·专题综述·

癌症相关认知功能障碍发病机制研究进展

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【摘要】 随着癌症诊断与治疗水平的进步，癌症患者生存率明显升高，使得癌症及其治疗相关并发症逐渐显现。其中，认知功能障碍可出现在癌症患者接受治疗前、治疗期间甚至治疗后数年，严重影响预后和功能独立性。国际上将这种癌症及其治疗引起的认知功能障碍称为癌症相关认知功能障碍，但目前国内外关于癌症相关认知功能障碍的认识仍十分不足，系统性癌症如何与中枢神经系统建立联系引起认知功能障碍和精神行为异常尚不十分明确。本文总结国内外近10年最新研究成果，梳理癌症相关认知功能障碍潜在发病机制研究进展，为进一步探索早期干预和综合管理策略提供思路。

【关键词】 肿瘤； 认知障碍； 综述

Research advance of the mechanism of cancer-related cognitive impairment

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【Abstract】 Advances in diagnostic and therapeutic strategies in cancer have significantly increased the survival of cancer patients, which causes cancer itself and its treatment related sequelae and side effects appearing in their later life. Patients with cancer before, during and even many years after completion of therapies can exhibit cognitive impairment, negatively affecting cancer survivors′ quality of life and functional independence. Internationally, patients with cancer complaining cognitive symptoms due to the disease itself and/or its therapy are called cancer-related cognitive impairment (CRCI). However, many aspects of the association between cancer and cognitive impairment remain uncertain. The definitive connection between systemic cancer and central nervous system is yet to be established. Therefore, this review summarizes the current evidence on potential pathophysiology in these patients with CRCI, emphasizing knowledge gaps and the potential strategies to address them.

【Key words】 Neoplasms; Cognition disorders; Review

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癌症和认知功能障碍均是我国发病率和病残率极高的疾病。2019年，Zhou等[1]在*Lancet*发表1990-2017年中国34个省级行政单位人口健康状况报告，肺癌和肝癌位列生存期缩短前5位病因。最新一项纳入我国46 011例60岁及以上人群的横断面研究显示，轻度认知损害（MCI）和痴呆发病率分别高达15.5%和6%[2]。随着癌症诊疗水平不断提高，死亡率明显下降：1991-2016年癌症总死亡率持续下降27%，2007-2016年男性和女性癌症死亡率每年下降1.8%和1.4%[3]。随着癌症患者生存期的延长，癌症自身及治疗相关后遗症和不良反应逐渐显现。自20世纪90年代以来，越来越多的研究证实癌症相关认知功能障碍（CRCI）的存在[4-5]。认知功能障碍可以出现在癌症病程的各阶段，尤其是化疗期间和化疗后，严重影响患者生活质量和功能独立性，亦给家庭和社会带来沉重负担[6]。目前，

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癌症相关认知功能障碍多指系统性癌症患者化疗后短期记忆和工作记忆、注意力、执行功能和(或)处理速度等认知域损害[7]。一项全国范围的前瞻性队列研究显示,乳腺癌患者化疗后6个月内认知功能障碍发生率明显高于年龄匹配的非癌症患者,这可能与基线时(化疗前)焦虑、抑郁以及认知储备降低有关[8]。亦有研究发现,30%～40%的癌症患者接受治疗前即有癌症相关认知功能障碍的临床证据,高达75%的患者在接受化疗过程中可能出现认知功能下降,60%的患者辅助治疗后可能出现认知功能下降[6,9],提示癌症自身及其辅助治疗均可能影响患者的认知功能。

尽管有证据证实癌症相关认知功能障碍的存在及其不良影响,但其潜在的生物学机制仍不十分清楚,认知功能下降是否完全由癌症自身、癌症治疗或心理因素造成尚不明确。系统性综述显示,化疗药物诱导外周血产生的超氧自由基可氧化修饰载脂蛋白A1,后者可升高外周血促炎性因子——肿瘤坏死因子-α(TNF-α),通过多种途径诱导脑实质氧化应激反应,进一步诱导细胞凋亡,影响认知功能[10-11]。众所周知,活性氧介导的脑组织氧化应激反应是阿尔茨海默病的重要发病机制之一,提示癌症相关认知功能障碍的可能病理生理学机制,但也有研究显示二者氧化应激的来源不尽相同[12]。系统性癌症如何与中枢神经系统建立联系从而引起认知功能下降和精神行为异常尚不十分明确。鉴于此,本文拟总结国内外近10年来最新研究成果,综述并梳理癌症相关认知功能障碍潜在发病机制研究进展,为探索早期干预和综合管理策略提供新思路。

