



小脑共济失调的神经机制与干预策略

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摘要 小脑是皮层下最大的运动结构, 负责运动的协调和精细调控. 遗传因素或内源/外源性非遗传因素可引起小脑结构和功能障碍从而导致小脑共济失调, 表现为姿势失衡、步态紊乱、肢体运动障碍、眼球运动失调以及言语沟通不畅等症状, 严重影响患者的生活质量并带来社会经济负担. 然而, 小脑共济失调致病因素的复杂多样为其防治带来了巨大的挑战. 因此, 本文围绕小脑共济失调的病因、症状和临床分型, 从神经元、神经环路和胶质细胞的结构和功能异常的角度, 系统总结小脑共济失调发生发展神经机制的最新研究进展, 并在分析临床小脑共济失调治疗现状的基础上, 提出并展望了靶向小脑神经元环路递质系统、小胶质细胞介导的神经炎症反应以及遗传性小脑共济失调的致病基因等药物和神经调控干预新策略, 以期对未来发展更有疗效的小脑共济失调疗法提供有益的参考.

关键词 小脑共济失调, 神经元兴奋性, 神经递质, 神经炎症, 治疗策略

共济失调(ataxia)一词源于希腊语, 意为缺乏秩序和不协调的, 其最典型的症状表现为步态、肢体或眼动的不平衡和不协调^[1]. 近年来, 共济失调发病率呈现出逐年上升的趋势, 给患者家庭及社会带来极大负担^[2,3]. 运动皮层及基底神经节、小脑等皮层下运动结构的异常均可能导致共济失调的发生^[1]. 其中, 小脑共济失调(cerebellar ataxia)是最为常见的一类共济失调疾病^[4]. 根据病因的不同, 可分为遗传性小脑共济失调(hereditary cerebellar ataxia)和获得性小脑共济失调(acquired cerebellar ataxia). 尽管这两

类小脑性共济失调的致病因素复杂多样, 但共性的病理特征均表现为小脑和/或其传入/传出神经通路的损伤、萎缩或功能障碍. 目前, 除少数发病机制十分明确的小脑共济失调外, 临床上尚缺乏有效的针对性治疗手段. 因此, 深入研究小脑共济失调发生发展的神经机制对于理解小脑的运动调控功能和研发新的治疗靶点和治疗策略具有重要意义. 本文综述了小脑共济失调的症状、分类、神经机制及相关治疗策略的研究进展, 并对未来潜在的治疗方向做出了展望.

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1 小脑共济失调的症状

小脑是中枢神经系统中最大的运动结构, 负责维持躯体平衡、调节肌肉张力、协调随意运动, 并参与运动学习(motor learning)^[5]. 因此, 小脑共济失调患者的典型临床症状和诊断体征包括姿势失衡、步态紊乱、肢体运动障碍、眼球运动失调以及言语沟通不畅等^[6], 而对姿势和步态的评估是小脑共济失调临床诊断的关键. 小脑共济失调患者常表现为姿势不稳和蹒跚的宽基步态; 肢体轮替运动障碍(dysdiadochokinesia), 轮替运动笨拙、缓慢和节律不均, 并倾向于将多关节运动分解成更简单、更准确的单关节运动; 辨距不良(dysmetria), 对运动目标的距离判断不准确, 常过度触碰目标; 部分患者在保持姿势(姿势性震颤)和运动(运动性震颤)时出现3~7 Hz的肢体非自主性震颤, 特别是在运动终末出现意向性震颤(intention tremor)^[7]. 此外, 小脑共济失调患者, 特别是小脑中线(蚓部)病变患者, 常表现出眼动异常^[8], 包括凝视诱发性眼球震颤(gaze-evoked nystagmus)、下跳性眼球震颤(downbeat nystagmus)和平滑追踪受损(impaired smooth pursuit). 部分小脑共济失调患者还会出现构音障碍(dysarthria), 表现为讲话含糊不清、用词不准确以及音节停顿延长^[9]. 上述临床症状的发生与不同类型小脑共济失调导致的小脑神经元和神经环路不同的结构和功能异常密切相关.

2 小脑共济失调的分类

临床上一般将小脑共济失调分为两大类: 遗传性小脑共济失调和获得性小脑共济失调^[6]. 遗传性小脑共济失调一般具有明显的家族史, 患者常由于遗传因素患有先天性的小脑共济失调. 常见的遗传性小脑共济失调包括脊髓小脑共济失调(spino-cerebellar ataxia, SCA)、发作性共济失调(episodic ataxia, EA)、Friedrich共济失调(Friedrich ataxia, FA)、毛细血管扩张性共济失调综合征(ataxia telangiectasia, AT)、脆性X综合征(fragile X syndrome, FXS)以及X连锁肾上腺脑白质营养不良(X-linked adrenoleukodystrophy, X-ALD). 其中, SCA和EA均为常染色体显性遗传性小脑共济失调, 分为多种亚型(SCA1-40和EA1-8), 致病基因和临床表型具有高度的异质性^[10]; 而FA和AT分别为编码

