细胞间黏附分子 1（ICAM-1）：一种可能参与铁死亡和帕金森病的炎症调节因子

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摘要

细胞间黏附分子 1（intercellular adhesion molecule 1，ICAM-1／CD54）是一种跨膜糖蛋白，被认为是白细胞募集过程中最重要的黏附分子之一。它由 ICAM1 基因编码，在炎症中发挥核心作用；其在溃疡性结肠炎和类风湿关节炎等多种炎症性疾病中的关键作用已得到充分证实。鉴于以小胶质细胞活化为突出特征的神经炎症，是帕金森病（Parkinson’s disease，PD）等神经退行性疾病的重要组成部分，本综述探讨 ICAM-1 是否参与这种进行性神经系统疾病，并尝试阐明其潜在机制。作者特别关注 ICAM-1、胶质细胞和铁死亡之间可能存在的相互作用。铁死亡是一种铁依赖性细胞死亡形式，近来已被认为与 PD 有关。综合现有证据，ICAM-1 可直接影响铁死亡，也可通过胶质细胞和 T 细胞产生间接影响。进一步阐明这些相互作用，可能为这种严重疾病提供新的干预策略。

关键词：ICAM-1；帕金森病；铁死亡；胶质细胞；T 细胞；神经炎症

1. 引言

细胞间黏附分子 1（ICAM-1／CD54）是一种跨膜糖蛋白，发现于 20 世纪 80 年代。它被鉴定为 ß 整合素淋巴细胞功能相关抗原 1（LFA-1，CD11a／CD18）的配体，同时也是启动关键黏附通路的重要开关[1,2]。此后，其在炎症反应及多种炎症性疾病中的关键作用已得到证实[3–9]。

虽然神经退行性疾病，尤其是 PD，可由神经炎症介质触发或加重，但 ICAM-1 与 PD 的关系尚未得到充分研究。开展该研究有多项依据。第一，神经炎症明确参与 PD[10–13]；第二，抑郁与 PD 共病已有大量记录[14–16]，而 ICAM-1 参与老年期抑郁也已得到验证[17]；此外，在 PD 患者以及经 1-甲基-4-苯基-1,2,3,6-四氢吡啶（MPTP）处理的非人灵长类 PD 模型中，均发现反应性星形胶质细胞表达 ICAM-1[18]。

因此，本综述旨在说明 ICAM-1 参与 PD 的潜在机制，重点讨论其与胶质细胞介导的神经炎症、近来被认为参与 PD 病理的铁死亡，以及 T 细胞反应之间的关系。作者在简要介绍 ICAM-1、PD、胶质细胞、T 细胞和铁死

亡后，尝试提供这些因素之间存在因果联系的有力证据，并期望由此发现新的 PD 治疗靶点。

1.1 ICAM-1

ICAM-1 最广为人知的功能涉及白细胞血管外渗，并被称为白细胞募集过程中最重要的黏附分子之一[19–21]。位于 19 号染色体的 ICAM1 基因，在内皮细胞中的表达可由多种细胞因子和炎症介质诱导，包括肿瘤坏死因子 α（TNF-α）、核因子 κB（NF-κB）、干扰素 γ（IFN-γ）、白细胞介素 1ß（IL-1ß）、IL-6，以及过氧化氢（HO）和 NADPH 氧化酶（NOX）活性[1,22–27]。

ICAM-1 表达于质膜，并与白细胞表达的 ß 整合素 LFA-1 和巨噬细胞抗原 1（MAC-1／CD11b／CD18）结合[28–30]。ICAM-1 与 LFA-1／MAC-1 的结合介导白细胞滚动、爬行、黏附以及穿过完整毛细血管壁的过程，即穿胞渗出。白细胞从循环系统离开并进入组织损伤或感染部位的血管外渗过程，常伴随炎症[30]。ICAM-1 与 LFA-1／MAC-1 结合后，会促使相邻内皮细胞间连接蛋白解离、细胞骨架重排，并激活内皮型一氧化氮合酶（eNOS），从而使白细胞能够跨内皮迁移[9,30–32]。不过，ICAM-1 的作用远不止白细胞跨膜迁移。

ICAM-1 还表达于神经元、免疫细胞、内皮细胞和上皮细胞等多种细胞，尽管基础状态下表达量较低[33–35]。其配体包括纤维蛋白原、黏蛋白 1（MUC1）、分化簇 43（CD43）、透明质酸、鼻病毒和恶性疟原虫[36–41]。ICAM-1 参与 T 细胞调控、巨噬细胞极化、细胞迁移、活性氧（ROS）生成，以及癌症发生和转移等众多生理过程[7,26,42–44]。动物模型显示，醛固酮和血管紧张素 II 可分别通过 ICAM-1 依赖机制诱发动脉粥样硬化和高血压[45–47]；给人输注血管紧张素 II 也会升高 ICAM-1[45]。ICAM-1 在动脉粥样硬化和心血管疾病中的作用已经得到广泛验证[8,46–48]，并且似乎在肠屏障和血脑屏障（BBB）通透性以及神经炎症中发挥基础作用[49–53]。除参与炎症调控外，ICAM-1 还参与伤口愈合和凋亡细胞清除[7,54,55]。

