·帕金森病与运动障碍性疾病·

亨廷顿病的发病机制和治疗进展

严雅萍　张宝荣

【关键词】 杭廷顿病；　综述文献
DOI:10.3969/j.issn.1672-6731.2011.01.008

亨廷顿病(HD)为遗传性进行性神经变性疾病，以异常的自主运动、认知功能障碍和精神疾病为临床特征，中老年发病，发病后10～15年死亡。已知致病基因为*IT15*基因，其1号外显子含有一段多态性三核苷酸[胞嘧啶-腺嘌呤-鸟嘌呤(CAG)]重复序列，当CAG重复拷贝数大于36次即引起发病[1-2]。*IT15*基因编码氨基末端(N末端)含有多聚谷氨酰胺(PolyQ)的大分子蛋白质亨廷顿蛋白(Htt)，目前对于变异Htt的致病机制尚不清楚。该病的主要病理表现为基底节区纹状体传出型棘状神经元大量缺失，此与其典型症状相关。目前的共识是：神经元变性累及脑内更多的区域，包括皮质结构[3-4]。关于亨廷顿病的发病机制是野生型Htt功能缺失(loss of function)还是突变型Htt毒性功能获得(gain of function)，尚存争论。

一、野生型Htt的功能

广泛表达的Htt对生物体具有重要作用，尤其是亨廷顿病患者受累的脑组织。由于该蛋白质氨基末端多聚谷氨酰胺的重复次数异常增多使野生型Htt功能下降，而纹状体神经元对Htt突变尤为敏感，从而影响胚胎发育、抗细胞凋亡和脑源性神经营养因子(BDNF)转录，以及轴突和囊泡转运。

1. Htt对胚胎发育的影响　*HTT*基因完全敲除小鼠只能存活至胚胎发育的第8.50天(胚胎发育共计21 d)，此后即开始形成原肠胚和中枢神经系统。有实验显示，当Htt表达水平降至50%以下时即可影响小鼠外胚层的发育，并最终导致神经管、大脑皮质和纹状体结构异常[3,5]。由此可见，Htt在小鼠胚胎发育的不同阶段均是不可或缺的，当其完全缺失或表达水平下降超过50%以上时即可在病变早期出现亨廷顿病之表型。然而，突变的Htt并未使功能完全缺失，因此亨廷顿病患者在出生早期发育正常，临床症状于出生后多年方才出现。动物实验研究表明，细胞内源性Htt缺失，表达突变的Htt则能够逆转早期的胚胎发育不良，提示Htt在胚胎发育过程中所起的作用并不依赖于多聚谷氨酰胺[6]。

2. Htt的抗细胞凋亡作用　Ho等[7]的细胞模型研究提示，高表达Htt可保护非神经细胞免受突变Htt毒性刺激的损害。而YAC18转基因小鼠纹状体细胞经原代培养后过表达野生型Htt，使纹状体细胞凋亡率降低[8]；相反，细胞内源性*HTT*基因被敲除后则易发生凋亡[9]。

3. Htt对脑源性神经营养因子转录的影响　脑源性神经营养因子是在纹状体神经元生存和皮质纹状体突触传递过程中发挥重要作用的神经营养因子[10]。在投射至纹状体的皮质神经元中，脑源性神经营养因子与Htt共定位[11]。大量动物实验结果证实，纹状体中的脑源性神经营养因子产生于大脑皮质并传递至纹状体[11-13]，当野生型Htt功能下降时，脑源性神经营养因子自身合成和投射至纹状体的数目同时减少，这可以解释某些神经元的选择性变性[10,14-15]。体内和体外研究证据提示，过表达Htt可使BDNF mRNA和蛋白质表达水平升高[15]；而野生型*HTT*基因完全敲除或半敲除的小鼠，其脑组织中BDNF mRNA表达水平降低[16-17]。对斑马鱼的观察可见，Htt表达水平下降可导致鱼的眼睛和大脑萎缩、脑室增大，而在胚胎发育过程中提高脑源性神经营养因子表达水平则上述表型可被逆转[18]。野生型Htt通过将抑制元素1沉默转录因子/神经元限制性沉默因子(REST/NRSF)汇集于细胞质中而阻止其与细胞核内的抑制元素1(RE1)/NRSE结合，进

基金项目：国家自然科学基金资助项目(项目编号：30770761)；浙江省自然科学基金资助项目(项目编号：X206960)

作者单位：310009 杭州，浙江大学医学院附属第二医院神经内科

通信作者：张宝荣(Email：brzhang@zju.edu.cn)