线粒体蛋白frataxin的*FRDA*基因(染色体定位于9q13~q21.1)和编码ATM蛋白激酶(ataxia-telangiectasia mutated kinase)的*ATM*基因(染色体定位于11q22~q23)突变引起的隐性遗传性小脑共济失调^[11]; FXS和X-ALD则为*FMRI*(fragile X mental retardation 1)基因转录沉默(5'端未翻译区域的CGG三联体大量扩增所致)^[12]和*ABCD1*基因(ATP结合盒转运蛋白超家族成员)突变^[13]引起的X染色体连锁遗传性小脑共济失调. 区别于遗传性小脑共济失调, 获得性小脑共济失调是由外源性或内源性非遗传因素引起的小脑慢性疾病. 血管损伤、肿瘤、感染自身免疫、酒精及药物(如甲硝唑等)中毒以及维生素缺乏均是获得性小脑共济失调的常见病因^[14]. 值得注意的是, 寨卡病毒感染也可能导致子代小脑共济失调的发生^[15]. 此外, 新生儿出生前后由于窒息、创伤或中风造成的小脑损伤会导致共济失调型脑瘫(ataxic cerebral palsy)的发生, 且其共济失调运动障碍在婴幼儿发育初期并不明显但随年龄增长而逐渐加重^[16]. 近年来的研究发现, 部分共济失调型脑瘫患者携带的基因突变可能与其病程进展密切相关^[17]. 小脑共济失调致病因素的多样性为其临床防治带来了极大的挑战. 因此, 解析小脑神经元和神经环路的结构、运作机制和生理功能, 以及不同致病因素导致的小脑结构和功能的病理性异常, 是深入理解小脑共济失调神经机制和发展、优化共济失调临床治疗策略的关键所在.

3 小脑共济失调的神经机制

3.1 小脑浦肯野细胞与共济失调

浦肯野细胞(Purkinje cell)是小脑皮层神经元环路中的主神经元和唯一的传出神经元^[5]. 它整合了来自小脑两大传入系统苔状纤维和爬行纤维的感觉和运动信息, 并将小脑皮层最终的感觉-运动整合信息传送至小脑核团和前庭核团. 诸多报道浦肯野细胞形态和功能异常在小脑共济失调中发挥关键作用. 解剖学和磁共振成像(magnetic resonance imaging, MRI)临床研究发现, SCA, AT和FXS等多种类型的小脑共济失调均伴有明显的浦肯野细胞形态或功能异常^[18](图1). 此外, 大量的基础研究表明, 小脑浦肯野细胞中多种基因的突变及其导致的浦肯野神经元功能活动异常均可诱发小脑共济失调. Becker等人^[19]发现在显性遗传性小

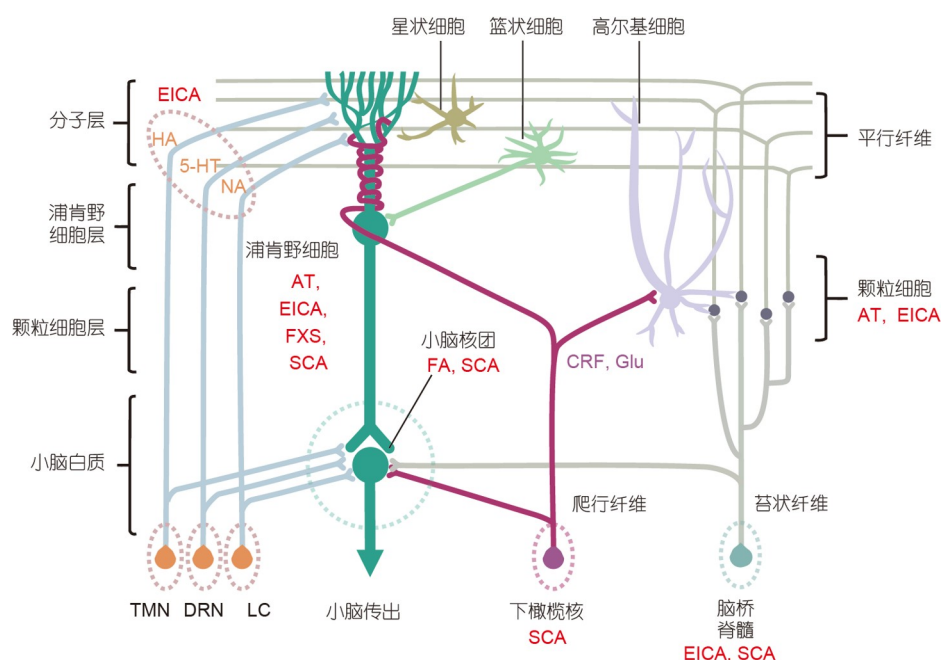


图 1 小脑神经元环路及其中细胞与不同类型小脑共济失调间的关系。该示意图显示了核心小脑微环路构筑。浦肯野细胞是小脑皮层唯一的主神经元和传出神经元,可被下橄榄核发出的爬行纤维和颗粒细胞发出的平行纤维共同激活,构成小脑皮层负责感觉-运动整合的神经元环路。浦肯野细胞进而投射至小脑核团这一小脑最终的整合和传出信息的节点。临床和基础研究均已揭示,某些特定类型的小脑共济失调(标注为红色字体)是由于小脑内部神经元环路和不同类型细胞的损伤所导致的。5-HT, 5-羟色胺; AT, 毛细血管扩张性共济失调综合征; DRN, 中缝核; EICA, 乙醇诱发的小脑共济失调; FA, Friedrich共济失调; FXS, 脆性X综合征; HA, 组胺; LC, 蓝斑; NA, 去甲肾上腺素; SCA, 脊髓小脑共济失调; TMN, 下丘脑结节乳头体核

Figure 1 Correlations between cerebellar neuronal circuits and their cells and different types of cerebellar ataxias. This schematic representation shows the architecture of the core cerebellar microcircuit. Purkinje cells, the principle and efferent neurons in the cerebellar cortex, are activated by climbing fibers originating from the inferior olive and parallel fibers of granule cells, and form the neuronal loop of sensorimotor integration in the cerebellar cortex. Purkinje cells in turn project to the cerebellar nuclei, which is the final integration node and transmit information out of the cerebellum. Clinical and experimental studies have found that some specific types of cerebellar ataxia (red font) are due to the damage of internal cerebellar neuronal circuits and different cells. Abbreviations: 5-HT, 5-hydroxytryptamine; AT, ataxia-telangiectasia; DRN, dorsal raphe nucleus; EICA, ethanol-induced cerebellar ataxia; FA, Friedrich ataxia; FXS, fragile X syndrome; HA, histamine; LC, locus coeruleus; NA, noradrenaline; SCA, spinocerebellar ataxia; TMN, tuberomammillary nucleus