ICAM-1 作为跨膜糖蛋白，从质膜延伸至胞质和细胞表面，因而能够参与信号转导、细胞骨架相互作用和配体结合[7,30,56]。它也可从细胞表面被酶切，形成能够自由循环的可溶性 ICAM-1（sICAM-1）[57,58]。ADAM10、ADAM17、基质金属蛋白酶 2（MMP-2）和 MMP-9 均可切割膜结合 ICAM-1[59–62]；白细胞弹性蛋白酶和组织蛋白酶 G，可能对选择性剪接产生的不同 ICAM-1 亚型尤其重要[63,64]。sICAM-1 也可直接由选择性剪接产生，此时缺乏跨膜和胞质结构域[30,65]。

体外研究发现，sICAM-1 浓度与细胞表面 ICAM-1 表达量呈定量关系[58,66]；但选择性剪接、蛋白酶活性和胞外结构域脱落都可能改变该关系，在体内分析时必须予以考虑[30,65,67]。一般人群血清 sICAM-1 浓度约为 100～450 ng/mL[4,68]。其升高与子宫内膜异位症、系统性红斑狼疮、类风湿关节炎、银屑病、阻塞性睡眠呼吸暂停、非酒精性脂肪性肝病、肺癌、心房颤动、肥胖、2 型糖尿病、糖尿病视网膜病变、妊娠期糖尿病和老年期抑郁等多种疾病相关[17,69–82]。较新的研究还显示，在溃疡性结肠炎中，ICAM-1 水平越高，预后越差[83]（图 1）。

图 1 ICAM-1 被认为参与或关联多种疾病。

综上，ICAM-1 在炎症中具有核心而多样的作用，并参与炎症反应启动；但在具体表型或疾病状态下，其全部作用仍待阐明。尤其值得探索的是，ICAM-1 在多大程度上以及通过何种机制参与 PD 病理。

1.2 帕金森病（PD）

PD 是一种进行性神经退行性疾病，其特征包括黑质致密部（SNpc）多巴胺能神经元逐渐退化、错误折叠的 α-突触核蛋白以路易小体形式聚集，以及胶质细胞失调。遗传和环境因素均为已知危险因素，但多数病例属于散发性或所谓特发性，即病因不明。

PD 具有运动和非运动症状。运动症状包括静止性震颤、运动迟缓、僵硬、肌张力障碍，以及姿势和步态异常；步态冻结也很常见[11,84]。常早于运动症状出现的非运动表现包括嗅觉部分或完全丧失、抑郁等情绪障碍、

多汗、低血压、疲劳、认知障碍、面部表情减少或无法识别他人言语和非言语线索、失眠或嗜睡等睡眠障碍、吞咽困难、便秘、恶心等胃肠道问题，以及泌尿和性功能障碍[11,85]。

由于多巴胺丢失是主要基础机制，治疗集中于补充多巴胺或替代其功能。金标准治疗为左旋多巴，同时可合用抑制多巴胺降解的药物，如单胺氧化酶抑制剂或儿茶酚-O-甲基转移酶抑制剂（分别包括司来吉兰／雷沙吉兰和托卡朋／恩他卡朋），以及较新的非麦角类多巴胺激动剂，如普拉克索、罗匹尼罗、罗替戈汀和阿扑吗啡[10,86]。卡比多巴与左旋多巴合用以防止后者在外周降解。

这些药物均可显著缓解症状，却不能阻止神经退行进展。最有效的左旋多巴不仅会在数月或数年后疗效下降，还可能诱发严重异动症，甚至比原始震颤更糟[10,87]。因此，迫切需要疗效更好且无此类不良作用的干预[11,88]。

大量证据表明神经炎症和氧化应激参与 PD[11,89–92]。氧化应激源于氧化物与抗氧化能力失衡，可导致 DNA、蛋白质和脂质受损[11]。PD 中的氧化物来源包括线粒体功能障碍、多巴胺代谢和胶质细胞等[11,89–92]。氧化应激和 ROS 可激活免疫细胞及免疫反应，最终引发炎症；炎症与氧化应激又存在双向关系，可能构成恶性循环[11,89–92]。线粒体损伤和 NOX 也参与该过程[90–92]。本综述重点阐明 ICAM-1 如何与氧化应激或炎症中间环节相互作用，以及其能否成为 PD 治疗靶点。

1.3 胶质细胞

胶质细胞在 19 世纪中叶首次被发现，最初称为“神经胶质”，因为人们认为它们只为神经元提供结构支持。如今已知，胶质细胞除结构支持外，还参与髓鞘形成[96,97]、能量和代谢调控[95,98,99]、BBB 形成[100,101]、突触发育与重塑[102,103]、体液和电解质稳态[104]、神经递质调节[105,106]、神经内分泌功能[107]、解毒[108,109]及先天免疫反应[110,111]。因此，其受损或失调可能导致神经精神和神经退行性疾病[13,97,112–116]，也可能成为新的治疗靶点[117]。例如，调节这些细胞中的烟碱型胆碱能受体（nAChR），可能用于干预 PD[13]、情绪障碍乃至药物成瘾[118]。

