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时空单细胞多组学解码大脑衰老:分子机制、干预主线与智能因果展望

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摘 要:大脑衰老是多细胞、多分子层级的复杂过程,同时也是阿尔茨海默病、帕金森病等神经退行性疾病的核心风险因素。传统组织水平研究受细胞异质性掩盖,长期难以揭示关键分子事件,形成认知瓶颈,这一局限推动了技术层面的创新探索。近年来,单细胞多组学与空间转录组学(spatial transcriptomics,ST)相继取得突破:前者清晰解析了不同细胞群体的衰老动态轨迹,明确少突胶质前体细胞(OPCs)、小胶质细胞的衰老易感性,神经元突触相关基因失调及染色质-转录网络重构规律,后者则进一步揭示非神经元细胞空间紊乱与免疫微环境失衡机制,为大脑衰老的多维度认知提供技术支撑。在干预领域,单细胞多组学技术的应用价值进一步拓展,不仅为潜在干预靶点筛选提供精准工具,也为药物研发、细胞疗法及多维度联合干预策略搭建验证平台。衰老细胞清除(senolytics)、NAD^+补充介导的能量代谢重塑、神经-免疫-血管单元稳态恢复等方向,已借助该技术构建“靶点筛选-机制验证-临床前转化”的完整研究链条,为大脑衰老的精准干预奠定坚实基础。展望未来,人工智能与因果扰动技术(如CRISPR-perturb-seq、谱系追踪)将与单细胞多组学深度融合:一方面,AI可通过多模态数据整合构建更精准的大脑“衰老时钟”及个体化风险预测模型;另一方面,因果扰动实验推动研究从单纯的相关性描述,迈向机制验证与干预效果模拟的新阶段,进而实现从静态图谱绘制到动态干预设计的跨越;同时,跨物种模型与类器官系统将成为关键验证环节,助力缩短基础研究到临床应用的转化周期。本综述系统总结截至2025年大脑衰老领域的最新研究进展,重点阐释了单细胞多组学技术在机制解析、干预靶点筛选及策略评估中的核心价值,同时展望人工智能与因果扰动技术结合的研究新范式。这些进展将共同推动该领域迈入精准化、智能化与个性化的新时代,为健康老龄化推进及神经退行性疾病防治提供重要理论依据与技术支撑。

关键词:大脑衰老;单细胞多组学;空间转录组;精准干预;人工智能;因果扰动
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Spatiotemporal single-cell multi-omics decoding of brain aging: molecular mechanisms, intervention trajectories, and intelligent causal perspectives

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Abstract: Brain aging is a complex process involving interrelated changes at cellular and molecular levels, and it represents a

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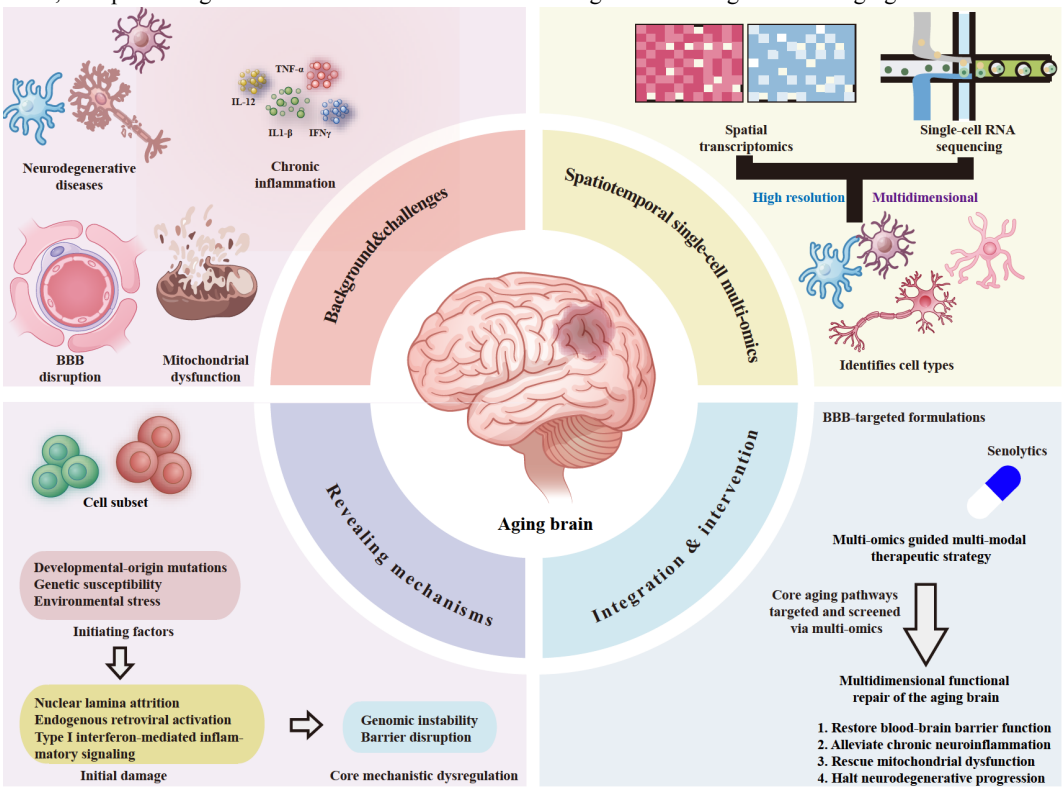
core risk factor for neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Conventional tissue studies are constrained by cellular heterogeneity, making it difficult to uncover cell-specific molecular events and key regulatory mechanisms associated with brain aging. Single-cell multi-omics and spatial transcriptomics (ST) serve as transformative technologies that provide the foundation for overcoming this challenge. This review summarizes advances in brain aging research through to 2025, elucidating the core value of these technologies in deciphering aging mechanisms, identifying intervention targets, and evaluating therapeutic strategies. It explores emerging paradigms integrating AI with causal perturbation techniques, providing a comprehensive overview on related fields. In mechanism analysis, single-cell multi-omics overcomes the limitations of bulk tissue analysis, enabling high-resolution profiling of aging dynamics across distinct brain cell populations. Studies confirm impaired differentiation capacity in oligodendrocyte precursor cells (OPCs), altered expression of myelin-related genes, and a shift toward a pro-inflammatory phenotype with phagocytic dysfunction in microglia. In neurons, dysregulation of synapse-related genes, along with chromatin accessibility and transcriptional regulatory network reorganization, drives aging. Spatial transcriptomics further elucidates spatial disorganization in non-neuronal cells and imbalances in the brain's immune microenvironment, highlighting the importance of region-specific aging patterns. In intervention studies, this technology provides precise tools for target screening, establishing a validation platform for drug development, cell therapies, and combined interventions. It builds a chain from "target discovery → mechanism validation → preclinical translation", laying the foundation for precision interventions. Future advancements will be driven by the convergence of AI, causal perturbation techniques (e.g., CRISPR-perturb-seq, lineage tracing), and single-cell multi-omics. AI can integrate multimodal data to construct precise "aging clocks" and risk prediction models for early identification. Causal perturbation techniques will advance research from correlation studies toward mechanism validation and intervention simulation. Cross-species models and organoid systems will bridge the gap between basic research and clinical applications, accelerating translation. Future research should focus on building integrated technology platforms, fostering interdisciplinary collaboration, and promoting translational outcomes to address the global challenge of brain aging-related diseases.