脑共济失调动物模型*Mwk*小鼠中, 阳离子通透性瞬时受体电位通道3(cation-permeable transient receptor potential channel 3, TRPC3)基因的点突变直接导致浦肯野细胞的发育异常、功能障碍和凋亡, 进而引发*Mwk*模型小鼠产生共济失调。Sausbier等人^[20]对大电导钙激活钾离子通道(large-conductance Ca^{2+} -activated K^{+} channel, BK channel)缺陷模型小鼠的研究发现, 突触后BK通道缺失导致细胞去极化阻滞, 引起小脑浦肯野细胞的自发放电活动显著减少, 这可能是BK通道缺陷模型小鼠产生运动协调障碍和共济失调的主要原因。Walter等人^[21]也发现由*CACNA2D2*基因点突变导致的P/Q型电压门控钙离子通道(P/Q-type voltage-gated calcium channels)缺失小鼠的小脑浦肯野细胞的起搏精度丧失, 导致浦肯野细胞编码突触活动的异常, 影响

小脑的正常功能, 从而引起运动障碍和共济失调。除此之外, 小脑浦肯野细胞条件性敲除3-磷酸肌醇依赖性蛋白激酶-1(3-phosphoinositide-dependent protein kinase-1, PDK1)可导致浦肯野细胞胞体、树突复杂程度以及自发放电频率的降低, 并出现步态紊乱和运动失调等共济失调样运动障碍^[22]。Yang等人^[23]发现WD40重复结构域蛋白Rack1(receptor for activated C kinase 1)通过颗粒神经元前体细胞以非细胞自主性方式影响小脑浦肯野细胞分化成熟, Rack1基因的缺失与小脑发育异常和共济失调运动缺陷密切相关。由于绒球小结叶中的浦肯野细胞直接投射至前庭核团, 构成前庭小脑的最终输出^[5], 并参与了眼球的向下平滑追踪运动, 其损伤是小脑共济失调患者发生下跳性眼球震颤的主要原因^[24]。

3.2 小脑核团神经元与共济失调

除了绒球小结叶之外, 绝大多数小脑皮层中的浦肯野细胞的轴突并不离开小脑, 而是投射到小脑核团。因此, 小脑核团神经元才是小脑真正的传出神经元。在每个小脑半球深部有三个主要核团, 由外向内依次为齿状核、间位核(某些哺乳动物又分为栓状核和球状核)和顶核^[5,25]。由小脑核团病变所引起构音障碍、辨距不良、吞咽困难等小脑共济失调症状往往比小脑皮层损伤更加严重^[26](图1)。Shakkottai等人^[27]通过沉默小鼠小脑核团中的小电导钙激活钾通道(small-conductance Ca^{2+} -activated K^{+} channel, SK channel)可使小脑核团神经元过度激活, 并成功诱发小脑共济失调样症状, 提示小脑核团神经元的功能活动异常在小脑共济失调的神经机制中发挥重要作用。在三对小脑核团中, 齿状核是皮层小脑的最终输出核团。Teixeira等人^[28]的临床研究显示, 小脑急性缺血性损伤导致的齿状核到对侧运动皮层兴奋性输入的缺失很可能是此类患者出现共济失调症状的重要原因之一, 而对齿状核进行深部脑刺激(deep brain stimulation, DBS)则可以明显改善相关共济失调症状。MRI研究也在FA患者和甲硝唑致小脑共济失调患者脑中发现了明显的齿状核损伤^[29]。间位核和顶核则是脊髓小脑的最终输出核团。本实验室的相关研究表明, 药理学阻断或基因敲减小脑间位核中的促肾上腺皮质激素释放因子(corticotropin releasing factor, CRF)的受体CRFR1和CRFR2均可导致大鼠出现步态紊乱、运动失衡等小脑共济失调样运动症状^[30]。而临床研究表明, 局灶性小脑损伤患者患侧肢体共济失调的程度与间位核的病变有直接关系^[31]。而顶核损伤大鼠的运动协调能力显著减弱^[25], 在平衡木行走和旋转棒跑步机上的运动表现均显著下降, 表现出共济失调样症状^[32]。灵长类动物和猫的顶核损伤也会导致严重的共济失调^[33]。Konczak等人^[31]的临床报道显示, 一些儿童和青少年小脑肿瘤切除后的顶核损伤会引起姿势控制紊乱与共济失调。

3.3 小脑的神经传入与共济失调

小脑皮层和核团均接受来自苔状纤维和爬行纤维这两大小脑传入系统的神经传入。苔状纤维起源于中枢神经系统中的许多部位, 如脊髓、前庭核和脑干中的一些核团, 为小脑提供有关正在进行中的运动信

