显示,小胶质细胞中核苷酸结合寡聚化结构域样受体蛋白3(NLRP3)的激活与帕金森病的发病相关[67];而NLRP3抑制剂MCC950可以减轻帕金森病患者全身炎症反应[68],以及抑制炎症小体激活,进而减少α-Syn聚集,改善运动功能,防止神经退行性变[69]。目前一种新型NLRP3抑制剂Inzomelid正在进行Ⅱ期临床试验(试验编号:NCT04015076)。

部分帕金森病的周围免疫系统激活由周围组织中致病性α-Syn驱动[64]。这一过程可加重脑组织炎症反应和神经退行性变,加速运动障碍进展[70]。硫唑嘌呤作为一种免疫抑制剂,广泛应用于一系列免疫相关性疾病的治疗[71]。2021年启动的Ⅱ期临床试验(试验编号:EudraCT 2018-003089-14)旨在探讨硫唑嘌呤治疗12个月是否可以延缓早期帕金森病患者的运动障碍进展以及停药6个月后是否仍维持疗效[71]。

辛伐他汀作为降胆固醇药物,可以通过免疫抑制等多种途径阻止啮齿类动物神经变性并改善其行为障碍,提示辛伐他汀可能具有疾病修饰治疗作用[72-73]。然而一项辛伐他汀(80 mg/d)治疗帕金森病的Ⅱ期临床试验(试验编号:NCT02787590)显示,主要终点结局指标——UPDRS运动评分治疗前后无显著变化,未能证实其疾病修饰治疗作用,故其具体作用尚待进一步研究[74]。

七、钙拮抗药和铁螯合剂

黑质致密部依赖L型电压门控性钙离子通道(VGCC,Cav1.3)的特定神经元群具有自发性起搏器特性,可以促进钙离子进入细胞[75]。细胞内钙离子内流可加速氧化应激、线粒体损伤和细胞凋亡[76]。研究显示,长期应用钙拮抗药的高血压患者罹患帕金森病的风险显著降低[77]。帕金森病大鼠模型研究显示,采用基因疗法沉默纹状体Cav1.3表达可预防和改善左旋多巴诱导的异动症[78]。依拉地平是一种具有中枢神经系统渗透性的二氢吡啶通道阻断药,对Cav1.3或Cav1.2具有高亲和性阻断作用,在帕金森病小鼠模型中显示出神经保护作用[79]。尽管Ⅱ期临床试验(试验编号:NCT00909545)显示,依拉地平治疗早期帕金森病具有良好的安全性和耐受性,且耐受剂量达10 mg/d[80],但随机对照Ⅲ期临床试验(试验编号:NCT02168842)并未显示该药具有降低患者UPDRS运动评分之功效[81]。

尸检和影像学研究业已证实,帕金森病患者黑质致密部铁离子超载[82-83]。铁离子超载可通过多种机制导致多巴胺能神经元凋亡,包括增加线粒体氧化应激、参与细胞程序性死亡和减少α-Syn聚集[84]。一项采用UPDRS评分和T_2*WI测量铁含量以评估帕金森病进展的小样本临床试验(试验编号:NCT01539837)显示,铁螯合剂去铁酮可以延缓疾病进展[85]。目前,一项大样本的去铁酮治疗帕金森病的随机安慰剂对照Ⅱ期试验(试验编号:NCT02655315)正在进行中[86]。应注意铁离子超载的干预时机可能影响结果,早期予以铁螯合剂有可能发挥治疗作用。

综上所述,尽管目前涌现出一系列潜在的疾病修饰治疗药物,但仍有诸多问题待解决。未来多组学、自适应试验设计将成为帕金森病药物试验的新方式,同时应考虑精准分层,采用远程监测、人工智能以及运动和非运动症状传感器量化临床评估,以提高临床试验的成功率。

利益冲突 无

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（收稿日期：2022-03-08）
（本文编辑：袁云）

·小词典·

中英文对照名词词汇（三）

寡克隆区带 oligoclonal band(OB)
光密度 optical density(OD)
国际抗癫痫联盟 International League Against Epilepsy(ILAE)
国际运动障碍学会 Movement Disorder Society(MDS)
国王帕金森病疼痛量表 King's Parkinson's Disease Pain Scale(KPPS)
过氧化物酶体增殖物激活受体γ peroxisome proliferator-activated receptor γ(PPARγ)
汉密尔顿焦虑量表 Hamilton Anxiety Rating Scale(HAMA)
汉密尔顿抑郁量表 Hamilton Depression Rating Scale(HAMD)
汉密尔顿抑郁量表24项 Hamilton Depression Rating Scale-24 Items(HAMD-24)
核苷酸结合寡聚化结构域样受体蛋白3 nucleotide-binding oligomerization domain-like receptor protein 3(NLRP3)
黑质致密部 substantia nigra pars compacta(SNc)
滑动窗相关法 Sliding Window Correlation(SWC)
坏死性白质脑炎 necrotizing leukoencephalitis(NLE)
坏死性脑膜脑炎 necrotizing meningoencephalitis(NME)
活性氧 reactive oxygen species(ROS)
Glasgow昏迷量表 Glasgow Coma Scale(GCS)
Burke-Fahn-Marsden肌张力障碍量表 Burke-Fahn-Marsden Dystonia Rating Scale(BFMDRS)
基于细胞的检测 cell-based assay(CBA)
基于组织的检测 tissue-based assay(TBA)
基质金属蛋白酶 matrix metalloproteinases(MMPs)
基质金属蛋白酶-9 matrix metalloproteinase-9(MMP-9)
Janus激酶2 Janus kinase 2(JAK2)
极低密度脂蛋白 very low density lipoprotein(VLDL)
急性症状性癫痫发作 acute symptomatic seizure(ASS)
1-甲基-4-苯基吡啶离子 1-methyl-4-phenylpyridine(MPP^+)
N-甲基-D-天冬氨酸受体 N-methyl-D-aspartate receptor(NMDAR)
Virchow-Robin间隙 Virchow-Robin space(VRS)
简化的McGill疼痛问卷 Short Form McGill Pain Questionnaire(SF-MPQ)
简易智能状态检查量表 Mini-Mental State Examination(MMSE)
胶质纤维酸性蛋白 glial fibrillary acidic protein(GFAP)