Key words: brain aging; single-cell multiomics; spatial transcriptomics; precision intervention; artificial intelligence; causal perturbation

全球正经历历史性人口老龄化转型,世界卫生组织(WHO)预测到2050年全球60岁以上人口将增至21亿,脑衰老及其相关神经退行性疾病由此成为全球公共卫生系统的重大挑战[1]。脑衰老不仅表现为认知功能下降、记忆力减退等生理性退行性改变,更是阿尔茨海默病(Alzheimer's disease,AD)、帕金森病(Parkinson's disease,PD)的首要风险因素。目前全球AD患者超5 000万,2050年预计激增至

1.52亿[2]。因此,对脑衰老机制的深入解析与干预策略开发,不仅直接关系个体健康寿命的延长,更对减轻社会医疗负担、维持老龄化社会稳定具有深远意义[3]。

传统脑衰老研究多依赖组织水平的批量分析,掩盖了细胞异质性与空间组织结构的关键信息,严重制约了对脑衰老机制的深入解析[4]。单细胞多组学与空间转录组学(spatial transcriptomics,ST)的突破性进展推动了该领域研究范式的重要转变。2024—2025年期间,多项前沿研究已彰显技术对机制解析与靶点筛选的支撑价值:*Nature Aging*刊发的研究通过单细胞多组学整合分析,揭示了脑衰老过程中表观遗传漂变与转录组紊乱的协同作用机制[5];另有研究利用ST绘制衰老大脑神经炎症信号的分布图谱,发现炎症信号在特定脑区形成“热点区域”[6]; *Genome Biology*发表的研究通过单细胞测序与随机森林算法,鉴定出脑衰老的新型生物标志物,实现了衰老程度的精准评估[7]。这些研究共同实现了从“整体描述”到“单细胞-空间精准解析”的认知跨越。

在干预主线方面,单细胞多组学不仅揭示了衰老相关的细胞亚群和关键通路,还逐步形成了“靶点筛选-机制验证-临床前转化”的逻辑框架。例如,基于单细胞图谱鉴定出的衰老胶质细胞可作为senolytics的直接靶点,线粒体功能障碍相关分子可用于代谢重塑干预,而“神经-免疫-血管单元”的异常互作则揭示了多维度联合干预的新方向。这种从机制到干预的闭环设计,使得研究不仅超越了描述性图谱阶段,更推动了可操作性强的精准干预方案的构建。

在未来展望中,人工智能(AI)与因果扰动技术的深度融合将为脑衰老研究提供全新范式。一方面,AI驱动的多模态整合可在跨组学和跨时空尺度上构建更精准的“衰老时钟”,实现个体化的衰老预测和干预效果评估;另一方面,因果扰动实验将突破传统研究的相关性限制,实现关键因子的因果验证与干预模拟。这种“AI+因果扰动”模式不仅能够精细化描绘衰老机制,还将推动衰老研究从静态图谱绘制迈向动态干预设计,加速成果从实验室走向临床应用。

综上,单细胞多组学与ST为大脑衰老研究提供了前所未有的时空分辨率与机制解析深度,在干预主线整合与智能因果探索的推动下,有望为实现全球健康老龄化目标提供核心科学支撑,对减轻神经退行性疾病负担、提升老龄化社会健康水平具有重要的科学价值和社会意义。

1 脑衰老的分子调控机制

脑衰老的核心特征包括认知功能衰退、脑功能异常及组织微环境失衡,其潜在机制涉及基因组不稳定性、能量代谢失衡、细胞间通讯紊乱等多维度级联反应,且这些异常呈现显著的细胞异质性与区域特异性。单细胞组学技术(如scRNA-seq、scATAC-seq)通过单细胞分辨率分析有助于精准识别衰老相关细胞亚群,揭示其特异性分子特征,从而将分子层面异常与临床认知表型建立关联[8];ST则补充了关键的空间维度信息,揭示不同脑区的衰老相关转录组差异,为理解脑功能异常的区域特异性机制提供直接证据[9]。

1.1 核内稳态的失衡:基因组不稳定性与表观遗传失调

细胞核稳态破坏是脑衰老的早期驱动力,主要表现为“DNA损伤累积-染色质结构紊乱-炎症信号激活”的级联反应。基于单细胞DNA测序(scDNA-seq)结合ST的联合分析揭示,衰老神经元中体细胞突变呈现与癌症单碱基替换特征5(single base substitution signature 5,SBS5)相似的突变特征,其丰度随年龄增加而显著升高[10]。一项研究对来自15名正常个体(年龄为4个月至82岁)前额叶皮层和海马的161个神经元进行全基因组测序,发现神经元体细胞单核苷酸变异(sSNVs)以每年15.5~22个的速度累积,其中大部分(约13.8个/年)是与SBS5高度相似的“A1”突变特征,该积累速率与年龄呈强正相关(R^2≈0.92~0.94),提示SBS5类突变是神经元衰老过程中的一种“时钟式”累积过程[9]。针对“部分突变可能源于早期发育期”的推测,若能在实验设计中结合单细胞谱系追踪技术(如Cre-loxP介导的细胞命运标记)追溯突变细胞的起源时间点,或可更精准阐明这类早期突变在后续神经功能衰退中的累积效应,而非仅依赖静态的突变丰度分析。目前部分突变通过破坏突触基因或调控元件加速衰退的机制仍缺乏直接的功能验证数据。针对该机制的干预围绕多维度展开:分子靶点聚焦DNA修复通路与表观遗传调控因子;细胞层面可通过基因编辑增强DNA修

复或采用HDAC抑制剂改善染色质开放度;在生活方式干预中,维生素E、白藜芦醇等抗氧化分子有助于减少DNA损伤累积。

此外,核纤层磨损与内源性逆转录病毒(endogenous retrovirus,ERV)激活也是细胞核稳态破坏的重要环节:核纤层蛋白B1(lamin B1)水平下降可解除ERV抑制,释放的大量ERV-RNA既可能破坏染色质拓扑结构,也能通过激活RIG-I样受体(RIG-I-like receptor,RLR)途径触发炎症反应[11,12]。使用逆转录酶抑制剂(如阿巴卡韦、齐多夫定等核苷类逆转录酶抑制剂)可通过抑制ERV的逆转录过程,减少ERV-RNA的产生与释放,进而延缓脑衰老相关的核内稳态失衡[13]。例如,阿巴卡韦处理衰老的人类神经元或口服给予老年小鼠,可减轻衰老相关的细胞和分子变化,包括抑制神经元衰老和炎症反应[14]。目前多尺度染色质相互作用测序技术(multiscale chromatin interaction sequencing,MUSIC)已揭示衰老相关的X染色体失活特异转录本(X-inactive specific transcript,XIST)调控与衰老相关的细胞功能衰退[15],但在ERV研究中仍受限于交联效率和算法解析能力[16]。