息、大脑皮层发出的运动指令和其他感觉的精确分级信息^[5]。苔状纤维的信息进入小脑后由皮层颗粒细胞接转, 后者的轴突上行到分子层后分叉并沿小脑叶片的长轴方向向两侧伸展从而形成平行纤维, 并与浦肯野细胞树突远端的末梢分枝形成兴奋性突触联系^[5]。临床研究发现, SCA2患者伴有明显的脑桥核苔状纤维萎缩^[34](图1)。而基础研究亦发现, 苔状纤维的功能异常与共济失调的病理机制密切相关。Gasbarri等人^[35]发现, 电损毁小脑中脚以阻断脑桥核苔状纤维的传入后, 大鼠的运动能力显著下降并表现出共济失调样症状。而在*Cbln1*缺陷的共济失调模型小鼠中, 小脑平行纤维和浦肯野细胞之间的突触连接出现异常, 注射人工合成的突触组织蛋白以重建突触连接则能够改善该模型小鼠的步态异常和运动障碍^[36]。浦肯野细胞条件性敲除接头蛋白Numb可造成平行纤维-小脑浦肯野细胞长时程抑制的缺失和小鼠协调性运动行为的异常^[37]。颗粒细胞条件性敲除脑膜瘤表达抗原6(meningioma expressed antigen 6, Mea6)的小鼠表现为平行纤维-浦肯野细胞神经递质释放的削弱和共济失调样运动功能异常^[38]。此外, 苔状纤维传入可能亦与乙醇诱发的小脑共济失调(ethanol-induced cerebellar ataxia, EICA)密切相关, 乙醇可通过抑制小鼠苔状纤维与颗粒细胞和高尔基细胞突触联系部位的一氧化氮合酶使得高尔基细胞活化, 从而增强其对颗粒细胞的抑制, 导致小脑对来自苔状纤维的感觉传入信息处理受损^[39]。

爬行纤维仅起源于延髓的下橄榄核, 它们上行到分子层后缠绕到浦肯野细胞的胞体和树突上, 可将运动误差信息传递给浦肯野细胞^[5]。临床研究发现, 诸多SCA亚型患者均伴有明显的下橄榄核萎缩^[40](图1)。对甲硝唑所致小脑共济失调患者脑部的MRI研究表明下橄榄核具有明显的损伤^[29]。而损毁下橄榄核以破坏爬行纤维的正常传入是最常用的小脑共济失调动物模型的造模方法之一。例如, 神经毒素3-AP是烟碱酰胺的一种抗代谢产物, 已被证明能对下橄榄核产生高度选择性的损伤, 常被用来建立小脑共济失调动物模型^[41]。Horn等人^[42]将海人藻酸(kainic acid)注射到猫下橄榄核中的头端内侧副橄榄核(rostral medial accessory olive)中, 造成了下橄榄核细胞的损伤, 从而构建出猫的小脑共济失调模型。本实验室先前的研究发现, 除谷氨酸外, 下橄榄核还可能发出直接的CRF能爬行纤维投射至小脑间位核, 而下调下橄榄核中的CRF表达, 导

致大鼠出现小脑共济失调样运动障碍^[30]。

除了起源于脑桥核和下橄榄核的苔状纤维和爬行纤维外,小脑还接受来自其他脑区的第三类传入,特别是单胺能神经传入,包括来自中缝核的5-羟色胺(5-hydroxytryptamine, 5-HT)能投射、来自蓝斑的去甲肾上腺素(noradrenaline, NA)能投射,以及来自下丘脑结节乳头体核的组胺能投射等^[43,44]。这些单胺能神经调质不仅参与了经小脑介导的正常运动功能的调控,其功能紊乱也在CA, EICA等遗传性和获得性小脑共济失调的病理机制中发挥作用(图1)。研究表明,5-HT能够通过作用于突触后5-HT_{2A}受体兴奋小脑核团神经元,并促进运动协调和运动平衡^[45]。与之一致,临床研究显示,小脑5-HT能神经传入异常,特别是小脑中5-HT含量不足,可引起小脑共济失调^[46],而补充左旋五羟色氨酸(5-HT的前体物质),可改善小脑共济失调患者的症状,如提高患者的站立时间、步速、语速和书写速度等。然而值得注意的是,由抑制脑内单胺氧化酶A活性引起的小脑5-HT含量的显著升高,却会导致经小脑的运动协调障碍和步态紊乱,而用药物干预使小脑内5-HT水平恢复正常后,又可显著缓解共济失调样运动障碍^[47]。近期的光遗传学研究也发现,激活小脑核团中的5-HT能神经纤维可促进由应激引起的肌张力异常和运动障碍^[48],提示了5-HT在小脑神经元环路中具有复杂的调控作用,小脑5-HT能神经传入的稳态对于小脑正常功能的发挥至关重要,而其失衡则可能与小脑共济失调样运动障碍密切相关。此外,源自蓝斑的NA能传入纤维可支配整个小脑皮层,在乙醇性小脑共济失调模型动物中,小脑皮层中NA的释放被显著抑制^[49]。来自下丘脑结节乳头体核组胺能纤维亦支配了小脑皮层和小脑核团。本实验室的系列研究工作揭示^[50-53],组胺能神经传入能够通过组胺H2受体及其下游耦联的HCN通道和/或H1受体兴奋小脑皮层和小脑核团神经元,并可快速促进经小脑介导的运动协调和平衡^[43,54-56]。实际上,一些组胺能药物可影响小脑共济失调样症状,如选择性H1受体阻断剂cetirizine可恶化小鼠的乙醇性小脑共济失调样症状^[57],而ciproxifan作为一种强效的H3受体阻断剂,能够引起大鼠共济失调样运动障碍^[58]。

3.4 小脑胶质细胞与共济失调

小胶质细胞是中枢神经系统中的主要免疫细胞。

已经知道,小脑中小胶质细胞(microglia)过度激活所引起的神经炎症反应是介导小脑共济失调的重要病理机制^[59]。在小脑共济失调模型动物以及FA, AT, FXS等患者中均可观察到早于运动障碍症状出现的小脑小胶质细胞的增殖和活化,提示其可能广泛地参与了共济失调中小脑神经炎症和神经元变性的病理进程^[60,61]。值得注意的是,相较于大脑皮层和丘脑等其他脑区中的小胶质细胞,小脑中的小胶质细胞在生理状态下呈高度警觉免疫表型(hyper-vigilant immune phenotype),表现为免疫抑制基因*CD47*, *CD300a*低表达,而免疫激活相关基因*trem1*, *trem3*高表达^[62]。并且,这种高度警觉免疫表型可随着衰老(aging)进一步增强,并可能与年龄依赖的迟发性小脑共济失调的发生相关。小脑小胶质细胞的高度警觉免疫表型很可能是遗传性共济失调患者实际上全脑基因缺陷,但却仅表现为小脑易感的一个重要原因。