主要胶质细胞包括小胶质细胞、星形胶质细胞、少突胶质细胞，以及突触胶质细胞或 NG2 细胞。以下先简要介绍各类细胞，再重点讨论它们与 ICAM-1 在神经炎症中的相互作用。

1.3.1 小胶质细胞

小胶质细胞占中枢神经系统（CNS）细胞的 10%～15%，覆盖成人脑实质相当大的区域。它们通过细小丝状伪足的快速运动持续监视周围环境，并迅速响应损伤。其起源与外周巨噬细胞相同，但被视为 CNS 固有免疫细胞[119,120]。小胶质细胞通过调节神经发生、突触形成和清除、介导 T 细胞浸润脑组织，以及清除病原体和细胞残骸，对维持脑稳态至关重要[121]。

另一方面，过度活化的小胶质细胞会造成神经炎症、神经元损伤或死亡，并促成包括 PD 在内的神经精神和神经退行性疾病[122–125]。持续应激可促使 IL-1ß、IL-6 等促炎介质释放，是其过度活化的重要原因[126–128]。

过去常按活化状态把小胶质细胞分为促炎 M1 型和抗炎 M2 型[121,129]；新证据认为其功能差异更多来自内在特性，应按功能分类，避免简单使用 M1／M2 状态划分[117,130,131]。

小胶质细胞表达钙敏感受体（CASR）、低密度脂蛋白受体相关蛋白 1（LRP1）、髓系细胞触发受体 2（TREM2）、nAChR，以及 TLR2、TLR4 等 Toll 样受体。TLR 是一类模式识别受体，可感知内源性碎片或病原体并启动先天免疫反应；由于其在神经退行性疾病中的重要作用，正被广泛研究为潜在治疗靶点[121,132–134]。

1.3.2 星形胶质细胞

星形胶质细胞因形似星状而得名[135]，依脑区不同可占全部脑细胞的 17%～61%。它们通过提供营养、监控和调节 pH 稳态、清除废物以及构成 BBB，维持神经元完整性和功能[135,136]。

星形胶质细胞含有胶质细胞源性神经营养因子（GDNF），可为多巴胺能神经元等神经细胞提供营养支持[137]；还含有胶质纤维酸性蛋白（GFAP），对维持细胞强度和 BBB 至关重要。GFAP 常用作星形胶质细胞标志物，也可能成为脑和脊髓疾病的生物标志物[138–142]。这些细胞还表达脑源性神经营养因子（BDNF），并含有脑内最高水平的牛磺酸。牛磺酸具有抗氧化和抗炎作用，是出生后脑发育所必需的游离氨基酸[143]。近期研究还表明，星形胶质细胞是介导稳态突触可塑性所需 TNF-α 的来源[144]。

星形胶质细胞与小胶质细胞共同构成抵御损伤的第一道防线；但促炎信号过度刺激时，两者可能协同导致神经元失调以及神经精神或神经退行性疾病[145–147]。阐明星形胶质细胞与小胶质细胞、以及星形胶质细胞与神经元之间的密切“串扰”，可能提供新的干预方式[137,148–150]。

1.3.3 少突胶质细胞

少突胶质细胞（OL）约占全部胶质细胞的 75%，是 CNS 髓鞘形成的主要来源[151]。除轴突髓鞘化外，它们还能分泌 GDNF 和 BDNF 以提供代谢和营养支持，控制细胞外钾浓度，并调节轴突生长[151,152]。其表达的 TLR 对髓鞘形成也很重要[96,153,154]。因此，少突胶质细胞失调可导致包括 PD 在内的多种神经系统疾病。

1.3.4 突触胶质细胞（NG2 细胞）

CNS 第四类主要胶质细胞为突触胶质细胞，也称神经／胶质抗原 2（NG2）细胞或少突胶质前体细胞（OPC）。NG2 细胞存在于白质和灰质，成年脑中仍可持续增殖[151,155,156]。除作为少突胶质前体外，它们还能转化为星形胶质细胞和神经元[151,155,156]。

NG2 细胞参与多发性硬化、阿尔茨海默病、癫痫、创伤性脑损伤、急性缺血性卒中、发育期神经血管单元形成、胶质瘤，以及实验性自身免疫性脑脊髓炎（EAE）等多种神经系统病理[157–161]。EAE 伴有 BBB 通透性和神经炎症增加。由于 NG2 细胞可与神经元沟通并影响神经元，它们也可能成为包括 PD 在内多种疾病的治疗靶点[162,163]。

1.4 ICAM-1 与胶质细胞

1.4.1 ICAM-1 与小胶质细胞

小胶质细胞表达 ICAM-1，并组成性表达 LFA-1 和 Mac-1，因此 ICAM-1 与小胶质细胞可在多种背景下直接相互作用[164,165]。ICAM-1 参与小胶质细胞活化[166–168]；活化的小胶质细胞又分泌 TNF-α，诱导血管内皮细胞表达 ICAM-1 并促进白细胞浸润[23,169,170]。