一步抑制RE1/NRSE的功能；但是Htt并不直接与REST/NRSF发生作用，而是通过形成包含HAP1、RILP和dynactin的亚单位即$p150^{Glued}$复合体与REST/NRSF相结合[19]。由于，*HTT*基因突变的存在使$p150^{Glued}$复合体解体，已经发生变异的REST/NRSF进入细胞核内，导致抑制性复合体形成并减少*BDNF*基因转录[19]。

4. Htt对轴突和囊泡转运过程的影响　Htt的表达部位主要位于神经元胞质内，尤其在囊泡相关蛋白质丰富的细胞器内表达明显增加[20]。加利福尼亚的研究者发现，果蝇神经元Htt表达水平降低后轴突转运受阻，野生型Htt具有促进哺乳动物神经元线粒体在轴突中快速转运的作用；而且与保留50% Htt相比，完全敲除*HTT*基因的果蝇其线粒体表型更明显，说明Htt的作用存在剂量效应[21]。

二、神经变性机制

1. 脑源性神经营养因子缺失致神经元变性　脑源性神经营养因子产生于大脑皮质，并顺向运输至纹状体。动物实验表明，纹状体神经元中的脑源性神经营养因子来源于大脑皮质，亨廷顿病患者皮质脑源性神经营养因子水平仅为正常人的50%[12]。由此认为，亨廷顿病患者皮质脑源性神经营养因子水平和分布直接影响纹状体对该突变的易感性，皮质脑源性神经营养因子水平的降低或升高可分别加重或减轻纹状体神经元缺失[22]。一项动物实验研究发现，脑源性神经营养因子敲除小鼠其基因表达水平与亨廷顿病患者尸体解剖所见纹状体病变相类似[22]。另外，敲除*BDNF*基因的R6/1系小鼠，其亨廷顿病表型提前出现，而且行为学表型更为严重[23]。上述结果均提示，脑源性神经营养因子表达水平降低在亨廷顿病的病理进展过程中起至关重要的作用。

2. 兴奋性机制和皮质纹状体功能失调　过量谷氨酸引起的兴奋性毒性可导致皮质神经元突触间联系和环路功能失调，此为兴奋性机制和皮质纹状体功能失调的首要原因。当发生亨廷顿病时，由于皮质传出纤维释放谷氨酰胺增加、胶质细胞摄取谷氨酰胺减少，导致谷氨酰胺受体过度激活。而且纹状体投射神经元突触后谷氨酰胺受体高反应性及其病理性下游通路均可致病[24-25]。

3. 蛋白酶体降解　突变的Htt可被蛋白酶体降解并由此加速神经变性的进程。例如：突变的Htt可被半胱氨酸蛋白酶剪切，而抑制上述剪切过程有助于减轻亨廷顿病转基因小鼠的病情[26]，进一步说明Htt片段较全长毒性更大。研究显示，Caspase-3和Caspase-7的剪切位点分别为第513和552位点，而Caspase-6和Caspase-2的剪切位点则分别位于第586和552位点[27-29]，此已被Caspases抑制剂和点突变的实验方法所证实[29]。除了半胱氨酸蛋白酶，钙蛋白酶亦参与Htt的剪切，虽然野生型和突变型Htt均能被剪切，但后者更易被剪切并产生氨基末端片段[29-30]。自发现*HTT*基因片段导致的神经元毒性比全长更严重以来，目前已将抑制Htt剪切过程作为治疗亨廷顿病的切入点，发现翻译后修饰起重要作用：Htt的S434位点被细胞周期蛋白依赖性激酶5（CDK5）磷酸化后即可阻止蛋白质的剪切过程；而S421位点磷酸化则可减少Caspase-6介导的Htt剪切和Caspase-6片段在细胞核内的聚集[31-32]。

4. 突变Htt的错误折叠、聚集和清除　对亨廷顿病而言，神经元变性的主要表现是由突变Htt引起的聚集物在纹状体神经元的聚集。突变Htt所产生的聚集物存在于大脑皮质神经元，青少年患者（38%～52%）较成年患者（3%～6%）更为常见，而且这种聚集物仅见于纹状体中等棘状神经元，苍白球和小脑鲜见[30]。生物化学分析表明，细胞核内聚集物主要由Htt片段组成，而细胞质内聚集物Htt片段和全长共存，但聚集物进入细胞核后毒性更大[33]；其毒性主要来源于聚集物囊括了其他含多聚谷氨酰胺的蛋白质，并使这些蛋白质失去生理功能。有许多细胞内蛋白质，例如转录因子和转录调控因子均含多聚谷氨酰胺结构，而聚集物则因汇集了可溶性动力蛋白而影响胞体与突触末端间的轴突转运能力[34-35]。聚集物在亨廷顿病中起主要毒性作用，最有力的证据是：随着病程的进展，聚集物亦相应增加。对于可调控表达突变Htt的转基因小鼠，出现行为和认知损害后，阻止其转基因系统继续表达突变的Htt，则小鼠原已形成的聚集物逐渐消失，且其行为和认知损害程度也得到缓解[36]。生物化学研究显示，聚集物难以被分解或发生变性，而神经元本身则具有降解细胞核内外聚集物的能力，因此有效的治疗方法即是减少聚集物的形成和使突变的Htt失活[36]。大量证据表明，泛素蛋白酶体系统不能完全降解突变的Htt，导致聚集物形成，与此同时其本身功能也失调[37]。另有实验亦支持上述研究结果，特异性蛋白酶体抑制剂可促进亨廷顿病神经元和模型动物脑组织中聚集物的形成，而过表达