小胶质细胞炎症激活后可通过调控浦肯野细胞神经元活动介导共济失调样症状的发生(图2)。本实验室发现小脑出血性卒中诱导的共济失调模型小鼠中,小脑小胶质细胞激活可以通过增加促炎细胞因子,如白细胞介素6(interleukin-6, IL-6)、白细胞介素1 β (interleukin-1 β , IL-1 β)和肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α),以及趋化因子C-C型趋化因子配体2(C-C motif ligand 2, CCL-2)的释放,招募炎性单核/巨噬细胞,导致小脑浦肯野细胞的凋亡及电生理功能异常^[63]。而在脑炎(encephalitis)患者和动物模型中,脑膜炎病毒感染能够引起CD8⁺ T细胞释放干扰素,从而诱导浦肯野细胞释放CCL-2招募小胶质细胞,进而导致浦肯野细胞的突触丢失和运动障碍^[64]。注射细菌脂多糖(lipopolysaccharide, LPS),通过病原相关分子模式(pathogen associated molecular pattern, PAMPs)激活小胶质细胞表面toll样受体4(toll-like receptor, TLR4)及下游的NF- κ B信号通路,引起小脑小胶质细胞促炎性激活,释放TNF- α 炎性介质和ATP,影响浦肯野细胞的内在兴奋性和突触传递,并导致共济失调样运动障碍^[65]。小胶质细胞对浦肯野细胞的功能调控一方面被认为是通过其分泌的炎性介质作用于浦肯野细胞中表达的多种炎性介质受体从而发挥作用^[59],而另一方面,过度活化的小脑小胶质细胞还能够直接吞噬浦肯野细胞并对突触及爬行纤维过度修剪^[66],是衰老和多种类型共济失调中浦肯野细胞丧失和小脑环路功能障碍的重要原因。

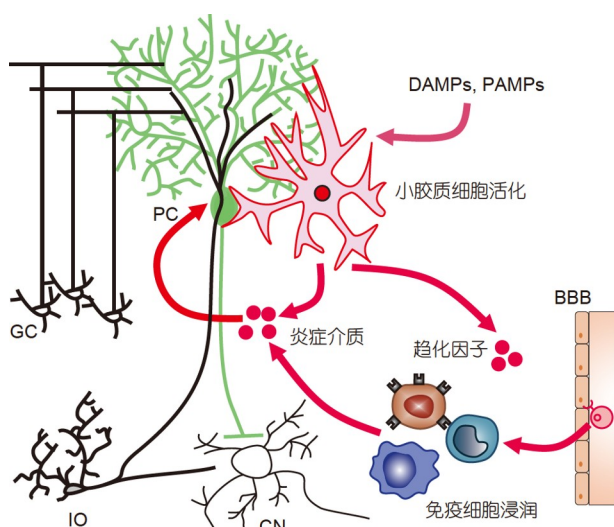


图 2 小脑小胶质细胞在小脑共济失调发病机制中的作用. 小脑中的小胶质细胞具有独特的高度警觉免疫表型, 可能导致小脑对神经炎症易感和小脑共济失调. 小脑小胶质细胞可被DAMPs或PAMPs激活. 活化的小胶质细胞增加对浦肯野细胞树突和胞体的吞噬, 导致浦肯野细胞的功能障碍恶化. 另一方面, 小胶质细胞的活化会导致促炎性细胞因子和趋化因子的产生. 这种小胶质细胞驱动的神经营养可进一步招募免疫细胞浸润. 而小胶质细胞的极化则加重浦肯野细胞在小脑共济失调中的退变. CN, 小脑核团; IO, 下橄榄核; BBB, 血脑屏障; GC, 颗粒细胞; PC, 浦肯野细胞; DAMPs, 损伤相关分子模式; PAMPs, 病原相关分子模式

Figure 2 Roles of cerebellar microglia in the pathogenesis of cerebellar ataxias. Cerebellar microglia represent a uniquely hypervigilant immune phenotype which may cause cerebellar vulnerability in neuroinflammation and cerebellar ataxias. Cerebellar microglia are activated by DAMPs or PAMPs. Increased engulfment of dendrites and soma of Purkinje cells are caused by activated microglia, which could exacerbate Purkinje cells dysfunction. Alternatively, activation of microglia leads to the production of proinflammatory cytokines and chemokines. Microglia-driven neuroinflammation further recruits immune cells. Microglial polarization aggravates Purkinje cell degeneration in cerebellar ataxias. Abbreviations: CN, cerebellar nuclei; IO, inferior olive; BBB, blood-brain barrier; GC, granule cell; PC, Purkinje cell; DAMPs, damage associated molecular patterns; PAMPs, pathogen-associated molecular patterns

事实上, 小胶质细胞的功能活动十分复杂. Ferro等人^[67]发现抑制小脑小胶质细胞的NF- κ B信号在野生型小鼠中可引起共济失调样运动障碍, 但小胶质细胞NF- κ B信号的缺失不影响浦肯野细胞的功能活动, 而是可能通过发育早期爬行纤维异常修剪而引起成年后小脑环路连接的障碍^[68]. 此外, 小胶质细胞的促炎性激活还参与了星形胶质细胞(astrocyte)的活化^[69]. 小脑中一类特殊的星形胶质细胞——伯格曼胶质细胞(Bergmann glia)可通过调控谷氨酸稳态和胞外钾离子平衡影响浦肯野细胞的功能活动^[70]. 在SCA1和SCA7