ICAM-1 还可通过间接机制激活小胶质细胞：血管内皮表达的 ICAM-1 促进白细胞跨内皮迁移并进入 CNS，继而引起小胶质细胞活化[171–174]；浸润 CNS 的白细胞还可能黏附于小胶质细胞[171,175]。因此，ICAM-1 与小胶质细胞之间存在正反馈环[166–168,171–174]。

1.4.2 ICAM-1 与星形胶质细胞

星形胶质细胞也表达 ICAM-1，其表达可由 TNF-α、IL-1ß 和 IFN-γ 上调[176–180]；反过来，ICAM-1 可促使星形胶质细胞释放包括 TNF-α 在内的炎症细胞因子[181,182]。

纤维蛋白原在多种神经炎症状态下升高，并可结合 ICAM-1，因此也可间接介导 ICAM-1 对星形胶质细胞的活化[183,184]。纤维蛋白原活化的星形胶质细胞进一步增强 ICAM-1 表达，促进 NO 和 ROS 生成，最终导致神

经元死亡[183,184]。ROS 还可能通过 NF-κB 依赖机制诱导星形胶质细胞产生 ICAM-1[185,186]。因此，两者之间同样存在正反馈环[179,181,183–186]。

1.4.3 ICAM-1 与少突胶质细胞

炎症条件下少突胶质细胞 ICAM-1 表达增加，被认为可能是对免疫原性损伤的防御机制[177,187]。少突胶质细胞与 T 细胞直接接触可诱导其损伤，而抗 ICAM-1 抗体能抑制 Th1 细胞与少突胶质细胞接触[187]。由于少突胶质细胞参与髓鞘形成，T 细胞诱导的损伤可能促成 EAE 等疾病中的神经退行性改变[187]。动物模型（包括狨猴）已显示抗 ICAM-1 抗体可抑制 EAE[188,189]。ICAM-1 还参与 T 细胞浸润 CNS，因此也可间接影响少突胶质细胞稳态[173,177,187]。

1.4.4 ICAM-1 与 NG2 细胞

促炎细胞因子会抑制 NG2 细胞成熟[190–192]。小胶质细胞可影响 NG2 细胞增殖、分化、迁移和凋亡；NG2 细胞又能调节小胶质细胞稳态和活化[193]，提示 ICAM-1 与 NG2 细胞之间存在间接联系。近期证据认为 NG2 细胞可通过激活免疫原性细胞启动神经炎症；但 NG2 蛋白似乎又是周细胞及两种胶质母细胞瘤细胞系中 ICAM-1 表达的负调节因子[194–196]。

1.5 ICAM-1、胶质细胞与 PD

神经炎症广泛参与 PD 病理生理，其中胶质细胞贡献显著[197,198]。近期荟萃分析显示，PD 患者脑脊液中的 TNF-α、IL-6、IL-1β、NO、趋化因子配体 2（CCL2）和 C 反应蛋白（CRP）均升高，进一步支持胶质细胞在神经炎症和 PD 中的作用[199]。

短暂活化的小胶质细胞具有保护作用，但长期活化被广泛认为参与 PD[200]。动物模型和 PD 患者黑质中均发现炎症型小胶质细胞[200,201]。与该表型相关的 TNF-α、IL-6、IL-1β 和 IFN-γ 均可诱导 ICAM-1 表达[1,22,23,199,202]。尸检研究还发现，PD 患者黑质及多个脑区中活化小胶质细胞增多，并且 ICAM-1、LFA-1、TNF-α 和 IL-6 表达升高[203]。

小胶质细胞除直接参与 PD 神经炎症外，还可诱导星形胶质细胞形成神经毒性反应表型（常称 A1 表型），加重 PD 病理[204–206]。星形胶质细胞参与清除 α-突触核蛋白等异常蛋白，小胶质—星形胶质细胞相互作用也可促进其清除；但 α-突触核蛋白积聚又能增加星形胶质细胞 ICAM-1 和 IL-6 表达[206–209]。PD 患者黑质中还可见星形胶质细胞和小胶质细胞增多、白细胞浸润，以及 ICAM-1 和 LFA-1 表达升高[18]。

异常和减少的髓鞘含量与 PD 症状相关[210,211]。PD 患者基底节发出的神经连接中，有 80% 显示髓鞘含量下降[212]；特发性 PD 患者的少突胶质细胞也减少[213]。α-突触核蛋白从神经元转移至少突胶质细胞，可能进一步加重病理[214,215]。由于炎症条件会增强少突胶质细胞 ICAM-1 表达，对其进行调节可能成为新的 PD 靶点[177,187]。

以上证据共同构成 ICAM-1、胶质细胞与 PD 之间的有力联系。

1.6 ICAM-1 与 T 细胞

循环中的白细胞在细胞因子和趋化因子等信号作用下，被募集至炎症部位，随后通过黏附分子介导的血管外渗和穿胞渗出跨过毛细血管壁。T 细胞也表达 LFA-1，可与 ICAM-1 相互作用以促进跨内皮迁移[216,217]。ICAM-1 不仅促进 T 细胞迁移[216,218]，还促进其活化[219,220]，并帮助 T 细胞与其他白细胞相互作用[219–221]。