一、癌症自身生物学效应

1.免疫炎症反应　近年研究显示,血液系统恶性肿瘤[13]和乳腺癌[14]等患者在接受任何辅助治疗前即已出现认知功能下降。横断面研究显示,无论是否接受化疗,乳腺癌及其他多种类型系统性癌症患者MRI显示,多个脑区的皮质表面积或厚度明显减少[15]。上述研究提示癌症自身可能对认知功能产生某些生物学影响。肿瘤微环境(TME)系包含肿瘤细胞、组织间质以及浸润性免疫细胞的复杂网络,这些细胞均可以产生炎性因子,主要有白细胞介素(IL)-6、IL-1β、IL-2、IL-8、IL-17、TNF-α和粒细胞集落刺激因子(G-CSF)等[16]。分析174例新确诊的乳腺癌患者的炎性标志物结果发现,与非癌症对照组(88例)相比,其血清白细胞介素-1受体阻断剂(IL-1Ra)明显升高[17]。一项纵向队列研究共检测75例早期乳腺癌患者化疗24个月内17种细胞因子水平,结果发现细胞因子水平随时间的推移而出现升高或降低的改变,并与特定认知域有关;这种相关性不仅体现在典型的促炎性因子如IL-6、TNF-α、IL-1β,还与多种类型细胞因子导致认知功能障碍的炎症环境有关[18]。癌症自身及其微环境可由于局部氧化应激反应或环境刺激产生炎性因子,后者通过直接透过血-脑屏障(BBB)或室周器官(CVOs)的高渗透性毛细血管[19]而进入脑组织并激活神经胶质细胞,诱导促炎性信号级联反应[20-21]或直接影响肿瘤微环境稳态和认知功能的重要神经元回路[22],从而与大脑建立联系;且进入脑实质前不断产生的炎性因子激活脉络丛和脑膜血管内血管周围巨噬细胞和树突状细胞,进一步促进炎性神经胶质细胞的极化,最终引起以认知功能为中心的神经元群的病理结构和生化变化[16,23]。

2.肿瘤源性细胞外囊泡　细胞外囊泡(EVs)是一组由细胞释放的,包含生物活性蛋白、核酸和脂质的异质性膜结合囊泡的总称,并根据生物学机制分为外泌体和脱落微泡[24]。细胞外囊泡除参与凝血、免疫调节、组织再生、血管生成和突触可塑性等多种正常生理过程外,还参与神经退行性变和癌症等病理过程[25]。在癌症背景下,细胞外囊泡参与炎症反应、血管生成、淋巴发生、细胞迁移与增殖、免疫抑制和侵袭等一系列与癌症进展有关的病理过程[26]。有证据表明,中枢神经系统损伤或疾病炎症反应的起始、扩散和缓解均有赖于炎性因子和微小RNA(miRNA),而这两种细胞因子均为细胞外囊泡所包含[27]。动物实验显示,将注射脂多糖的供体小鼠血清中外泌体静脉注射至受体后,可诱导中枢神经系统炎症反应,且受体小鼠体内可见小胶质细胞活化、神经胶质增生、促炎性因子(IL-6和TNF-α)增加以及炎性miRNA-155产生等一系列变化[28]。此外,越来越多的证据表明,细胞外囊泡可以作为神经系统正常发育和生理功能以及正常神经元再生过程中进行细胞通讯的新介质[29]。在营养缺乏和氧化应激条件下,神经元可通过内化吸收少突胶质细胞释放的外泌体以提高自身活性[30];星形胶质细胞释放含热休克蛋白70(HSP70)的外泌体亦可促进神经元存活[31];神经元摄取小胶质细胞源性外泌体可诱导其产生鞘氨醇,增强兴奋性神经传递[32],提