中, 其早于神经元变性出现功能紊乱或凋亡, 进一步“放大”了神经炎症和谷氨酸毒性, 加剧了浦肯野细胞的凋亡^[71,72]. 近期一项研究发现, 光遗传学操控慢性激活伯格曼胶质细胞可通过触发兴奋性毒诱导与SCA1相似的共济失调病理表型^[73]. 也有研究表明, 小脑星形胶质细胞的活化在共济失调发生发展不同阶段中的作用可能不尽相同, 早于运动障碍发生前抑制星形胶质细胞的NF- κ B促炎信号可加重浦肯野神经元的功能障碍和运动缺陷, 反之在SCA1发病晚期抑制星形胶质细胞的NF- κ B促炎信号则可减轻运动障碍^[60], 提示小脑共济失调中星形胶质细胞导致的神经营养具有多种关键作用.

4 小脑共济失调的治疗

4.1 小脑共济失调的药物治疗

治疗小脑共济失调的目标是提升患者的运动相关能力和生活质量. 最理想的治疗方法是对小脑疾病进行针对性的病因治疗, 但其仅能用于治疗发病机制简单且明确的小脑共济失调类型, 如由维生素缺乏所引起的小脑共济失调就可以通过补充体内缺乏物质来有效缓解甚至完全治愈^[74]. 然而, 小脑共济失调的分型众多, 且神经机制十分复杂. 但考虑到小脑神经元功能活动的异常是各类共济失调发生发展的共同神经机制, 目前常用的临床治疗药物主要集中于调控小脑神经元的发放频率上. 然而, 遗憾的是, 除了氨基吡啶和乙酰唑胺被公认可用于治疗EA外, 对于遗传性小脑共济失调目前尚缺乏有效的治疗药物^[75].

氨基吡啶是Kv1电压门控钾离子通道的选择性阻断剂, 可以增加包括小脑浦肯野细胞在内的神经元的兴奋性, 从而改善遗传原因所导致的小脑共济失调^[76]. 氨基吡啶有两种类型: 3,4-二氨基吡啶(3,4-diaminopyridine, 3,4-DAP)和4-氨基吡啶(4-aminopyridine, 4-AP), 后者是脂溶性的, 比3,4-DAP更容易穿透血脑屏障. 动物研究表明, 4-AP可提高浦肯野细胞在EA2模型小鼠中起搏的精度^[77]. Weisz等人^[78]通过对EA2模型^{*tottering*}小鼠的研究发现, 4-AP和3,4-DAP可通过提高疾病的发病阈值来降低疾病发作频率. 一项针对EA2的4-AP随机交叉试验发现, 患者疾病发作次数减少, 生活质量得到提高^[79]. 除此之外, 患有小脑萎缩和SCA6的患者也可以通过3,4-DAP恢复症状^[80]. 4-AP的随机对

照试验(randomized controlled trial, RCT)显示, 施加一定剂量的4-AP可以改善小脑共济失调患者下跳性眼球震颤并减少姿势摇摆^[81]。一项正电子发射计算机断层扫描成像(positron emission computed tomography, PET)的临床研究也显示, 4-AP治疗期间, 患有下跳性眼球震颤的患者小脑皮层的代谢活性明显增加, 下跳性眼球震颤症状得到缓解^[82]。

乙酰唑胺是一种碳酸酐酶抑制剂, 因此可导致CO₂在脑内积聚, 阻断阴离子运输并增加γ-氨基丁酸(γ-aminobutyric acid, GABA)水平, 从而调节小脑神经元的发放频率^[4]。乙酰唑胺常被用作抗癫痫治疗, 也在临床上用于治疗EA, 在66%的EA2病例中, 乙酰唑胺可显著减少其疾病的发作次数^[75]。对6例重症急性脑损伤患者进行的为期88周的公开标记试验结果显示, 乙酰唑胺使他们的姿势摆动和共济失调症状有所改善, 改善效果在48周后趋于稳定^[83]。然而, 乙酰唑胺的副作用(如肾结石、高水化、感觉异常和剂量相关的胃肠紊乱)往往限制了其在临床治疗中的应用。近期研究还发现了另一种抗癫痫药物——丙戊酸, 在常染色体隐性遗传性共济失调SCAR20(spinocerebellar ataxia, autosomal recessive 20)中能够减少浦肯野细胞死亡并降低神经炎症, 减缓SCAR20小鼠的病理进程^[84], 提示部分抗癫痫药物的“老药新用”在以浦肯野细胞死亡为特征的遗传性小脑共济失调防治中具有潜在的应用价值。

4.2 小脑共济失调的神经调控治疗

除药物治疗外, DBS, 经颅直流电刺激(transcranial direct current stimulation, tDCS)及经颅磁刺激(transcranial magnetic stimulation, TMS)等神经调控技术也已应用于临床小脑共济失调的治疗。其中, DBS为有创性神经调控疗法, 仅在少数小脑卒中引起的共济失调患者中被报道采用。结果表明DBS刺激小脑齿状核可改善患者的震颤和共济失调样运动障碍, 但对肌张力异常没有影响^[28]。相较于DBS, tDCS和TMS具有无创伤、安全性高的优势。采用阳极tDCS刺激右侧小脑皮层和蚓部治疗小脑共济失调患者的运动障碍症状, 如步态、平衡、姿势、运动性/姿势性震颤、辨距不良等均有一定程度的改善效果^[85-88]。TMS采用70~75 mm八字形线圈TMS刺激中风患者小脑患侧皮层, 能够改善患者共济失调尤其是姿势和步态方面的评分指标, 并