热休克蛋白(如hsp40和70等)和分子伴侣蛋白时,突变Htt所形成的聚集物则减少,罹患亨廷顿病的果蝇和小鼠的生命周期显著延长[38-39]。蛋白酶体降解酶仅能降解多聚谷氨酰胺邻近的序列,对多聚谷氨酰胺本身并无降解作用,而未被降解的部分更容易聚集。最新研究显示,细胞质中的所有降解酶唯有嘌呤霉素敏感性氨基肽酶(PSA)可以降解多聚谷氨酰胺[40],但目前尚无明确的证据表明嘌呤霉素敏感性氨基肽酶能够延缓疾病的发生与发展。然而,亦有资料提示,突变Htt形成的聚集物并不引起动物神经元缺失和行为异常[41-42],而且有些促进聚集物形成的化合物却具有缓解上述症状之功效[43],其证据来源于转基因小鼠实验研究[44]。总之,Htt突变致聚集物是产生毒性作用还是保护性作用取决于受累细胞类型和疾病发病阶段[45-46],据认为,小聚集物甚至单体的毒性作用可能更大,而大的聚集物则有保护作用[47-49]。因此,聚集物形成的早期过程更值得关注。

5. 自噬功能异常 与蛋白酶体途径类似,部分突变Htt也通过自噬途径降解。自噬过程首先是部分细胞质成分被一种"自噬体"和"自噬空泡"的双膜结构包裹,继而与溶酶体结合并最终被降解[50]。Ravikumar等[49]首次提出自噬负性调节因子哺乳动物雷帕霉素靶蛋白(mTOR),当聚集物形成时雷帕霉素靶蛋白即被包裹其内,从而促进突变Htt片段的清除。此项发现与之前关于亨廷顿病患者脑组织自噬空泡增加的研究结果相一致[51],而且添加自噬促进剂或增加自身基因表达水平均可以促进对突变Htt的清除以及减少聚集物的形成,并且改善果蝇或小鼠行为学表型[42]。相反,当自噬溶酶体途径被抑制后可溶性Htt表达水平、聚集物形成及其毒性作用均显著增加,目前已知突变Htt K444位点发生乙酰化即能够促进自噬进而减轻自身毒性作用[52]。在上述过程中,自噬体与溶酶体的结合至关重要[53],倘若无此过程自噬体将聚集并增加其毒性。上述结果提示,控制溶酶体功能可能是一种新的治疗方法。近期研究亦发现,Htt被溶酶体清除主要依赖于溶酶体相关膜蛋白2A(LAMP2A),随着年龄的增长其表达水平逐渐降低,突变Htt聚集并诱发神经变性[54-55],若于疾病早期提高溶酶体相关膜蛋白2A功能有可能延缓亨廷顿病的发病。

6. 线粒体功能失调致神经变性 亨廷顿病患者神经元线粒体功能缺陷的首项研究证据来自尸体解剖所显示的大脑皮质神经元线粒体超微结构组织病理学改变[56-57],以及影像学显示的能量代谢缺陷[53]。随着磁共振波谱(MRS)的应用,发现症状性亨廷顿病患者基底节区和丘脑呈现N-乙酰天冬氨酸(NAA)缺失,神经元富含此种氨基酸,其代谢变化可反映线粒体功能[58-59]。此外PET研究也已证实,亨廷顿病早期患者大脑皮质和基底节区即出现乳酸合成增加,提示糖分解速度加快[60]。与亨廷顿病细胞模型和动物模型观察结果相似,亨廷顿病患者中枢和周围神经组织中诸多参与氧化磷酸化的酶如线粒体呼吸链复合体活性下降[61-62]。总之,突变Htt主要通过氧化应激、钙调节功能失调等途径导致神经元线粒体功能失调[63-64]。