示神经细胞和支持细胞均可以通过分泌外泌体参与细胞通讯。肿瘤源性细胞外囊泡可能通过介导神经元之间的通讯参与生理和病理过程(突触生长和可塑性),从而影响大脑活动和认知功能[33]。研究显示,中枢神经系统肿瘤如胶质母细胞瘤通过表达外泌体以促使肿瘤源性长链非编码RNA(lncRNA)SBF2-AS1细胞内转移,重塑肿瘤微环境;或外泌体分泌促渗透性因子(如信号素3A)破坏血管内皮屏障完整性,诱导认知功能障碍[34-35]。对于系统性癌症而言,细胞外囊泡可能通过激活癌细胞脑转移破坏血-脑屏障完整性、分泌促渗透因子诱导血-脑屏障通透性增加,及诱导外周血免疫应答触发大脑应激反应等多种途径,从而影响认知功能[36]。

3.血-脑屏障功能紊乱 血-脑屏障是由内皮细胞通过与神经血管单元(NVU)的周细胞、星形胶质细胞、神经细胞和小胶质细胞相互作用而形成的屏障结构。血-脑屏障既可以限制血液中潜在的神经毒性成分、病原体等进入脑组织,还可以控制中枢神经系统所需营养与能量代谢物质和血液中必要分子的转运,以及将脑组织代谢产物输送至外周,以维持中枢神经系统稳态和功能[37]。血-脑屏障具有很强的调节作用,但也十分脆弱,结构中任何一种成分破坏均可能诱导异常神经元信号、破坏突触完整性和血-脑屏障通透性,进一步导致缺血性卒中、阿尔茨海默病、脑肿瘤和系统性炎症等中枢神经系统疾病,而这些疾病最明显的共同发病机制即为神经炎症性改变对血-脑屏障功能障碍和疾病进展的影响[37-38]。正如前文所述,癌细胞和肿瘤微环境产生的炎性因子可以通过破坏血-脑屏障完整性或增加其通透性进入中枢神经系统,激活神经胶质细胞并进一步诱导促炎性信号级联反应,影响认知功能。一项体内外血-脑屏障模型研究显示,乳腺癌分泌的细胞外囊泡可以通过血管内皮细胞转胞吞作用或者室周器官破坏血-脑屏障完整性进入脑组织[39]。血-脑屏障主动外排转运功能紊乱可以导致β-淀粉样蛋白(Aβ)等毒性物质清除障碍,脑组织积聚的Aβ可促进tau蛋白发生病理改变,诱导或加重认知功能障碍,这与阿尔茨海默病的病理学机制十分相似[40]。此外,持续的血管生成和免疫抑制是癌症的典型特征,病理性血管生成与血-脑屏障异常血流量和功能失调有关[41]。血管生成素-2(Ang-2)是多形性胶质母细胞瘤早期的血管标志物,不仅可以调节血管发育、成熟和即时血管反应,其过表达还可以导致周细胞缺陷、血管内皮细胞完整性破坏,干扰血-脑屏障功能[42]。由此可见,癌症自身释放的免疫炎性因子、细胞外囊泡以及异常血管生成等病理改变均可破坏血-脑屏障完整性和生理功能,同时血-脑屏障功能紊乱还可加剧脑组织病理性蛋白沉积,进一步加重认知功能障碍。