且在刺激一个月后, 仍旧对行走测试(10 meter walk test)和平衡测试(Berg balance scale)具有改善效应^[89,90]。而通过双线圈TMS刺激中风患者健侧齿状核, 可以改善震颤和共济失调运动障碍症状, 但对肌张力障碍效果不佳^[91]。

5 展望

一方面, 氨基吡啶和乙酰唑胺等临床现有的小脑共济失调治疗药物主要针对神经元的放电活动进行调节, 作用机制较为单一。并且, 这些药物靶向的离子通道或生物酶分布广泛, 选择性不强。因此, 往往导致治疗效果不理想且伴随较大的副作用。另一方面, 神经调控疗法治疗小脑共济失调尽管在临床治疗中取得了一定的疗效, 但其尚不明晰的治疗机制极大地限制了这一策略的进一步优化和发展。随着对小脑共济失调相关基础及临床研究的深入, 特别是对小脑共济失调发病原因、病理及神经机制的进一步深入解析, 靶向小脑中神经递质系统、小脑小胶质细胞诱发的神经炎症反应、反义寡核苷酸(antisense oligonucleotide, ASO)靶向致病基因和靶标明确的神经调控技术均可能为未来小脑共济失调的临床治疗提供新的思路。

(i) 靶向小脑中神经递质系统治疗共济失调。小脑中的许多神经递质系统, 如CRF能^[92]、5-HT能、组胺能和去甲肾上腺素能系统的功能紊乱均在小脑共济失调的病理机制中发挥关键作用。不同于氨基吡啶、乙酰唑胺等传统的离子通道类或酶抑制剂类药物缺乏神经元作用类型的选择性, 受体表达的异质性为靶向小脑中神经递质受体的药物提供了可选择性作用于小脑皮层浦肯野细胞, 以及小脑皮层和核团内不同类型神经元的可能性, 从而有助于选择性调控表型域相关的特定环路, 提高治疗效果和减少副作用。事实上, 5-HT, CRF, 组胺和NA的受体类型均十分复杂, 且我们和其他实验室的研究表明, 各受体亚型在小脑中的表达和功能存在明显的异质性。在小脑中, 几乎所有的5-HT受体亚型(5-HT₁-5-HT₇共计14个受体亚型)均有表达^[93]。我们发现小脑顶核(脊髓小脑的最终输出之一, 其损伤常引起患者肢体不协调)中仅表达5-HT_{2A}受体, 该受体的选择性激活能够通过提高顶核神经元兴奋性, 减小大鼠的步基宽, 提高大鼠在旋转棒跑步机和平衡木上的运动平衡和协调能力^[45]。而CRF受体亚型

CRFR1和CRFR2在小脑间位核谷氨酸能投射神经元而非GABA能中间神经元上特异性表达. 激动小脑间位核中的CRFR1和CRFR2能够显著改善由3-乙酰吡啶(3-acetylpyridine, 3-AP)诱导的小脑共济失调模型大鼠的步态紊乱和运动失调等运动障碍^[30]. 组胺受体亚型中, 除H4尚不明确外, H1, H2和H3受体被报道分别高表达于豚鼠小脑皮层的颗粒细胞层和分子层、大鼠的小脑核团以及浦肯野细胞-小脑核团的神经末梢. 其中组胺H2受体的分布模式与CRF受体相类似, 在小脑核团中仅特异性地表达于投射神经元而非中间神经元, 亦在运动协调中发挥关键作用^[43]. $\text{NA}\alpha$ 受体各亚型在小脑中亦有广泛的分布, 且发挥不同的运动调控作用. 其中 α_{1d} 肾上腺素受体敲除小鼠在高速旋转棒跑步机测试中表现出更好的运动协调性和更强的肌张力^[94], 而 α_{2a} 肾上腺素受体缺乏小鼠的运动协调能力减弱, 表现出共济失调样症状^[95]. 理解小脑中上述单胺类及神经肽类递质系统对小脑神经元电活动和运动功能的调制是重建运动控制的治疗方案的重要一环^[96]. 但是, 鉴于小脑中神经元类型以及小脑微结构和小脑环路的复杂性, 尚需要进一步理清这些神经递质其受体亚型在小脑中的分布规律、功能作用和精细神经机制.

(ii) 靶向小脑中小胶质细胞介导的神经炎症反应治疗共济失调. 考虑到小脑小胶质细胞的高度警觉免疫表型可能是小脑成为共济失调易感性脑区的重要原因, 靶向小脑小胶质细胞及其介导的神经炎症反应将为广泛治疗多种类型的小脑共济失调提供潜在的治疗策略. 本实验室前期的研究工作发现, 使用Ki20227, minocycline以及bindarit这三种已开展临床试验的药物, 可以分别清除小胶质细胞、抑制小胶质细胞促炎性激活和抑制CCL-2合成, 均能够改善卒中引起的小鼠小脑神经炎症水平增高和共济失调样症状^[63]. 而在SCA1小鼠发病早期清除小胶质细胞, 则能够减少促炎症因子的表达并缓解运动障碍^[97]. 给予AT小鼠非甾体抗炎药布洛芬, 能够抑制小胶质细胞的激活并延缓共济失调样运动障碍的发生^[98]. 在3-AP诱导的共济失调大鼠模型中, 通过脑室内给予TGF- β 1抑制小胶质细胞促炎性活化, 能够改善3-AP模型大鼠共济失调样运动缺陷^[99]. 在LPS诱导的炎性小脑共济失调和FA动物模型中, 通过移植正常动物的骨髓间充质干细胞、造血干细胞或前体细胞, 均能够促进形成稳态的或抑炎性的

小胶质细胞, 从而保护神经元凋亡并缓解运动障碍^[100]. 因此, 进一步解析小脑中小胶质细胞在不同遗传性和非遗传性共济失调中的作用及下游神经机制, 可能为进一步确定靶向小脑中小胶质细胞这一策略的适用范围和发展基于小胶质细胞下游关键分子的治疗策略提供重要参考.