从技术发展与机制验证角度看,若将成簇规律间隔短回文重复序列-扰动测序(clustered regularly interspaced short palindromic repeats-perturb-seq,CRISPR-perturb-seq)与图神经网络(graph neural network,GNN)融合,或可验证"ERV-RNA→染色质重塑→炎症"的因果链,进而构建"ERV-RNA-拓扑关联结构域-炎症轴"作为新的干预框架,但目前仍需明确拓扑关联结构域边界改变是否先于炎症信号激活,这有待通过时间序列高通量染色体构象捕获技术(high-throughput chromosome conformation capture,Hi-C)与炎症因子检测的联合实验验证,从而为后续脑衰老机制深化与干预策略优化提供更精准的方向。

1.2 能量代谢枢纽的失灵:线粒体-突触互作

电生理-转录组线粒体模型(electrophysiology-transcriptomics mitochondrial model,E-TCMito模型)是解析脑衰老中线粒体功能异常的重要工具,其核心在于揭示"神经元电活动-转录组调控-线粒体功能"的动态互作关系,为理解衰老相关突触功能衰退提供了明确的机制框架。基于单细胞RNA测序(scRNA-seq)与代谢组学(metabolomics)的联合分析显示,衰老过程中可观察到钙信号传递效率下降、钙调蛋白依赖性激酶II(calcium/calmodulin-dependent protein kinase II,CaMKII)活性减弱、环磷腺苷反应元件结合蛋白(cAMP response element-binding protein,CREB)结合效率降低,这些变化进一步导致线粒体基因转录水平降低、ATP生成不足,最终对长时程增强(long-term potentiation,LTP)及突触可塑性产生损害[17-21];该机制链条不仅与现有"衰老导致能量代谢失衡-突触功能衰退"的认知相符,也为后续干预策略的开发提供了明确靶点。

ST技术在脑衰老能量代谢研究中发挥重要作用。通过对来自15个脑区、7个年龄段的1 076个小鼠脑样本进行时空转录组分析,揭示了衰老过程中线粒体功能异常具有明显的脑区特异性[22]。其中,衰老相关的基因表达变化在不同脑区呈现显著的空间异质性:白质纤维束(如胼胝体)显示出最强烈的衰老相关转录组变化,而内嗅皮层则相对稳定[23]。围绕该机制的干预研究与动态监测技术已形成多维度体系:分子层面,聚焦TFAM、NRF1等核心调控因子;细胞干预层面,Humanin可通过激活PI3K/Akt通路、清除ROS,减少Aβ诱导的神经元凋亡[24-26],且其表达水平下降与mtDNA突变、IL-6/STAT3炎症通路激活密切相关[27];生活方式干预方面,规律运动可增强线粒体生物合成,与烟酰胺核糖(nicotinamide riboside,NR)补充形成协同互补效应[28,29]。在动态监测技术上,新型荧光探针(如四甲基罗丹明甲酯)、近红外探针能够实时追踪线粒体膜电位(mitochondrial membrane potential,ΔΨm),发现老龄神经元突触前膜中ΔΨm去极化比例显著升高[30-32]。不过这类探针在深层脑区的信号穿透性仍存在局限,未来结合双光子成像技术或可进一步提升监测的空间分辨率。

从技术发展潜力来看,多模态AI的整合分析(影像+转录组+代谢组学)有望建立"线粒体衰老时钟",实现对脑衰老进程的精准量化;若进一步结合CRISPR敲除实验,或可系统验证不同干预手段(NR+运动+抗氧化剂)的协同效应,进而筛选出最优干预组合[33,34]。需要注意的是,当前干预研究多基于动物模型,后续需在临床队列中验证个体差异对干预效果的影响,提升其临床转化价值。

1.3 内部稳态的失守:血-脑脊液屏障破坏

血-脑脊液屏障(BCSFB)损伤是脑衰老的关键

环节，现有研究已明确其核心机制与干预方向：组织蛋白酶CTSS可切割CLDN1，破坏紧密连接结构，导致屏障通透性升高，外周炎症因子侵入脑脊液加剧神经炎症[35-38]；而可溶性血管细胞黏附分子-1（sVCAM-1）水平升高被认为是潜在无创监测标志物[39-43]。scRNA-seq分析显示，衰老过程中脉络丛上皮细胞（CPE）的异质性发生显著变化，干扰素敏感反应元件（ISRE）依赖的基因表达模式仅在CPE细胞亚群中出现。形态学观察显示，衰老的CPE细胞失去约11%的高度，细胞核变得不规则，细胞间连接减少，表明BCSFB功能受损[44]。ST与单细胞多组学的联合应用进一步揭示了衰老过程中BCSFB破坏的分子机制：脉络丛巨噬细胞分泌大量CTSS，降解脉络丛上皮细胞间的CLDN1，从而破坏BCSFB。通过对单细胞（single-cell）和单细胞核（single nucleus）测序分析，结合空间映射技术，研究者构建了发育、成年和衰老小鼠脑脉络丛的细胞图谱，发现衰老过程中上皮细胞激活宿主防御程序，驻留巨噬细胞上调白介素-1β（IL-1β）等炎症相关信号基因[45]。干预体系已形成多维度布局：分子层面的干预手段包括CTSS抑制剂与CLDN1保护剂；细胞层面可通过基因编辑修复上皮细胞或细胞移植强化屏障；在生活方式上，抗炎饮食与规律运动能从源头降低外周炎症，减缓屏障破坏。这三类手段的协同应用或比单一干预更易实现屏障功能的长效维持。

从技术发展视角看，未来通过多模态大模型推断（整合DCE-MRI、PET与组学数据），有望精准预测屏障通透性变化；利用CRISPR-perturb-seq验证CTSS/CLDN1通路的因果作用，形成“预测-验证-干预”的新型闭环框架。然而目前多模态数据的标准化整合仍面临挑战，统一分析流程有望进一步提升预测精度与转化效率[46,47]。