二、抗肿瘤治疗相关机制

1.药物化疗 癌症化疗不良反应常表现为周围神经病变、耳毒性、肺纤维化、肝肾功能异常等[43]。近年来,癌症化疗后出现认知功能障碍陆续见诸报道,有学者把这种化疗引起的注意力、记忆力、学习和语言功能等认知域损害现象称为“化疗脑”或“化疗雾”[44]。化疗诱导认知功能障碍(CICI)既可发生在化疗期间也出现在化疗后数年[6,45]。一项全国范围的纵向队列研究显示,Ⅰ~Ⅲc期乳腺癌患者化疗后6个月内出现记忆力、注意力和执行功能等多个认知域明显损害[46]。化疗药物与认知功能之间存在剂量-反应关系:Collins等[47]对60例早期乳腺癌术后患者分别于化疗开始前和每个化疗周期结束后行神经心理学测验,发现化疗组认知功能随着化疗时间的推移(即化疗药物剂量增加)呈进行性下降。另外,化疗药物多种多样,但仅小部分药物对认知功能和神经的影响见诸报道,主要包括烷化剂(环磷酰胺)、抗代谢药(甲氨蝶呤和5-氟尿嘧啶)、细胞毒性抗生素(阿霉素)、抗微管药物(紫杉醇和多西紫杉醇)、单克隆抗体(曲妥珠单抗和利妥昔单抗)以及免疫检查点抑制剂(CPI)[48]。化疗诱导认知功能障碍的具体病因与发病机制尚不十分明确。基于现有研究证据,假设的发病机制涉及多个层面,包括药物直接神经毒性作用、免疫功能失调、氧化应激反应以及脑血流动力学变化等[48-49]。顺铂是肺癌常用化疗药物,由铜摄取蛋白铜转运体1(CTR1)介导透过血-脑屏障,诱导脑网络异常、葡萄糖代谢障碍和认知功能障碍[50]。动物实验显示,全身给药的化疗药物如顺铂、卡莫司汀等作用于中枢神经系统祖细胞,其增殖所产生的少突胶质细胞对髓鞘形成和神经可塑性十分重要,而髓鞘轴突构成大脑白质[47,51];5-氟尿嘧啶与大鼠胼胝体髓鞘减少和少突胶质细胞转录因子2(Olig-2)表达失调有关[52]。接受甲氨蝶呤治疗的癌症模型大鼠在6和16个月后可见明显的脑白质内少突胶质细胞及其祖细胞数目减少、胼胝体体积减少和髓鞘碱性蛋白(MBP)减少等[53],提示化疗药物毒性作用与认知相

关脑区的髓鞘形成和白质异常有关。另外，这些药物毒性作用还可能影响海马神经细胞坏死和凋亡增加、增殖减少，干扰海马等区域的神经发生，进而影响学习能力和记忆力[54-55]。其次，化疗药物可以促进外周血炎性因子释放透过血-脑屏障或诱导中枢神经系统释放炎性因子，通过介导神经免疫炎症反应、影响表观遗传学修饰等途径，引起认知功能障碍。研究显示，阿霉素可以诱导外周血炎性因子和TNF-α水平升高，后者通过受体介导的内吞作用透过血-脑屏障引起脑组织TNF-α积聚，诱导重要生物分子氧化和亚硝化根硝化损伤、线粒体功能障碍以及神经元凋亡等[56-57]。另一方面，化疗药物可以激活小胶质细胞进一步释放促炎性因子（如IL-6和TNF-α）或改变星形胶质细胞和少突胶质细胞之间的相互作用，抑制海马的神经发生和白质髓鞘可塑性，干扰神经递质传递和轴突形成，从而诱导认知功能障碍[58-60]。动物实验显示，大鼠注射5-氟尿嘧啶4周后，体内炎症介质IL-1β、TNF-α和环氧合酶-2（COX-2）水平明显升高，而抗炎性因子IL-10水平下降[52]。Lyon等[61]认为，炎性因子可能触发Zeste同源蛋白2增强子（EZH2，一种重要的DNA修复酶）介导的DNA甲基化和染色体不稳定性（端粒缩短），引起细胞死亡或基因表达异常，最终导致化疗诱导认知功能障碍。活性氧（包括自由基和过氧化物）的生成与生物系统的抗氧化防御机制之间失衡引起的氧化应激反应被认为是化疗诱导认知功能障碍的另一潜在发病机制。动物实验表明，阿霉素可以增加大鼠对钙离子介导的脑线粒体通透性转换孔（PTP）的敏感性，增加线粒体膜的通透性，进而导致线粒体肿胀和破裂，诱导脑组织氧化应激反应[62]。甲氨蝶呤通过与叶酸代谢途径中的酶相互作用增加大鼠小脑丙二醛水平，诱导氧化应激[63]。化疗激活的氧化应激反应（活性氧积聚）不仅可以诱导线粒体DNA变异、降低中枢神经系统的抗氧化能力，造成认知功能障碍[64]；还可以通过加重血栓形成，干扰脑小血管灌注或转录因子3介导的脂毒性脑微血管损伤等途径破坏脑血管，造成类似于血管性痴呆（VaD）机制的认知损害[65]。