1.7 ICAM-1、T 细胞与 PD

T 细胞在 PD 中具有多样作用，并可能受到多巴胺影响[222]。其外周亚群浓度异质性明显，受性别、年龄、疾病严重程度和病程等特征影响[223,224]。总体上，PD 患者 Th1 和 Th17 细胞增加，而 Th2 和调节性 T 细胞（Treg）减少[224]；部分患者还具有 α-突触核蛋白特异性 T 细胞[225–227]。

炎症条件下，CNS 内皮细胞会表达 ICAM-1 等黏附分子，促进免疫细胞和抗体迁移浸润[225,228]。多种动物研究（包括非人灵长类）及人体尸检研究均支持 PD 中存在 T 细胞浸润 CNS[229–234]。MPTP 小鼠中，内皮细胞 ICAM-1 和 T 细胞 LFA-1 表达分别升高；给予 ICAM-1 或 LFA-1 抗体可减少免疫学和行为改变[231]。PD 患者尸检还观察到 CD8 T 细胞与多巴胺能细胞直接接触[231,233]。ICAM-1／LFA-1 轴也可介导 Th17 诱导的多巴胺能神经元死亡[35]。因此，ICAM-1 与 T 细胞的相互作用可视为 PD 病理的一部分。

PD 中 ICAM-1 表达升高可能主要发生于内皮细胞、BBB 和胶质细胞[18,203,235–238]。关于循环 sICAM-1，虽然有研究发现 PD 患者 ICAM1 基因表达下降[239]，但其血清、血浆和脑脊液 sICAM-1 又可升高[231,240–242]。ICAM1 基因表达在 PD 中如何转化为蛋白生成，仍需进一步确定。

2. 铁与铁死亡

铁死亡是一种铁依赖性、受调控的细胞死亡形式，与其他细胞死亡机制不同[243,244]。“铁死亡”术语和概念提出于 2012 年，而铁在非凋亡性细胞死亡中的核心作用早在 2008 年已被发现[244,245]。此后，铁死亡被认为参与肝、肾、肠、肺、心脏、血细胞和神经系统等多类疾病[246–248]。

二价铁（Fe^{2}）与过氧化氢反应生成羟自由基（· OH），诱导脂质过氧化，即芬顿反应：$Fe^{2} + HO \rightarrow Fe^{3} + \cdot OH + OH$[244]。该反应最终导致细胞膜脂质过氧化和细胞死亡[244,246,249]。铁还可与脂质氢过氧化物反应并激活花生四烯酸脂氧合酶（ALOX），生成烷氧自由基[246,249]。ALOX 氧化多不饱和脂肪酸（PUFA），形成脂质氢过氧化物，继而生成丙二醛（MDA）和 4-羟基壬烯醛。由于 PUFA 对铁死亡至关重要，合成 PUFA 的 ACSL4 和 LPCAT3 也参与该过程[249]。

HO 来源多样，包括超氧化物（O）经超氧化物歧化酶（SOD）还原[250]；多巴胺经单胺氧化酶 B 代谢也会产生 HO[251]。线粒体是超氧化物的重要来源，因为电子可从电子传递链逸出并与氧反应[250]。NOX 则以 NADPH 为电子供体生成超氧化物[249,250]。SOD 处理超氧化物后，过氧化氢酶可将两分子 HO 还原为水和氧；但有铁存在时，HO 可进入芬顿反应并生成强氧化性的羟自由基[244]。

铁死亡细胞具有异常线粒体等特征。除铁外，脂质代谢和谷胱甘肽稳态同样调控铁死亡。谷胱甘肽过氧化物酶 4（GPX4）是主要调节因子，利用谷胱甘肽（GSH）还原过氧化磷脂和胆固醇[244,246]。因此，胱氨酸—谷氨酸逆向转运体 xCT（SLC7A11）也参与铁死亡：它将胱氨酸运入胞质，同时把谷氨酸运出；胱氨酸随后通过 NADPH 依赖机制转为半胱氨酸，而半胱氨酸是谷胱甘肽合成的限速氨基酸。小分子 erastin 可通过抑制 SLC7A11 诱导铁死亡[252]。

GPX4 和 SLC7A11 的表达受转录因子 Nrf2 调节。Nrf2 由 KEAP1 隔离和控制，并结合抗氧化反应元件（ARE）[252,253]。Nrf2 还调控谷胱甘肽合成酶、铁输出蛋白 1（FPN1）、血红素加氧酶 1（HO-1）、转铁蛋白受体（TFRC）和铁蛋白重链 1（FTH1）等铁死亡相关基因[253]。相反，转录因子 Bach1（BTB 结构域及 CNC 同源物 1）抑制多种 Nrf2 调节基因，可通过降低谷胱甘肽和铁代谢相关基因表达而诱导铁死亡[252–255]。

铁蛋白自噬是一种特殊自噬形式，可调节铁蛋白降解，近来被认为在铁死亡中发挥重要作用。铁蛋白负责受控储存和释放细胞内铁，因此铁蛋白自噬也是维持铁稳态的新参与者[250,253]。