1.4 异质性验证体系：机制-扰动功能验证模型

在脑衰老过程中，神经元（尤其是海马、内嗅皮层兴奋性神经元）、小胶质细胞、脉络丛巨噬细胞及少突胶质细胞是易受影响的关键细胞类型，其退变特征与分子机制具有细胞特异性：神经元主要表现为基因组不稳定性和突触功能衰退，ERV激活介导的染色质紊乱及线粒体能量代谢失衡可能是重要驱动因素；小胶质细胞易发生过度活化，通过分泌促炎因子加剧神经炎症，miR-155-SOCS1通路异常可能是关键调控节点；脉络丛巨噬细胞在衰老过程中高表达蛋白酶CTSS，或可特异性降解CLDN1，参与BCSFB破坏；少突胶质细胞则表现为髓鞘合成相关基因表达下调、线粒体代谢减弱，与白质纤维束衰老相关转录变化相关[48-51]。基于上述研究，可通过细胞分群可视化、多组学关联分析及细胞组成量化，明确衰老相关的细胞类型特征[52]。

多模态AI与CRISPR-perturb-seq的整合为解析上述机制提供了重要支撑，但当前仍存在理论架构先进与实施细节碎片化的矛盾。AI模型方面，SpaMI、CLARIFY等框架在多组学整合与因果推断中具有优势，但缺乏公开可用的开源实现，且参数透明度不足，可能影响研究可重复性；实验层面，CRISPR-perturb-seq的体内实验参数异质性较高，尚未形成统一标准；在评估体系上，传统结构方程模型指标可用于模型拟合，但反事实因果评估仍处于探索阶段。未来或可通过建立开放科学平台共享标准化协议、开发支持多模态整合的开源AI框架、构建脑衰老研究“因果基因组学标准”等方式，推动该领域从数据驱动向因果驱动转型[53-55]。

综上所述，我们可以构建一个脑老化的整合模型：启动因素（如发育起源突变、遗传易感性、环境压力）随年龄增长，引发初始损伤（核纤层磨损、体细胞突变累积、外周炎症）。这些损伤导致核心机制失控：基因组失稳（ERV复活）和屏障破坏（CTSS-CLDN1轴）。两者共同触发并放大慢性神经炎症，该过程又因线粒体功能障碍产生的ROS而加剧。最终，能量危机和保护性信号（如Humanin）的缺失导致功能性输出崩溃——突触可塑性下降和认知衰退（图1）。未来研究方向包括利用单细胞多组学技术绘制人脑衰老的细胞图谱，精准定位启动衰老的关键细胞类型和分子事件[56]；开发同时靶向多个环节（如兼顾染色质稳定与屏障修复）的联合治疗策略；以及利用sVCAM-1等新型标志物进行早期诊断和干预效果评估。

2 细胞机制与跨尺度交互作用

2.1 神经-免疫-血管单元互作：衰老稳态的关键失衡

大脑稳态依赖神经元、免疫细胞和血管系统的精密协作，这一网络被称为“神经-免疫-血管单元”（Neuro-Immune-Vascular Unit，NIVU）。年轻状态下，NIVU通过维持血脑屏障（BBB）完整性、免疫监测和神经血管耦合，保障神经元功能和能量供给[57]。

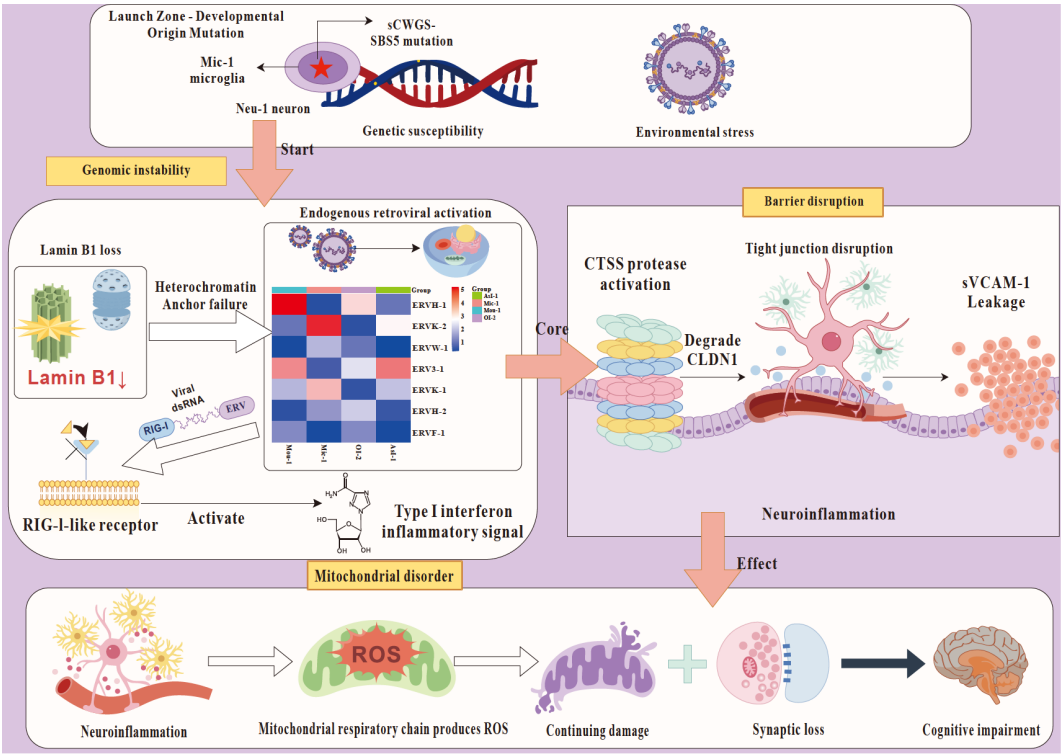


图1 遗传-环境驱动的神经退行性损伤机制

scWGS:单细胞全基因组测序;SBS5:单碱基替换特征5;Mic-1:小胶质细胞1(小胶质细胞相关标识);Neu-1:神经元1(神经元相关标识);Lamin B1:核纤层蛋白B1;RIG-I:维甲酸诱导基因I;viral dsRNA:病毒双链RNA;ERV:内源性逆转录病毒;ERV-RNA:内源性逆转录病毒RNA;IFN:干扰素;CTSS:组织蛋白酶S;CLDN1:紧密连接蛋白1;sVCAM-1:可溶性血管细胞黏附分子1;ROS:活性氧。本图由Figdraw绘制。

Figure 1 Genetic-environmental driven mechanism of neurodegenerative injury

scWGS: single-cell whole genome sequencing; SBS5: single base substitution signature 5; Mic-1: microglia 1 (microglia-related marker); Neu-1: neuron 1 (neuron-related marker); RIG-I: retinoic acid-inducible gene I; viral dsRNA: viral double-stranded RNA; ERV: endogenous retrovirus; ERV-RNA: endogenous retrovirus RNA; IFN: interferon; CTSS: cathepsin S; CLDN1: claudin 1; sVCAM-1: soluble vascular cell adhesion molecule 1; ROS: reactive oxygen species. This figure was drawn with Figdraw.