2.其他辅助治疗　除药物化疗外，激素或内分泌治疗药物、靶向治疗（如抗血管生成药物）以及免疫治疗等亦可引起认知功能障碍。乳腺癌的内分泌治疗药物主要包括选择性雌激素受体调节剂（SERMs，如他莫芬）和芳香化酶抑制剂（Ais，如来曲唑）两种类型。有证据表明，他莫芬治疗可以影响乳腺癌患者记忆力、语言功能、执行功能和信息处理速度等特定认知域[66]。细胞系模型显示，他莫昔芬可通过调节胞吐和囊泡的儿茶酚胺储存影响神经元活性，还可以作用于电压门控性钾离子通道（VGKC），干扰神经递质的分泌，从而影响认知功能[67]。予以灵长类动物来曲唑后，可见其空间工作记忆力损害，这可能与用药后海马组织雌二醇水平升高，海马神经元兴奋性降低有关联[68]。一项纳入75例接受靶向治疗的转移性肾细胞癌患者的前瞻性研究显示，约31.03%（18/58）患者出现信息处理速度和工作记忆力损害，且这种认知功能障碍与疲劳无关[69]。Mulder等[70]的横断面研究比较接受血管内皮生长因子受体抑制剂（舒尼替尼或索拉非尼）靶向治疗的转移性肾细胞癌或胃肠道间质瘤患者、未经治疗的转移性肾细胞癌患者以及健康对照者的认知功能，其结果显示，癌症患者认知功能尤其是学习能力、记忆力和执行功能明显下降，且接受抗血管生成治疗的癌症患者上述认知功能障碍更严重。靶向抗血管生成药物如舒尼替尼可能通过阻碍血管内皮生长因子受体2（VEGFR2）信号转导、自噬以及过度激活的凋亡机制诱导认知功能障碍[71]。以免疫检查点抑制剂和嵌合抗原受体T细胞（CAR-T）为主的免疫治疗剂是癌症治疗最有前景的方法。现阶段，抗肿瘤治疗药物引起认知功能障碍的研究证据多集中于化疗和靶向治疗，缺乏免疫治疗与认知功能之间关系的关键性基础与临床研究[72-73]，可能与新型抗肿瘤治疗常联合用药，临床研究缺乏足够样本量且无法排除联合化疗或放疗对认知功能的干扰有关[74]。一项前瞻性多中心Ⅱ期临床试验显示，接受CAR-T疗法的难治性大B细胞淋巴瘤患者可出现神经系统症状如谵妄、认知功能障碍、脑病等，骨髓抑制以及细胞因子释放综合征（CRS）[75]。CAR-T疗法通过活化T淋巴细胞并募集邻近免疫细胞释放一系列炎性因子和集落刺激因子（CSF）导致细胞因子释放综合征，可影响包括中枢神经系统在内的多个器官和系统[76-77]。放疗是转移性肿瘤和头颈部恶性肿瘤十分重要的治疗方法。有证据提示，放疗参数如总剂量、每部分剂量、治疗体积等均对认知功能存在负面影响[78]。McDowell等[79]的队列研究表明，接受强放疗的鼻咽癌患者可出现中至高比例的认知功能障碍和精神行为异常，特别是淡漠、去抑制和执行功能障碍。一项横断面

研究探讨78例接受放疗的原发性脑肿瘤患者，结果显示，患者海马组织易受放疗影响，高剂量照射左侧海马可以导致语言学习和记忆障碍[80]。一项系统性综述表明，急性放疗可以通过触发中枢神经系统炎症性改变，损伤神经元、神经胶质细胞及其祖细胞，破坏支持结构完整性等，协同改变大脑和海马祖细胞龛中的信号微环境，引起进行性神经元丢失和认知功能障碍[81]。