(iii) ASO靶向致病基因治疗小脑共济失调. 各类遗传性小脑共济失调遗传背景的解析和分类的完善, 使得靶向单基因突变导致的共济失调的致病基因成为潜在治疗策略, 如SCA亚型中常见的过度CAG重复毒性片段常用作临床治疗靶点^[101]. ASO是人工合成的靶向目的基因mRNA的短链片段, 可以从转录水平上影响其蛋白表达水平乃至mRNA剪接缺陷^[102]. 目前, 临床上已经开展了针对杜氏肌营养不良、脊髓性肌萎缩和淀粉样变性等疾病的ASO治疗^[103], 而针对罕见的致命性神经退行性疾病, 基于ASO方法在14个月内就能够建立起一个有效的治疗方案^[104]. 临床前研究表明, 静脉注射经化学修饰的ASO能够高效通过血脑屏障, 在AT模型小鼠中纠正异常剪接的*Atm* mRNA^[105]. 另一项研究通过筛查AT患者的ATM突变位点, 并设计靶向剪接异常外显子区域的ASO成功恢复了患者淋巴细胞中ATM的蛋白表达水平^[106]. 针对SCA1模型小鼠, 研究人员在早期(六周)注射靶向*Atxn1*基因异常CAG片段的ASO, 能够在24周内检测到*Atxn1* mRNA水平的降低, 并能够在较长的时程中增强模型动物的运动能力和浦肯野细胞放电活动^[107]. SCA3是最常见的显性遗传性共济失调^[108], 在动物模型上分别注射靶向*Atxn3*基因的CAG片段, 剪接体外显子8~10毒性片段和ATXN3蛋白表达的ASO均能够长效缓解浦肯野细胞电活动异常和运动障碍^[109]. 相类似地, 在SCA2和SCA7模型动物中, 单次ASO注射能长效地降低毒性蛋白的表达水平从而改善其病理症状^[110,111]. 尽管ASO治疗相对简单且高效, 但是临床运用同样受到很多因素的制约, 如ASO易被核酸酶降解, 细胞内递送效率较低和脱靶导致的非特异性结合等. 因此, 发展和优化ASO药物是未来对于遗传背景明确的单基因突变导致的小脑共济失调实现精准治疗的重要方向.

(iv) 靶标明确的神经调控疗法治疗小脑共济失调. DBS, tDSC和TMS治疗小脑共济失调的神经机制一直未明是目前制约这一治疗策略发展的关键因素. 目前认为DBS的治疗效果可能与微结构可塑性和皮层

重组有关^[112]。在卒中模型小鼠中, 光遗传学激活小脑齿状核能够模拟DBS的治疗效果, 其引起的生长相关蛋白43(growth-associated protein 43)表达上调可能参与了小脑皮层的可塑性变化^[113]。在选择性沉默橄榄-小脑谷氨酸能投射的肌张力障碍和*Car8^{wdl}*突变的共济失调小鼠模型中, 运用13和130 Hz的小脑间位核DBS刺激均可以改善小鼠的肌张力障碍、肢体失调和步态不稳, 且刺激的改善效果可以维持数日^[114]。这种治疗效果依赖于小脑环路功能的完整性, 浦肯野细胞功能障碍会削弱间位核DBS的治疗作用, 提示在小脑共济失调早期神经元尚未变性就进行干预, 能够获得较好的治疗效果。tDSC和TMS则被认为可以分别通过电刺

激和磁刺激改变神经元的电活动。其中tDSC通过刺激改变神经元膜的极性, 从而改变其触发动作电位的阈值^[115], 而磁刺激可对局部神经元产生长时程增强(高频刺激, >5 Hz)或长时程抑制(低频刺激, 小于1 Hz)的效应^[116]。然而, 考虑到小脑与丘脑、基底神经节、海马、下丘脑和杏仁核等不同脑区之间存在着广泛的神经连接, 小脑刺激的功效亦可能因为下游靶区的不同分子效应、下游脑区精确的投射谱以及不同下游环路的功能差异而有所不同。因此, 进一步深入解析小脑的功能投射谱, 并立足小脑共济失调的分子、细胞和神经环路机制发展靶标明确的小脑刺激策略可能是未来小脑共济失调非药物治疗的重大突破方向。

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Neural mechanism and therapeutic strategy of cerebellar ataxia

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The cerebellum is the largest subcortical motor structure, mainly responsible for motor coordination and control. Cerebellar damage and dysfunction caused by hereditary or endogenous/exogenous factors will lead to cerebellar ataxia. Patients with cerebellar ataxia suffer from balance and gait dysfunction, limb movement deficits, oculomotor abnormalities, as well as dysarthria, which seriously affect their quality of life and constitute a heavy social and economic burden. However, the diverse pathogenesis poses great challenges in the prevention and treatment of cerebellar ataxia. Here we review the current knowledge of the etiology, symptoms, and clinical classification of cerebellar ataxia. The latest research progress on the neural mechanism of cerebellar ataxia has been summarized, in particular, from the view of the structure and dysfunction of neurons, neural circuits, and glial cells in the cerebellum. Furthermore, based on the current clinical treatment of cerebellar ataxia, we also propose and discuss the advantages and disadvantages of new strategies of targeting the neurotransmitter system of cerebellar circuitries, microglia-mediated neuroinflammation, virulence genes of hereditary cerebellar ataxia, as well as brain stimulation intervention during the treatment of cerebellar ataxia. This review may provide a useful reference for the development of more effective therapies for cerebellar ataxia in the future.

cerebellar ataxia, neuronal excitability, neurotransmitter, neuroinflammation, therapeutic strategy

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