衰老破坏这一平衡,引发跨细胞互作失调,是认知功能下降和神经退行性疾病的重要驱动因素[58]。

血管老化与BBB功能障碍是衰老过程中重要的病理环节。随年龄的增长,内皮细胞和周细胞受到持续的氧化应激与线粒体损伤,导致紧密连接蛋白(如Claudin-5和ZO-1)表达下调,屏障通透性增加。血管内皮生长因子(VEGF)、基质金属蛋白酶-9(MMP-9)以及ROS等分子进一步加剧了血管渗漏,这些因素均可视为潜在干预靶点[59-62]。针对该机制,可通过基因编辑增强内皮细胞的抗氧化能力,干细胞移植则有望修复受损的血管壁,抑制MMP-9活性则有助于维持BBB的完整性。规律的有氧运动和以地中海饮食为代表的健康饮食方式能够改善脑血流,降低血管渗漏风险,从而与分子及细胞层面的干预形成互补[63-65]。

免疫失调与慢性炎症是驱动老年脑功能衰退的关键因素。衰老的小胶质细胞出现TNF-α、IL-1β以及NLRP3炎症小体的过度激活[66,67],硬脑膜淋巴管功能下降进一步限制了代谢废物的清除,导致炎症循环加剧[68,69]。为此,可采用CRISPR技术下调促炎基因,或通过调节性T细胞及工程化小胶质细胞来改善微环境,炎症小体抑制剂的使用亦能有效缓解慢性炎症。此外,保持规律的作息和摄入富含多酚的食物能够显著降低系统性炎症水平,从而帮助恢复脑内免疫稳态。

在跨细胞互作失调方面,衰老的内皮细胞损伤会释放信号分子,激活小胶质细胞和星形胶质细胞;其中,星形胶质细胞进一步分泌炎症因子,加剧BBB的破坏。同时,神经元释放的危险相关分子模式(DAMPs)又反向促进免疫系统的过度活化,形成典型的恶性循环[68,70]。TGF-β、TNF-α和IL-1β等炎症因子成为关键的分子靶点。针对这些靶点,可采

用抗体阻断关键因子,或利用工程化星形胶质细胞进行跨细胞修复。此外,规律的体育锻炼能够改善神经血管耦合,削弱炎症级联反应,从而在生活方式层面上对抗这一恶性循环。

2.2 AI与因果扰动:跨模态整合的新思路

传统研究多集中于相关性描述层面,而前沿趋势则是将多模态AI推断与因果扰动实验相结合,形成一种更具解释力的研究范式。具体而言,多模态AI推断通过整合scRNA-seq、ST以及代谢组学数据,借助GNN和多模态大模型,能够推断出细胞亚群之间的因果通讯网络[71];此类模型虽已在细胞通讯预测中展现优势,但目前仍面临代谢组学数据整合难度大、批次效应干扰等技术挑战[72],且针对衰老研究的定量性能基准(如AUC、ΔR^2)尚未形成统一标准。随后,因果扰动验证则利用CRISPR-perturb-seq与谱系追踪技术,通过单细胞分辨率的基因扰动与转录组分析,系统性验证AI预测的通路功能[73],该技术已在衰老调控基因筛选中获得应用,但体内实验仍受限于成本较高、周期较长的问题[74]。这种"预测-验证-干预"的闭环探索,突破了传统描述性分析的局限,为衰老网络研究提供了更为系统的动态因果解析视角,也为揭示衰老机制及开发干预策略提供了新的可能[75]。需指出的是,该范式目前仍缺乏广泛认可的端到端成功案例,模型可解释性与鲁棒性仍需进一步提升,其临床转化价值仍有待更多临床队列验证[76]。

2.3 创新性理论框架:NIVU"三层干预模型"

基于现有证据,本研究提出NIVU"三层干预模型":分子层聚焦靶向NIVU稳态失衡相关关键分子,包括炎症因子、紧密连接蛋白及ROS,通过精准调控这些分子的表达或活性以改善单元功能;细胞层借助干细胞替代、工程化免疫细胞及CRISPR介导的基因修复技术,助力重建NIVU细胞层面的稳态;生活方式层则将运动、饮食与睡眠管理作为低成本且易推广的策略,从系统层面强化NIVU的保护效应。与此同时,AI技术与因果扰动技术在三层干预间发挥整合桥梁作用,既能通过多组学数据整合识别各层级关键调控靶点,又能模拟预测不同干预组合的潜在协同效应,为NIVU功能异常相关脑衰老的精准个体化治疗提供工具支撑,其设计逻辑与NIVU稳态失衡驱动脑衰老的核心机制相呼应(图2)。

2.4 衰老细胞清除与再生调控:靶向衰老的"清道夫"策略

细胞衰老(cellular senescence)在早期具有抑癌和促进修复的作用,但随着年龄增长,衰老细胞在大脑等组织中逐渐累积[77]。这些细胞通过"衰老相关分泌表型"(senescence-associated secretory phenotype,SASP)持续释放炎症因子和蛋白酶,造成慢性炎症和微环境紊乱,从而加速神经退行性病变[78,79]。

2.4.1 大脑中衰老细胞的鉴定与作用

在大脑中,衰老细胞的鉴定与作用主要依赖于分子靶点,最常用的标志物是$p16^{INK4a}$和$p21^{Cip1}$。这些标志物不仅见于小胶质细胞、星形胶质细胞与少突胶质前体细胞(OPCs),部分神经元中也能观察到。其中,衰老的胶质细胞是SASP的主要来源,可分泌TNF-α、IL-6以及基质金属蛋白酶(MMPs),从而营造出一种毒性炎症环境。AD模型进一步表明,Aβ斑块周围的衰老小胶质细胞和星形胶质细胞能够促进tau蛋白病理扩散[80,81]。

针对这些衰老细胞的干预策略主要分为两大类。细胞层面的干预包括利用基因工程或免疫细胞疗法选择性抑制SASP通路;通过CRISPR技术下调IL-1β等关键促炎因子,也被证实能够有效减轻炎症反应。生活方式层面的干预则强调规律的体育锻炼和适度的饮食限制,这两者能够改善全身代谢状态并降低炎症水平,进而间接减少大脑中衰老细胞的积累。综合来看,分子标记的精准检测、细胞层面的精准干预以及健康的生活方式共同构成了应对大脑衰老细胞的多维策略。