2.1 铁死亡与 PD

大量数据支持铁死亡参与 PD 病理生理[85]。铁可在 PD 患者黑质中积聚并导致多巴胺能神经元死亡[85,256]。PD 还伴随脂质过氧化、铁代谢异常、GSH 减少和 ROS 生成，这些变化也反映在患者黑质基因表达差异中[85,251,257–259]。多巴胺能与非多巴胺能神经元、小胶质细胞、星形胶质细胞、少突胶质细胞、NG2 细胞以及内皮细胞／周细胞，均可出现铁死亡相关基因表达差异[259]。

α-突触核蛋白参与铁代谢和 PUFA 合成，可诱导脂质过氧化并增加多巴胺能神经元铁死亡风险[85,246,260–262]。铁还可促进不稳定的多巴胺氧化，形成 6-羟多巴胺（6-OHDA）和多巴胺醌（DAQ）[263,264]。DAQ 可促进 GPX4 降解，增强神经元对铁死亡的易感性[264,265]。Fe^{3} 还可能被脂质氢过氧化物还原，形成可生成 6-OHDA 和羟自由基的铁—多巴胺复合物[263,266]。6-OHDA 可从铁蛋白释放铁，提高游离铁浓度，形成自由基生成的恶性循环；其代谢产生 HO，进一步增强毒性[263]。

铁死亡还可能参与 BBB 损伤[85,267]。PD 患者 BBB 中可见铁增加、脂质过氧化增强和抗氧化物浓度下降[267]。患者存在涉及 α-突触核蛋白的 BBB 损害[268–271]，其中紧密连接蛋白和黏附分子受到破坏，共同促成疾病病理[267,270]。

2.2 胶质细胞与铁死亡

胶质细胞与铁代谢及铁死亡存在复杂、多面的相互作用。它们含有铁蛋白，可成为 CNS 内铁的直接来源；铁蛋白浓度在衰老及病理状态下升高[263]。胶质细胞还可分别通过分泌铜蓝蛋白和铁调素，促进铁跨 BBB 流入并抑制其外排[263,272]。肝脏产生的肽类激素铁调素对铁稳态至关重要[85]。胶质细胞也可借助细胞因子对铁转运体的调控，促进 CNS 铁积聚[273]。

由于胶质细胞调节 CNS 铁稳态并参与铁死亡诱导，它们可能在神经退行中具有关键作用[274]。活化的星形胶质细胞可分泌 CXCL3R 配体 CXCL10 并降低 SLC7A11 表达，诱导神经元铁死亡[275]；另一方面，它们也可通过 BDNF 和 Nrf2 依赖机制保护多巴胺能神经元免于铁死亡[276,277]。小胶质细胞同样具有双重性：LPS 活化的小胶质细胞可保护神经元抵抗谷氨酸诱导的铁死亡[278]；但胶质细胞自身也可发生铁死亡并促成神经退行[279]。NG2 细胞尤其易发生铁死亡，而 CNS 中铁浓度最高的少突胶质细胞，可能通过分泌铁蛋白重链保护自身[246,277,280,281]。

铁死亡细胞释放的损伤相关分子模式（DAMP）还可激活胶质细胞[253,282–284]。DAMP 来源于受损或死亡细胞，是先天免疫反应的一部分。胶质细胞表达 TLR 等模式识别受体，可识别 DAMP 并被激活，从而促成神经退行[283,284]。不过，DAMP 介导的小胶质细胞活化在某些情况下也具有神经保护作用[284]，这与“急性活化可保护、慢性活化可导致退行”的观点一致[200,201]。

2.3 T 细胞与铁死亡

在肿瘤细胞中，T 细胞可通过 IFN-γ 介导的 SLC7A11 抑制和 ACSL4 活化诱导铁死亡，这已成为重要的先天抗肿瘤免疫反应[285–289]。T 细胞还可能通过提高神经元转铁蛋白受体 1（TfR1）表达，促成神经元铁死亡[290]。两者关系具有双向性：神经元铁死亡可激活 T 细胞[291,292]，T 细胞自身也可发生铁死亡[289]；不过，铁死亡的免疫原性似乎弱于其他细胞死亡形式[244,246]。

2.4 ICAM-1 与铁死亡

据作者所知，ICAM-1 与铁死亡在不同背景下的相互作用尚未得到充分研究。多项实验提示两者可能存在直接双向关系。脊髓挫伤模型中，铁死亡抑制剂 SRS 16-86 可降低 ICAM-1 以及其他蛋白和细胞因子的表达[293]；在糖尿病神经病变大鼠模型中，SRS 16-86 同样降低 ICAM-1、IL-1ß 和 TNF-α[294]。铁死亡抑制剂 ferrostatin-1（Fer-1）可抑制氧化低密度脂蛋白诱导的内皮细胞 ICAM-1 表达[295–297]；铁死亡诱导剂 erastin 则增加 ICAM-1 表达并激活跨内皮迁移[298]。这些直接相互作用仍需在其他模型和背景中验证。

在铁死亡中居核心地位的 HO、脂质过氧化物和 ROS，也参与 ICAM-1 表达[23,26,236,299–302]。HO 可提高内皮细胞 ICAM-1 表达[23,299,300]，尽管部分研究因方法差异未观察到该效应[169,303]。HO 似乎通过 ICAM1 启动子中的 AP-1 和 Ets 顺式调控元件增强表达[23,299]，并参与 ICAM-1 翻译后修饰[304–306]。重度子痫前期女性的高脂质过氧化物血浆，也可提高人脐带内皮细胞 ICAM-1 表达[302]。