三、癌症与认知功能障碍的共同危险因素

衰老是包括癌症和神经退行性变在内的多种疾病的常见危险因素，被认为是线粒体活性、DNA损伤或修复系统受损等一系列导致基因组不稳定的累积不良反应[82]。癌症与认知功能障碍相关的神经退行性变可能有共同的调节细胞生存和死亡的信号转导通路。*p53*是常见抑癌基因，其变异或功能障碍可以破坏细胞基因组，在癌症发生发展中发挥重要作用。系统性综述提出假说，在衰老的神经元中，调控细胞周期和凋亡的蛋白如P53的功能紊乱可能影响神经元的可塑性和功能，揭示*p53*基因在癌症和神经退行性变发展中的桥梁作用[83-84]。有证据表明，DNA甲基化和组蛋白乙酰化在激活和抑制癌症基因中发挥重要作用，而这些表观遗传学修饰异常与神经退行性变进展亦有关[85]。载脂蛋白E(ApoE)在损伤后的神经元修复和可塑性中发挥作用，其*ε4*等位基因(*ApoEε4*)与阿尔茨海默病相关认知功能障碍和颅脑创伤密切相关[86]。研究显示，与未携带*ApoEε4*的癌症幸存者相比，接受化疗且至少有1个*ApoEε4*等位基因的癌症患者各项认知域评分均明显降低[87]。此外，ApoE的抗炎症反应特性和参与神经发生准确性的作用均可以被化疗药物引起的氧化应激和炎症反应影响[88]。由此可见，癌症相关认知功能障碍是免疫系统、遗传因素、宿主行为和社会心理状态等多因素相互作用、互为因果的复杂病理学机制过程，完全解释其发病机制仍需进一步开展临床研究和动物模型。

综上所述，癌症患者出现认知功能障碍较既往普遍认知常见，癌症相关认知功能障碍可发生在癌症治疗前、治疗期间、甚至治疗后10余年之久，主要累及执行功能、信息处理速度、记忆力和注意力4个认知域。目前，癌症相关认知功能障碍的病因与发病机制尚不十分明确，可能与癌症自身生物学效应、癌症治疗不良反应以及癌症和认知功能下降共同的潜在危险因素等相关。未来需要进一步开展相关临床与基础研究以阐明癌症相关认知功能障碍的确切机制，以更详细诊断和管理此类患者。

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·小词典·

中英文对照名词词汇（三）

可溶性淀粉样前体蛋白α
α secretase form of soluble amyloid precursor protein（sAPPα）
可提取性核抗原 extractable nuclear antigen（ENA）
快速眼动睡眠期行为障碍
rapid eye movement sleep behavior disorder（RBD）
扩散加权成像 diffusion-weighted imaging（DWI）
扩散张量成像 diffusion tensor imaging（DTI）
辣根过氧化物酶 horseradish peroxidase（HRP）
老年人快速认知筛查量表
Quick Cognitive Screening Scale for Elder（QCSS-E）
老年抑郁量表 Geriatric Depression Scale（GDS）
酪氨酸激酶抑制剂 tyrosine kinase inhibitors（TKIs）
类风湿关节炎 rheumatoid arthritis（RA）
类风湿因子 rheumatoid factor（RF）
粒细胞集落刺激因子
granulocyte-colony stimulating factor（G-CSF）
粒细胞-巨噬细胞集落刺激因子
granulocyte-macrophage colony-stimulating factor（GM-CSF）
连线测验 Trail Making Test（TMT）
链霉抗生物素蛋白-生物素-过氧化物酶复合物
streptavidin-biotin-peroxidase complex（SABC）
临床痴呆评价量表 Clinical Dementia Rating Scale（CDR）
磷酸盐缓冲液 phosphate-buffered saline（PBS）
颅脑创伤 traumatic brain injury（TBI）
路易体痴呆 dementia with Lewy bodies（DLB）
路易小体 Lewy body（LB）
美国阿尔茨海默病学会 Alzheimer's Association（AA）
美国放射学会 American College of Radiology（ACR）
美国国家老龄化研究所-阿尔茨海默病学会
National Institute on Aging-Alzheimer's Association（NIA-AA）