7. 细胞转录功能异常 有关亨廷顿病转录调控异常的证据显示,编码信号神经肽和神经递质受体的mRNA在纹状体神经元中呈特异性减少[65-68],以及R6/2系小鼠模型D1和D2受体mRNA转录异常改变[69-70]。DNA微阵列研究表明,在亨廷顿病神经元和动物模型中存在大量的基因表达改变,临床症状出现之前即已存在基因调控异常改变,说明转录调控异常在亨廷顿病的发病过程中起重要作用[34]。

三、亨廷顿病治疗原则

与大多数神经变性疾病相同,目前对亨廷顿病亦无有效的治疗方法,现针对上述不同发病机制的治疗方案作一扼要介绍[71-72]。

1. 减轻兴奋性毒性的药物 由谷氨酸释放增加和N-甲基-D-天冬氨酸(NAMD)受体活性上调所引起的兴奋性毒性,是导致亨廷顿病细胞死亡的主要原因。(1)利血平:为中枢神经系统谷氨酸神经传导抑制药,对亨廷顿病小鼠模型有较好保护作用,但临床试验显示其虽对控制舞蹈样动作有效但不能持久[73-74]。(2)金刚烷胺:其药理作用为阻断NAMD受体,对延缓病程和改善认知功能的效果优于利血平[75]。(3)丁苯那嗪:为多巴胺抑制药,可同时改善舞蹈样动作和减少纹状体神经元缺失,其不良反应包括抑郁、帕金森综合征等,目前已通过美国食品与药品管理局(FDA)审批[76-77]。

2. 增加脑源性神经营养因子表达水平 脑源性神经营养因子表达水平下降对亨廷顿病表型有所贡献。目前,有关重组脑源性神经营养因子、脑源性神经营养因子拟似体、诱导剂、*BDNF*基因治疗和细胞移植等研究尚处于基础研究阶段[78-79]。

3. 抑制Caspases活性药物 全长Htt被

Caspases剪切后产生毒性更大的氨基片段,其在亨廷顿病的神经病理过程中起重要作用。米诺环素为第2代四环素类药物,主要抑制Caspase-1和Caspase-3活性[80],临床试验发现,治疗6个月后能有效改善患者精神症状,治疗1年后可稳定运动和精神方面的症状[81-82]。至于该药长期应用的安全性和远期效果有待进一步认证。

4.减少Htt聚集药物 聚集物形成是亨廷顿病发生与发展过程中的重要特征,但其究竟起何作用尚有待进一步研究加以证实。刚果红通过破坏已形成的寡聚体结构而抑制异常多聚谷氨酰胺的寡聚化,阻止ATP缺失和Caspases激活,其在小鼠模型的效果仍有待进一步验证[83]。此外,C2-8等虽已在果蝇、小鼠模型中取得一定治疗效果[84-85],但仍需临床实践验证。抑制Htt聚集物形成和促进已形成的聚集物被清除是两个不同的治疗方向,后者可应用如雷帕霉素靶蛋白抑制药雷帕霉素等,但其免疫抑制方面的不良反应阻碍了其在临床的推广应用[49]。

5.改善线粒体功能药物 突变Htt可阻碍线粒体能量产生和细胞呼吸,导致细胞内ATP水平降低,从而促进细胞凋亡、氧化压力和兴奋性毒性。肌酐能够有效改善线粒体的呼吸功能和抗氧化作用,对亨廷顿病小鼠具有显著的神经保护作用[86],临床试验发现对减轻亨廷顿病患者体质量和改善神经症状有一定效果,但是其最佳治疗剂量仍有待临床实践的检验[87]。其他改善线粒体功能的药物,如辅酶Q10(CoQ10)、二十碳五烯酸(EPA)等均有待进一步的临床验证。

6.调控基因转录异常的药物 转录调控异常是亨廷顿病病理过程中的早期事件[34]。组蛋白去乙酰化酶(HDAC)抑制药辛二酰苯胺异羟肟酸(SAHA)和丁酸钠能够通过增加组蛋白乙酰化水平,进而使染色质结构更加松弛而有利于基因转录。尽管临床试验显示上述组蛋白去乙酰化酶抑制药是安全的,但其在抑制生长、促进凋亡、致染色质结构不稳定及其他不良反应方面不容忽视[88-89]。

7.其他药物或治疗方法 改良的细胞内抗体,包括重组抗体和抗体片段能够透过血-脑屏障作用于Htt片段,降低突变Htt表达水平,从而减轻细胞死亡;此类细胞抗体在行为学上的效果业已在转基因小鼠实验中得到验证[90]。但这些研究仍处于早期研究阶段,在抗原选择、胞质稳定性和可溶性,以及转运途径的选择等方面尚未获得肯定的结果。此外,细胞移植亦是目前研究的热点,包括胎脑纹状体祖细胞、胚胎干细胞移植术等,前者由于治疗效果不能持久故未在临床推广[91],而后者的研究尚需解决移植后能否成功诱导亨廷顿病变性的神经元等问题[81]。

参 考 文 献

[1] The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell, 1993, 72:971-983.