一项近期研究进一步提示 ICAM-1 可调节铁死亡：在 LPS 刺激的巨噬细胞和人脐带内皮细胞中，重组 ICAM-1（rICAM-1）增加细胞内 ROS 和 Fe^{2}，并降低 GPX4 和 SLC7A11 表达，可能由 PTGS2 介导；抑制 PTGS2 后，rICAM-1 对铁死亡参数的影响被抑制，提示 PTGS2 在该相互作用中具有机制作用[307]。ICAM-1 不同作用的具体机制仍需阐明。

2.5 ICAM-1、胶质细胞、T 细胞、铁死亡与 PD

多巴胺氧化和线粒体功能障碍被广泛视为 PD 的基础特征。多巴胺氧化似乎参与诱导线粒体功能障碍，包括散发性 PD[308,309]。神经元和小胶质细胞自身的线粒体功能障碍均可激活小胶质细胞，促使 TNF-α、IL-1ß 等炎症细胞因子释放，最终导致神经炎症和神经退行[310,311]。这种自我维持的级联早在二十年前已被提出，当时具体步骤尚不清楚[312]。

现已知道，小胶质细胞释放的炎症细胞因子可破坏 BBB，并诱导 ICAM-1 等黏附分子表达，促进包括 T 细胞在内的白细胞浸润[310]。浸润后，胶质细胞，尤其是小胶质细胞释放的细胞因子，会刺激 T 细胞分化：初始 T 细胞偏向 Th1 和 Th17，而向 Treg 的分化受到抑制[310,313]。CD8 T、Th1 和 Th17 细胞又释放炎症细胞因子，进一步把小胶质细胞推向炎症性和神经毒性表型[310]。IL-17 还可增加小胶质细胞黏附分子表达[310,314]。胶质细胞与 T 细胞相互活化的恶性循环，被认为推动 PD 中持续存在的神经炎症和神经退行[198,230,310]。

虽然 α-突触核蛋白可能破坏 BBB[271,315]，但 T 细胞浸润似乎早于其在脑内积聚[233]。PD 患者脑脊液 ICAM-1 升高还与 α-突触核蛋白升高相关[242]。α-突触核蛋白开始在黑质积聚后，神经元对铁死亡的易感性增加[85,246,260–262]；此时活化的胶质细胞和 T 细胞同时存在，并进一步增强铁死亡[170,260,261,267,273,310]。神经元铁死亡又反过来激活 T 细胞和胶质细胞，继续扩展炎症—退行循环[283,291,292]。黑质中丰富的 ICAM-1 可能促进 T 细胞诱导的多巴胺能神经元死亡，并加强胶质细胞与 T 细胞的相互作用[18,35,166–168,203]。

α-突触核蛋白可增强星形胶质细胞 ICAM-1 表达[207]；黑质中存在表达 ICAM-1 的星形胶质细胞，并可通过 ROS／NF-κB 依赖机制进一步促进自身 ICAM-1 表达[18,183–186]。更重要的是，炎症环境释放的细胞因子增强 ICAM-1，并可导致铁死亡[1,22,23,177,316]。由此可能形成另一恶性循环：铁死亡增加内皮细胞 ICAM-1，造成 BBB 破坏并促进 T 细胞浸润，继而增加细胞因子释放、神经炎症和神经退行[85,267,293,298,310]。

ICAM-1、胶质细胞、T 细胞和铁死亡之间这些直接与间接的相互作用，不仅说明了可能导致 PD 的机制（图 2），也提供了新的干预方向。PD 黑质中铁积聚、脂质过氧化、ROS 和 ICAM-1 增加，以及 GSH 减少之间的关联，进一步支持疾病中可能存在直接的 ICAM-1—铁死亡轴[18,85,203,251,257,258,310]。虽然仍属间接证据，多种形式的运动近来被认为可能调节铁死亡，并与 PD 患者脂质过氧化、HO、铁积聚和 sICAM-1 下降相关[317–320]。

图 2 ICAM-1、胶质细胞、T 细胞和铁死亡可能通过双向相互作用影响帕金森病的病理生理。

3. 新型干预

PD 迫切需要新的治疗方案[11,88]。ICAM-1 以及 ICAM-1—铁死亡轴可能成为有前景的新靶点。ICAM-1 抗体结合后，内皮细胞会将 ICAM-1 内化，随后再循环回质膜[321]。ICAM-1 抗体可通过抑制白细胞相互作用发挥抗炎潜力[321]，并已在体内研究中减轻 PD 病理和症状[231,322]。

例如，在 MPTP 小鼠中，ICAM-1 抗体减少多巴胺能细胞死亡、胶质细胞活化、肠道菌群失调和行为变化[322]；LFA-1 与 ICAM-1 抗体也可减轻免疫学和行为改变[231]。抑制 ICAM-1 或 LFA-1 还可降低 MPTP 小鼠黑质 Treg 浓度[323]。与过氧化氢酶结合的 ICAM-1 抗体，能够抑制 HO 对内皮细胞的毒性[321,324,325]。动物研究也表明，结合抗氧化酶的 ICAM-1 抗体可减轻实验性创伤性脑损伤中的多种神经病理，包括胶质细胞活化[326,327]。多项临床前研究因此支持 ICAM-1 抗体减轻毒性或神经退行过程的能力。