2.4.2 衰老细胞清除(Senolytics)的治疗潜力

在分子层面,Dasatinib与Quercetin等小分子药物已被证实能够选择性清除$p16^{INK4a}$阳性衰老细胞[82];INK-ATTAC转基因小鼠则被广泛用作验证这些药物效能的实验工具[83];在细胞干预方面,对老年小鼠进行衰老细胞清除后,可显著降低全身炎症水平[84],改善认知功能,并有效延缓多种组织病变的进程[85,86]。此外,生活方式的调节同样发挥重要作用[87]。富含多酚和白藜芦醇等抗氧化成分的饮食能够减轻氧化应激,从而抑制衰老细胞的形成[88];此类饮食干预与药物治疗相互补充,形成多层次的抗衰老策略[89]。

综上所述,分子靶向药物、细胞层面的干预以及抗氧化饮食的综合应用,为衰老细胞清除提供了多

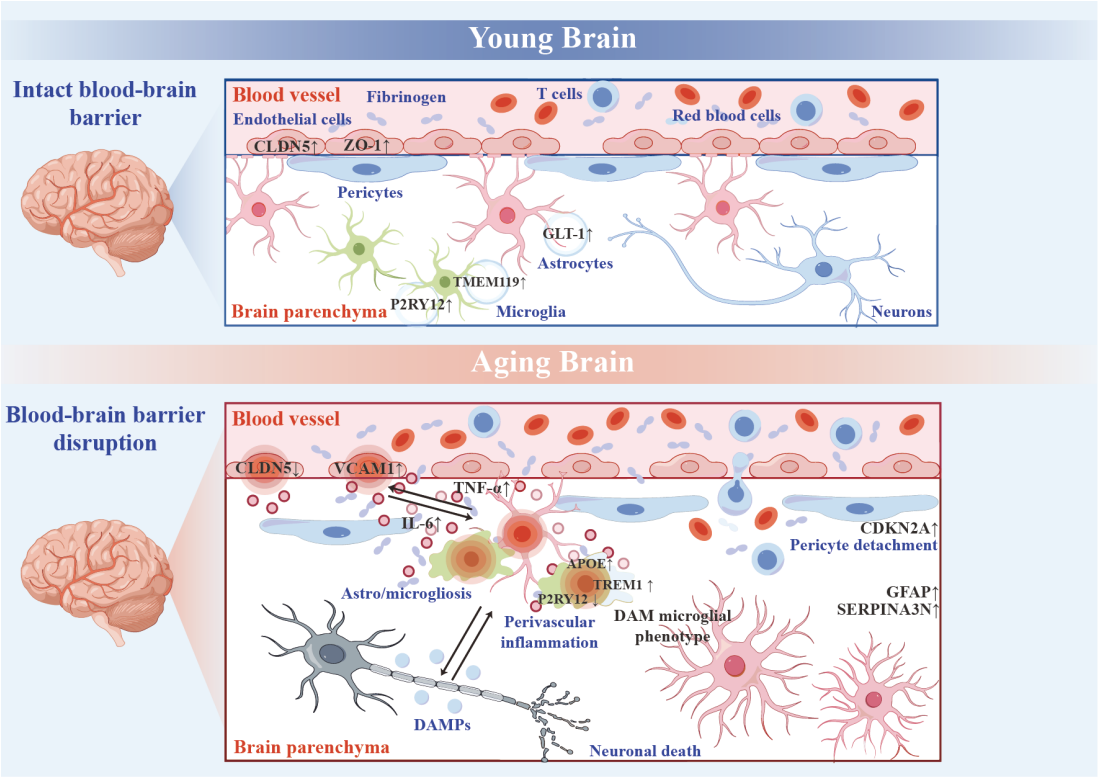


图2 神经-免疫-血管单元(NIVU)在年轻与衰老状态下的比较

上图(年轻大脑):一个功能完整的NIVU,其分子特征表现为稳态基因的高表达。血脑屏障结构紧密,内皮细胞高表达紧密连接蛋白(如CLDN5、ZO-1)。小胶质细胞处于静息的"哨兵"状态,其特征为稳态基因(如*Tmem119*、*P2ry12*)的高表达。星形胶质细胞功能正常,高表达谷氨酸转运体(如GLT-1)以维持突触稳态。神经元网络完整,神经血管耦合高效。下图(衰老大脑):一个功能失调的NIVU。单细胞转录组揭示了其深刻的分子重编程。血脑屏障出现渗漏,伴随内皮细胞紧密连接蛋白(Claudin-5)下调和黏附分子(VCAM-1)上调。小胶质细胞转化为疾病相关状态,其特征是稳态基因(*P2ry12*)丢失和衰老相关基因(*Apoe*、*Trem2*)上调。星形胶质细胞呈现反应性表型(GFAP、Serpina3n上调),周细胞表达衰老标志物(Cdkn2a)。此外,脑实质中弥漫的衰老相关分泌表型因子(如IL-6、TNF-α)与外周浸润的免疫细胞共同构成了慢性的促炎环境,加剧神经元损伤与突触丢失。箭头(↑/↓)示意与年轻状态相比,关键分子表达的相对变化。本图由Figdraw绘制。

Figure 2 Comparison of Neuro-Immune-Vascular Unit (NIVU) in young and aged states

Upper panel (young brain) shows a functionally intact NIVU with molecular characteristics of high expression of homeostatic genes. The blood-brain barrier is tightly structured, and endothelial cells highly express tight junction proteins (e.g., Claudin-5, ZO-1). Microglia are in a resting "sentinel" state, characterized by high expression of homeostatic genes (e.g., *Tmem119*, *P2ry12*). Astrocytes function normally and highly express glutamate transporters (e.g., GLT-1) to maintain synaptic homeostasis. The neuronal network is intact, and neurovascular coupling is efficient. Lower panel (aged brain) shows a dysfunctional NIVU. Single-cell transcriptomics reveals profound molecular reprogramming. The blood-brain barrier is leaky, accompanied by downregulation of tight junction protein (Claudin-5) and upregulation of adhesion molecule (VCAM-1) in endothelial cells. Microglia transform into a disease-associated state, characterized by loss of homeostatic gene (*P2ry12*) and upregulation of aging-related genes (*Apoe*, *Trem2*). Astrocytes exhibit a reactive phenotype (upregulation of GFAP, Serpina3n), and pericytes show senescence markers (Cdkn2a). In addition, senescence-associated secretory phenotype factors (e.g., IL-6, TNF-α) diffused in the brain parenchyma and immune cells infiltrated from the periphery together form a chronic pro-inflammatory environment, exacerbating neuronal damage and synaptic loss. Arrows (↑/↓) indicate the relative changes in the expression of key molecules compared with the young state. This figure was drawn with Figdraw.