[2] 林珉婷, 甘世锐, 陈万金, 等. Huntington病两家系基因分析. 中国现代神经疾病杂志, 2008, 8:124-128.

[3] Auerbach W, Hurlbert MS, Hilditch-Maguire P, et al. The HD mutation causes progressive lethal neurological disease in mice expressing reduced levels of huntingtin. Hum Mol Genet, 2001, 10:2515-2523.

[4] 陈彪, 郑晓立. 蛋白质组学技术在神经变性疾病研究中的应用. 中国现代神经疾病杂志, 2008, 8:4-7.

[5] White JK, Auerbach W, Duyao MP, et al. Huntingtin is required for neurogenesis and is not impaired by the Huntington's disease CAG expansion. Nat Genet, 1997, 17:404-410.

[6] Leavitt BR, Guttman JA, Hodgson JG, et al. Wild-type huntingtin reduces the cellular toxicity of mutant huntingtin in vivo. Am J Hum Genet, 2001, 68:313-324.

[7] Ho LW, Brown R, Maxwell M, et al. Wild type Huntingtin reduces the cellular toxicity of mutant Huntingtin in mammalian cell models of Huntington's disease. J Med Genet, 2001, 38:450-452.

[8] Leavitt BR, van Raamsdonk JM, Shehadeh J, et al. Wild-type huntingtin protects neurons from excitotoxicity. J Neurochem, 2006, 96:1121-1129.

[9] Zhang Y, Leavitt BR, van Raamsdonk JM, et al. Huntingtin inhibits caspase-3 activation. EMBO J, 2006, 25:5896-5906.

[10] Zuccato C, Cattaneo E. Role of brain-derived neurotrophic factor in Huntington's disease. Prog Neurobiol, 2007, 81(5/6): 294-330.

[11] Fusco FR, Chen Q, Lamoreaux WJ, et al. Cellular localization of huntingtin in striatal and cortical neurons in rats: lack of correlation with neuronal vulnerability in Huntington's disease. J Neurosci, 1999, 19:1189-1202.

[12] Gharami K, Xie Y, An JJ, et al. Brain-derived neurotrophic factor over-expression in the forebrain ameliorates Huntington's disease phenotypes in mice. J Neurochem, 2008, 105:369-379.

[13] Baquet ZC, Gorski JA, Jones KR. Early striatal dendrite deficits followed by neuron loss with advanced age in the absence of anterograde cortical brain-derived neurotrophic factor. J Neurosci, 2004, 24:4250-4258.

[14] Gauthier LR, Charrin BC, Borrell-Pages M, et al. Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. Cell, 2004, 118:127-138.

[15] Zuccato C, Ciammola A, Rigamonti D, et al. Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. Science, 2001, 293:493-498.

[16] Zuccato C, Belyaev N, Conforti P, et al. Widespread disruption of repressor element-1 silencing transcription factor/neuron-restrictive silencer factor occupancy at its target genes in Huntington's disease. J Neurosci, 2007, 27:6972-6983.

[17] Zuccato C, Tartari M, Crotti A, et al. Huntingtin interacts with REST/NRSF to modulate the transcription of NRSE-controlled