小鼠 ICAM-1 抗体的 F(ab’) 片段可抑制 EAE；与小鼠 IgG2a ICAM-1 单克隆抗体不同，该片段在体外不会激活人中性粒细胞[188,328]。金黄色葡萄球菌胞外黏附蛋白（Eap）可与多种配体相互作用，其中包括结合 ICAM-1、抑制 ICAM-1／LFA-1 相互作用，并已显示能够抑制 EAE[329]。调节 NG2 蛋白表达也可能成为调控 ICAM-1 的可行靶点[194]。

多种癌细胞高度表达 ICAM-1；与抗癌药物偶联的 ICAM-1 抗体，近来已作为新型癌症治疗方法接受体内评估[330,331]。除 ICAM-1 抗体外，这些新策略尚未在 PD 背景下研究，但现有数据提示其潜在价值。

左旋多巴在氧化应激中的作用仍有争议[332–335]；在生理相关条件下，它似乎具有抗氧化活性[333,335]。然而，接受左旋多巴治疗的 1、2 期特发性 PD 患者血浆 sICAM-1 升高，提示 ICAM-1 在治疗早期尤其相关[240]。左旋多巴诱导的异动症伴随炎症细胞因子和 ROS 增加，并会在全身炎症存在时加重[336,337]。

因此，把增强多巴胺的治疗与抗 ICAM-1 治疗结合，不仅可同时处理 PD 的多个关键病理机制，还可能通过减轻不良作用，与现行方法产生协同效应。以创新方式靶向 ICAM-1 和／或 ICAM-1—铁死亡轴，可能成为治疗或减轻 PD 的有前景方案。

4. 结论

近期研究表明，ICAM-1 通过激活胶质细胞，以及促进 T 细胞活化和迁移，在 PD 病理中发挥核心作用。胶质细胞和 T 细胞均与铁死亡直接相关，因此 ICAM-1 与铁死亡之间存在间接联系。ICAM-1 也可能直接参与铁死亡，而且这种直接作用很可能发生于 PD 背景中。虽然后一联系仍需进一步确认，但综合现有知识，ICAM-1 是一个值得关注的 PD 治疗靶点。

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缩略语

- 6-OHDA：6-羟多巴胺
- AD：阿尔茨海默病
- ADAM10／17：解整合素与金属蛋白酶 10／17
- ALOX：花生四烯酸脂氧合酶

- ARE：抗氧化反应元件
- BBB：血脑屏障
- BDNF：脑源性神经营养因子
- CASR：钙敏感受体
- CCL2：趋化因子配体 2
- CD43：分化簇 43
- CNS：中枢神经系统
- CRP：C 反应蛋白
- CSF：脑脊液
- DA／DAergic：多巴胺／多巴胺能
- DAMP：损伤相关分子模式
- DAQ：多巴胺醌
- EAE：实验性自身免疫性脑脊髓炎
- eNOS：内皮型一氧化氮合酶
- Fer-1：Ferrostatin-1
- FPN1：铁输出蛋白 1
- FTH1：铁蛋白重链 1
- GDNF：胶质细胞源性神经营养因子
- GFAP：胶质纤维酸性蛋白
- GPX4：谷胱甘肽过氧化物酶 4
- GSH：谷胱甘肽
- HO：过氧化氢
- HO-1：血红素加氧酶 1
- ICAM1／ICAM-1：细胞间黏附分子 1
- IL-1ß／IL-6：白细胞介素 1ß／6
- IFN-γ：干扰素 γ
- LFA-1：淋巴细胞功能相关抗原 1
- LPS：脂多糖
- LRP1：低密度脂蛋白受体相关蛋白 1
- MAC-1：巨噬细胞抗原 1
- MDA：丙二醛
- MMP-2／9：基质金属蛋白酶 2／9
- MPTP：1-甲基-4-苯基-1,2,3,6-四氢吡啶

- MUC1：黏蛋白 1
- nAChR：烟碱型胆碱能受体
- NF-κB：核因子 κB
- NG2：神经／胶质抗原 2
- NO：一氧化氮
- NOX：NADPH 氧化酶
- Nrf2：核因子红系 2 相关因子 2
- OL：少突胶质细胞
- OPC：少突胶质前体细胞
- OS：氧化应激
- PD：帕金森病
- PRR：模式识别受体
- PUFA：多不饱和脂肪酸
- ROS：活性氧
- sICAM-1：可溶性细胞间黏附分子 1
- SN／SNpc：黑质／黑质致密部
- SOD：超氧化物歧化酶
- TfR1／TFRC：转铁蛋白受体 1／转铁蛋白受体
- TLR：Toll 样受体
- TNF-α：肿瘤坏死因子 α
- TREM2：髓系细胞触发受体 2
- VCAM-1：血管细胞黏附分子 1

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