维度的治疗潜力,值得在未来的临床研究中进一步探索与验证。

2.4.3 再生调控与未来挑战

衰老细胞清除的间接再生效应体现在:该过程并非直接诱导组织再生,而是通过去除SASP这一"炎症污染源",恢复干/祖细胞的正常功能,进而提升神经发生潜能[90]。当前该领域仍面临多重挑战:一是衰老细胞异质性显著,不同细胞群体的SASP组成存在明显差异[80,91],增加了靶向干预的复杂性;二是部分衰老细胞在组织修复过程中可能发挥保护作用,如何精准识别并区分有害衰老细胞与具有保护功能的衰老细胞,仍是亟待解决的难题[92];三是

虽可借助单细胞组学与ST技术绘制衰老细胞图谱，为发现更特异的干预靶点提供支持[93,94]，但图谱数据与功能验证的结合仍需进一步深化。

未来衰老细胞研究可围绕两大方向展开：在多模态AI推断层面，通过整合scRNA-seq、表观组学及空间组学数据，利用GNN技术，有望预测衰老细胞与邻近细胞间的潜在因果关系，为解析衰老微环境互作机制提供新视角；在因果扰动验证层面，借助CRISPR-perturb-seq技术对AI预测的关键调控关系进行实验验证，进而构建“预测-验证-干预”的研究闭环，推动衰老细胞干预从相关性分析迈向因果机制驱动的精准设计。

2.4.4 创新性干预框架：SIN

为提升衰老细胞干预策略的精准性与系统性，本研究提出“衰老-干预关联框架”（senescence-intervention nexus，SIN）：分子层聚焦开发新型衰老标志物与高特异性Senolytics药物，为衰老细胞的精准识别与靶向清除提供分子基础[95-97]；细胞层通过免疫重塑、基因编辑或细胞重编程技术，探索精准清除或功能性转化衰老细胞的路径，以减少SASP对局部微环境的扰动[98-100]；生活方式层则通过饮食调整、规律运动及抗炎生活习惯的养成，从机体整体层面延缓衰老细胞积累速率[101-103]；同时，AI推断与因果扰动技术作为跨层支撑工具，不仅可整合多组学数据识别各层级关键调控靶点，还能预测不同干预组合的协同潜力[104,105]。该框架强调“分子-细胞-生活方式”的跨尺度整合，推动衰老细胞清除研究从单一实验探索迈向系统化、个体化干预阶段，其设计逻辑与衰老细胞调控的核心机制相呼应，为衰老机制解析及干预策略优化提供理论支撑。

3 技术前沿与干预启示

3.1 单细胞空间多组学：跨维度解码大脑衰老

单细胞空间多组学为解析大脑衰老提供了前所未有的分辨率。该技术能够同时获取转录组、表观组与空间坐标，揭示衰老过程中的细胞异质性与微环境重构。

在分子靶点方面，通过scRNA-seq鉴定出星形胶质细胞和OPCs的异质性标志物，为分子干预提供新靶点[106]。scRNA-seq与snRNA-seq整合进一步揭示了性别与区域特异性配体-受体对，为理解AD等疾病的病理通讯提供线索[107]。scATAC-seq显示神经干细胞（NSCs）染色质可及性变化，提示其为脑衰老的上游信号[108]。这些方法现已成为理解大脑衰老机制的重要手段。在细胞干预的策略方面，可利用基因修饰或干细胞疗法矫正染色质与转录失衡[109]。相比之下，运动与饮食有关的生活方式干预方面，可通过调控相关通路改善表观遗传状态，与分子干预形成互补，为构建脑老化干预体系提供了方向。

3.2 活体成像与跨物种模型：在真实环境中解析衰老

先进成像技术（如双光子显微镜、光学相干断层扫描）使研究者能在活体中动态观察神经网络与血管功能[110,111]。从分子靶点来看，活体成像提示脑衰老或伴随血管密度下降与钙稳态异常，为血管修复和钙信号调控相关研究提供了方向。细胞干预方面，在非人灵长类动物的研究中，单核RNA测序技术（如基于纳升液滴的方法）已被用于个体细胞的转录组分析，整合单细胞成像与组学数据的机器学习分析揭示了大脑区域特异性转录改变[112,113]，该结果为细胞疗法跨物种验证提供了重要证据。在生活方式干预领域，长期监测数据表明，规律运动和环境丰富化可改善血管耦合与突触可塑性[114]，提示生活方式干预所具有的动态价值，并能与分子、细胞层面的干预形成互补。

在当前脑衰老研究中，跨物种模型为解析人类脑衰老核心规律提供了关键工具，主要包括“小鼠-猴-人类”细胞共培养模型与基因编辑跨物种模型两类：2024年，艾伦脑科学研究院构建“小鼠NSCs-恒河猴皮层神经元”共培养体系，通过单细胞功能验证发现过表达人类*SIRT3*基因的小鼠NSCs可通过分泌外泌体使猴神经元氧化应激水平降低40%，该保护效应进一步在人类诱导多能干细胞（iPSCs）分化的神经元中得到验证，为跨物种保守的衰老调控通路提供了直接证据[115]；而在基因编辑模型方面，研究人员通过将AD风险基因*APOE ε4*敲入小鼠下丘脑构建的跨物种模型显示脑衰老速度加快2倍；ST分析表明，小鼠下丘脑第三脑室周围细胞的炎症基因表达模式与人类老年脑样本高度相似（相关系数r=0.82），这为模拟人类脑衰老的区域特异性分子特征提供了理想模型[116,117]。

3.3 多组学驱动的衰老时钟：从预测到干预

多组学研究推动了“衰老时钟”的建立。蛋白质组学观测到GFAP、NEFL、GDF15、LTBP2等分子为重要早期监测指标，可在痴呆前10年发生异常波

动[28]。在分子靶点层面,血浆中BCAN和BAG水平的变化与衰老存在明显的因果关系,具备强大的内在干预潜力[32]。在细胞干预领域中,利用CRISPR-perturb-seq技术干预特定通路,可验证衰老蛋白的因果效应,为靶向干预机制提供了机制层面的依据。同时,在生活方式干预方面,饮食与运动亦可影响多条代谢通路,为非药物干预提供实证支持[118],并能与分子、细胞层面的干预协同作用,共同为基于"衰老时钟"的精准干预提供新视角。

3.4 AI与因果扰动的融合

AI与大模型在解析衰老机制的多组学整合中发挥不可或缺的作用。在多模态AI推断中,研究者整合转录组、表观组、空间组学和蛋白质组数据,运用GNN与大模型推断细胞间因果关系。在因果扰动验证中,在此基础上,利用CRISPR-perturb-seq验证AI预测的关键因子,例如在Néstor-Guillermo早衰症(NGPS)机制研究中,通过整合患者成纤维细胞的多组学数据,AI预测核糖体蛋白RPS3A、信号分子PAFAH1B1等是BANF1突变介导蛋白质合成失调的关键调控因子,后续利用CRISPR-perturb-seq特异性敲低这些基因,或可改善NGPS细胞的核膜畸形、微核形成等异常表型,降低细胞翻译错误率;在秀丽隐杆线虫模型中观察到突变体寿命延长,为该调控通路在衰老加速中的作用提供了实验支持[119];在脑衰老相关的小胶质细胞过度活化机制研究中,通过AI整合scRNA-seq、ST及染色质可及性数据,预测小胶质细胞中miR-155下游靶基因SOCS1是抑制炎症风暴的关键节点,后续利用CRISPR-perturb-seq技术靶向激活SOCS1表达,使小胶质细胞分泌的IL-1β、TNF-α等促炎因子水平呈现下调趋势,神经元突触损伤减轻,为"miR-155-SOCS1-炎症轴"的因果调控关系提供了实验佐证[120],进而形成"推断-验证-模拟"的闭环。该模式不仅提升了衰老机制的解释力,也为干预组合的预测提供了平台。