neuronal genes. Nat Genet, 2003, 35:76-83.
[18] Diekmann H, Anichtchik O, Fleming A, et al. Decreased BDNF levels are a major contributor to the embryonic phenotype of huntingtin knockdown zebrafish. J Neurosci, 2009, 29:1343-1349.
[19] Shimojo M. Huntingtin regulates RE1-silencing transcription factor/neuron-restrictive silencer factor (REST/NRSF) nuclear trafficking indirectly through a complex with REST/NRSF-interacting LIM domain protein (RILP) and dynactin p150 Glued. J Biol Chem, 2008, 283:34880-34886.
[20] Velier J, Kim M, Schwarz C, et al. Wild-type and mutant huntingtins function in vesicle trafficking in the secretory and endocytic pathways. Exp Neurol, 1998, 152:34-40.
[21] Trushina E, Dyer RB, Badger JD 2nd, et al. Mutant huntingtin impairs axonal trafficking in mammalian neurons in vivo and in vitro. Mol Cell Biol, 2004, 24:8195-8209.
[22] Strand AD, Baquet ZC, Aragaki AK, et al. Expression profiling of Huntington's disease models suggests that brain-derived neurotrophic factor depletion plays a major role in striatal degeneration. J Neurosci, 2007, 27:11758-11768.
[23] Canals JM, Pineda JR, Torres-Peraza JF, et al. Brain-derived neurotrophic factor regulates the onset and severity of motor dysfunction associated with enkephalinergic neuronal degeneration in Huntington's disease. J Neurosci, 2004, 24:7727-7739.
[24] DiFiglia M. Excitotoxic injury of the neostriatum: a model for Huntington's disease. Trends Neurosci, 1990, 13:286-289.
[25] Goldberg YP, Nicholson DW, Rasper DM, et al. Cleavage of huntingtin by apopain, a proapoptotic cysteine protease, is modulated by the polyglutamine tract. Nat Genet, 1996, 13:442-449.
[26] Graham RK, Deng Y, Slow EJ, et al. Cleavage at the caspase-6 site is required for neuronal dysfunction and degeneration due to mutant huntingtin. Cell, 2006, 125:1179-1191.
[27] Hermel E, Gafni J, Propp SS, et al. Specific caspase interactions and amplification are involved in selective neuronal vulnerability in Huntington's disease. Cell Death Differ, 2004, 11:424-438.
[28] Wellington CL, Singaraja R, Ellerby L, et al. Inhibiting caspase cleavage of huntingtin reduces toxicity and aggregate formation in neuronal and nonneuronal cells. J Biol Chem, 2000, 275:19831-19838.
[29] Davies SW, Turmaine M, Cozens BA, et al. Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. Cell, 1997, 90:537-548.
[30] DiFiglia M, Sapp E, Chase KO, et al. Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. Science, 1997, 277:1990-1993.
[31] Luo S, Vacher C, Davies JE, et al. Cdk5 phosphorylation of huntingtin reduces its cleavage by caspases: implications for mutant huntingtin toxicity. J Cell Biol, 2005, 169:647-656.
[32] Warby SC, Chan EY, Metzler M, et al. Huntingtin phosphorylation on serine 421 is significantly reduced in the striatum and by polyglutamine expansion in vivo. Hum Mol Genet, 2005, 14:1569-1577.
[33] Yang W, Dunlap JR, Andrews RB, et al. Aggregated polyglutamine peptides delivered to nuclei are toxic to mammalian cells. Hum Mol Genet, 2002, 11:2905-2917.
[34] Cha JH. Transcriptional signatures in Huntington's disease. Prog Neurobiol, 2007, 83:228-248.
[35] Nucifora FC Jr, Ellerby LM, Wellington CL, et al. Nuclear localization of a non-caspase truncation product of atrophin-1, with an expanded polyglutamine repeat, increases cellular toxicity. J Biol Chem, 2003, 278:13047-13055.
[36] Yamamoto A, Lucas JJ, Hen R. Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease. Cell, 2000, 101:57-66.
[37] Tydlacka S, Wang CE, Wang X, et al. Differential activities of the ubiquitin-proteasome system in neurons versus glia may account for the preferential accumulation of misfolded proteins in neurons. J Neurosci, 2008, 28:13285-13295.
[38] Vacher C, Garcia-Oroz L, Rubinsztein DC. Overexpression of yeast hsp104 reduces polyglutamine aggregation and prolongs survival of a transgenic mouse model of Huntington's disease. Hum Mol Genet, 2005, 14:3425-3433.
[39] Warrick JM, Chan HY, Gray-Board GL, et al. Suppression of polyglutamine-mediated neurodegeneration in Drosophila by the molecular chaperone HSP70. Nat Genet, 1999, 23:425-428.
[40] Bhutani N, Venkatraman P, Goldberg AL. Puromycin-sensitive aminopeptidase is the major peptidase responsible for digesting polyglutamine sequences released by proteasomes during protein degradation. EMBO J, 2007, 26:1385-1396.
[41] Kuemmerle S, Gutekunst CA, Klein AM, et al. Huntington aggregates may not predict neuronal death in Huntington's disease. Ann Neurol, 1999, 46:842-849.
[42] Saudou F, Finkbeiner S, Devys D, et al. Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions. Cell, 1998, 95:55-66.
[43] Bodner RA, Outeiro TF, Altmann S, et al. Pharmacological promotion of inclusion formation: a therapeutic approach for Huntington's and Parkinson's diseases. Proc Natl Acad Sci USA, 2006, 103:4246-4251.
[44] Slow EJ, Graham RK, Osmand AP, et al. Absence of behavioral abnormalities and neurodegeneration in vivo despite widespread neuronal huntingtin inclusions. Proc Natl Acad Sci USA, 2005, 102:11402-11407.
[45] Moffitt H, McPhail GD, Woodman B, et al. Formation of polyglutamine inclusions in a wide range of non-CNS tissues in the HdhQ150 knock-in mouse model of Huntington's disease. PLoS One, 2009, 4:E8025.
[46] Sathasivam K, Hobbs C, Turmaine M, et al. Formation of polyglutamine inclusions in non-CNS tissue. Hum Mol Genet, 1999, 8:813-822.
[47] Arrasate M, Mitra S, Schweitzer ES, et al. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. Nature, 2004, 431:805-810.
[48] Bennett EJ, Shaler TA, Woodman B, et al. Global changes to the ubiquitin system in Huntington's disease. Nature, 2007, 448:704-708.
[49] Ravikumar B, Vacher C, Berger Z, et al. Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. Nat Genet, 2004, 36:585-595.
[50] Ventruti A, Cuervo AM. Autophagy and neurodegeneration. Curr Neurol Neurosci Rep, 2007, 7:443-451.
[51] Kegel KB, Kim M, Sapp E, et al. Huntingtin expression stimulates endosomal-lysosomal activity, endosome tubulation, and autophagy. J Neurosci, 2000, 20:7268-7278.
[52] Jeong H, Then F, Melia TJ Jr, et al. Acetylation targets mutant huntingtin to autophagosomes for degradation. Cell, 2009, 137:60-72.
[53] Orr AL, Li S, Wang CE, et al. N-terminal mutant huntingtin associates with mitochondria and impairs mitochondrial trafficking. J Neurosci, 2008, 28:2783-2792.
[54] Thompson LM, Aiken CT, Kaltenbach LS, et al. IKK phosphorylates Huntingtin and targets it for degradation by the

proteasome and lysosome. J Cell Biol, 2009, 187:1083-1099.
[55] Cuervo AM, Dice JF. Regulation of lamp2a levels in the lysosomal membrane. Traffic, 2000, 1:570-583.
[56] Gárdián G, Vécsei L. Huntington's disease: pathomechanism and therapeutic perspectives. J Neural Transm, 2004, 111(10/11):1485-1494.
[57] Goebel HH, Heipertz R, Scholz W, et al. Juvenile Huntington chorea: clinical, ultrastructural, and biochemical studies. Neurology, 1978, 28:23-31.
[58] Jenkins BG, Koroshetz WJ, Beal MF, et al. Evidence for impairment of energy metabolism in vivo in Huntington's disease using localized 1H NMR spectroscopy. Neurology, 1993, 43:2689-2695.
[59] Moffett JR, Ross B, Arun P, et al. N-Acetylaspartate in the CNS: from neurodiagnostics to neurobiology. Prog Neurobiol, 2007, 81:89-131.
[60] Kuhl DE, Markham CH, Metter EJ, et al. Local cerebral glucose utilization in symptomatic and presymptomatic Huntington's disease. Res Publ Assoc Res Nerv Ment Dis, 1985, 63:199-209.
[61] Browne SE. Mitochondria and Huntington's disease pathogenesis: insight from genetic and chemical models. Ann NY Acad Sci, 2008, 1147:358-382.
[62] Feigin A, Leenders KL, Moeller JR, et al. Metabolic network abnormalities in early Huntington's disease: an [(18)F]FDG PET study. J Nucl Med, 2001, 42:1591-1595.
[63] Butterfield DA, Howard BJ, LaFontaine MA. Brain oxidative stress in animal models of accelerated aging and the age-related neurodegenerative disorders, Alzheimer's disease and Huntington's disease. Curr Med Chem, 2001, 8:815-828.
[64] Panov AV, Gutekunst CA, Leavitt BR, et al. Early mitochondrial calcium defects in Huntington's disease are a direct effect of polyglutamines. Nat Neurosci, 2002, 5:731-736.
[65] Arzberger T, Krampfl K, Leimgruber S, et al. Changes of NMDA receptor subunit (NR1, NR2B) and glutamate transporter (GLT1) mRNA expression in Huntington's disease: an in situ hybridization study. J Neuropathol Exp Neurol, 1997, 56:440-454.
[66] Augood SJ, Faull RL, Emson PC. Dopamine D1 and D2 receptor gene expression in the striatum in Huntington's disease. Ann Neurol, 1997, 42:215-221.
[67] Augood SJ, Faull RL, Love DR, et al. Reduction in enkephalin and substance P messenger RNA in the striatum of early grade Huntington's disease: a detailed cellular in situ hybridization study. Neuroscience, 1996, 72:1023-1036.
[68] Norris PJ, Waldvogel HJ, Faull RL, et al. Decreased neuronal nitric oxide synthase messenger RNA and somatostatin messenger RNA in the striatum of Huntington's disease. Neuroscience, 1996, 72:1037-1047.
[69] Cha JH, Frey AS, Alsdorf SA, et al. Altered neurotransmitter receptor expression in transgenic mouse models of Huntington's disease. Philos Trans R Soc Lond B Biol Sci, 1999, 354:981-989.
[70] Cha JH, Kosinski CM, Kerner JA, et al. Altered brain neurotransmitter receptors in transgenic mice expressing a portion of an abnormal human huntington disease gene. Proc Natl Acad Sci USA, 1998, 95:6480-6485.
[71] Zuccato C, Valenza M, Cattaneo E. Molecular mechanisms and potential therapeutical targets in Huntington's disease. Physiol Rev, 2010, 90:905-981.
[72] 吴志英. 亨廷顿病的分子发病机制及治疗进展. 中国现代神经疾病杂志, 2009, 9:238-241.
[73] Squitieri F, Ciammola A, Colonnese C, et al. Neuroprotective effects of riluzole in Huntington's disease. Eur J Nucl Med Mol Imaging, 2008, 35:221-222.
[74] Seppi K, Mueller J, Bodner T, et al. Riluzole in Huntington's disease (HD): an open label study with one year follow up. J Neurol, 2001, 248:866-869.
[75] Lee ST, Chu K, Park JE, et al. Memantine reduces striatal cell death with decreasing calpain level in 3-nitropropionic model of Huntington's disease. Brain Res, 2006, 1118:199-207.
[76] Frank S, Ondo W, Fahn S, et al. A study of chorea after tetrabenazine withdrawal in patients with Huntington disease. Clin Neuropharmacol, 2008, 31:127-133.
[77] Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. Neurology, 2006, 66:366-372.
[78] Zuccato C, Cattaneo E. Brain-derived neurotrophic factor in neurodegenerative diseases. Nat Rev Neurol, 2009, 5:311-322.
[79] Pérez-Navarro E, Canudas AM, Akerund P, et al. Brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4/5 prevent the death of striatal projection neurons in a rodent model of Huntington's disease. J Neurochem, 2000, 75:2190-2199.
[80] Chen M, Ona VO, Li M, et al. Minocycline inhibits caspase-1 and caspase-3 expression and delays mortality in a transgenic mouse model of Huntington disease. Nat Med, 2000, 6:797-801.
[81] Aubry L, Bugi A, Lefort N, et al. Striatal progenitors derived from human ES cells mature into DARPP32 neurons in vitro and in quinolinic acid-lesioned rats. Proc Natl Acad Sci USA, 2008, 105:16707-16712.
[82] Bonelli RM, Hodl AK, Hofmann P, et al. Neuroprotection in Huntington's disease: a 2-year study on minocycline. Int Clin Psychopharmacol, 2004, 19:337-342.
[83] Wood NI, Pallier PN, Wanderer J, et al. Systemic administration of Congo red does not improve motor or cognitive function in R6/2 mice. Neurobiol Dis, 2007, 25:342-353.
[84] Zhang X, Smith DL, Meriin AB, et al. A potent small molecule inhibits polyglutamine aggregation in Huntington's disease neurons and suppresses neurodegeneration in vivo. Proc Natl Acad Sci USA, 2005, 102:892-897.
[85] Ehrnhoefer DE, Duennwald M, Markovic P, et al. Green tea (-)-epigallocatechin-gallate modulates early events in huntingtin misfolding and reduces toxicity in Huntington's disease models. Hum Mol Genet, 2006, 15:2743-2751.
[86] Ferrante RJ, Andreassen OA, Jenkins BG, et al. Neuroprotective effects of creatine in a transgenic mouse model of Huntington's disease. J Neurosci, 2000, 20:4389-4397.
[87] Tabrizi SJ, Blamire AM, Manners DN, et al. High-dose creatine therapy for Huntington disease: a 2-year clinical and MRS study. Neurology, 2005, 64:1655-1656.
[88] Hogarth P, Lovrecic L, Krainc D. Sodium phenylbutyrate in Huntington's disease: a dose-finding study. Mov Disord, 2007, 22:1962-1964.
[89] Butler R, Bates GP. Histone deacetylase inhibitors as therapeutics for polyglutamine disorders. Nat Rev Neurosci, 2006, 7:784-796.
[90] Southwell AL, Ko J, Patterson PH. Intrabody gene therapy ameliorates motor, cognitive, and neuropathological symptoms in multiple mouse models of Huntington's disease. J Neurosci, 2009, 29:13589-13602.
[91] Bachoud-Lévi AC, Gaura V, Brugières P, et al. Effect of fetal neural transplants in patients with Huntington's disease 6 years after surgery: a long-term follow-up study. Lancet Neurol, 2006, 5:303-309.

（收稿日期：2010-12-20）