3.5 创新性框架:iBAIF模型

在系统整合现有研究证据的基础上,本研究旨在提出"脑衰老整合干预框架"(Integrative Brain Aging Intervention Framework,iBAIF)。该框架在分子层面,识别并靶向衰老相关标志物和调控因子,据此开展针对性靶向干预;在细胞层面,通过活体成像和跨物种模型验证分子靶点的生物学功能,并利用细胞疗法探索受损细胞的修复策略;生活方式层面将以饮食、运动和认知训练作为低成本的干预手段,不断改善机体整体系统环境来调控衰老进程;在跨层整合方面,AI与CRISPR-perturb-seq联合驱动因果推断与干预模拟,实现个体化预测和动态调控。该框架突出"分子-细胞-生活方式"的三级主线,并引入AI与因果扰动作为跨层工具,形成具有原创性的脑衰老干预模型。

4 干预策略与转化医学

4.1 分子靶向与细胞疗法

在脑衰老相关干预研究中,不同层面的探索均取得阶段性进展。分子层面,多巴胺受体(D1R、D3R、D4R)与GLP-1受体成为重点关注对象,其中D3R激动剂可提升多巴胺水平,促进BDNF分泌,并能与D1R协同改善PD患者的运动障碍及左旋多巴副作用,而D4R对神经振荡的调控作用提示其在认知功能改善中具有潜在价值[121];此外,GLP-1受体激动剂(GLP-1RA)在脑缺血、代谢性认知障碍及神经退行性疾病模型中表现出神经保护作用,机制涉及抗炎、维持线粒体稳态及增强突触可塑性[122]。细胞层面,间充质干细胞(MSCs)及其外泌体(MSCs-Exos)为研究热点方向,MSCs移植在衰弱综合征模型中已完成I/II期临床试验,初步证实其安全性并展现出一定疗效[123];MSCs-Exos可通过上调SIRT1通路实现延缓衰老与神经元保护[124-126],其"无细胞"特性有望规避免疫排斥及肿瘤发生风险。生活方式干预层面,运动与科学营养调控可协同调控多巴胺与GLP-1信号轴,改善机体炎症与代谢环境[127];规律睡眠则对维持突触稳态、保护认知功能具有积极作用[128],为脑衰老调控提供了低成本且易实施的辅助路径。

4.2 社会心理-生物学整合干预

在社会心理-生物学整合干预的研究框架下,相关研究已在多个维度展开。分子层面,端粒-TERT轴是该领域的关键干预靶点,其中TERT激活偶联物(TAC)可促进端粒合成、减轻炎症反应并有助于维持认知功能[126],同时非编码RNA与组蛋白乙酰化等表观遗传机制,能通过调控自噬相关基因的表达进一步降低炎症水平[129,130];细胞层面,通过工程化改造免疫细胞或小胶质细胞,能够重塑脑内免疫微环境,借助基因编辑技术修复星形胶质细胞与内皮细胞功能,有望恢复BBB与BCSFB的结构完整性;生活方式干预层面,抗炎饮食、规律运动、睡眠管理及认

知训练均能发挥延缓衰老的作用，其中虚拟现实-工具性日常生活活动（Virtual Reality-Instrumental Activities of Daily Living，VR-IADL）在轻中度痴呆患者中已实现认知改善效果[131,132]，为社会心理因素与生物学干预的协同开展提供了实践依据。

4.3 多维度联合干预

在多维度联合干预衰老的研究中，分子、细胞及生活方式层面的探索围绕核心机制形成协同体系：分子层面，PI3K/AKT、mTOR、AMPK与SIRT通路共同构成代谢与表观修饰调控网络，是干预的核心环节[133,134]，尿石素A可通过miR-34a-SIRT1/mTOR轴改善认知功能与衰老相关表型[135]；细胞层面，MSCs及MSCs-Exos与mTOR/AMPK调控药物联用，在能量代谢、自噬激活、炎症抑制三方面形成协同效应，而神经调控设备（如经颅磁刺激）与细胞疗法的结合，可能进一步增强神经网络可塑性；生活方式层面，热量限制（CR）与规律运动可降低ROS水平、改善细胞Ca^{2+}稳态并增强抗凋亡能力，此外，一项为期40个月的食蟹猴研究显示，二甲双胍通过激活Nrf2信号通路减缓衰老时钟并改善认知功能[136]，各维度干预共同为衰老调控提供了多元路径。

4.4 AI与因果扰动的支撑

在多模态AI推断中，整合转录组、空间组学、蛋白质组与影像学，运用GNN和多模态大模型推断衰老关键节点，并预测多重干预的协同效应。在因果扰动验证中，通过CRISPR-perturb-seq与类器官/NHP模型验证AI预测结果，形成“推断-验证-干预”的转化闭环。

4.5 理论框架：Tri-PILOT

基于上述研究证据，我们提出脑衰老干预的三层精准干预模板（Tri-layer Precision Intervention Template，Tri-PILOT）框架：分子层以靶向多巴胺/GLP-1受体、TERT、自噬-表观轴及mTOR-AMPK-SIRT调控网络为核心；细胞层重点围绕MSCs/MSCs-Exos、工程化免疫细胞/胶质细胞，以及BBB/BCSFB修复展开；生活方式层注重制定运动、饮食、睡眠与认知训练的周期化干预处方；跨层整合层面则依托AI技术与CRISPR-perturb-seq技术的协同应用，推动衰老相关因果关系推断与干预组合优化，最终实现个体化、动态化的治疗方案。该框架不仅总结了现有的干预模式，更提出了一套模板化实施路径，使脑衰老干预具备更高的精准性、智能性与可操作性（表1）。

5 总结与展望

单细胞多组学与空间组学技术正在重塑我们对

表1 神经保护与认知改善干预策略的分类及机制

Table 1 Classification and mechanisms of neuroprotective and cognitive-enhancing intervention strategies

干预/通路/因素	主要作用/结果	机制/类别
Gamma振荡激活	改善认知障碍及帕金森病症状	神经调控
GLP-1受体激动剂（GLP-1RA）	神经保护	药物
二甲双胍	神经保护	药物
热量限制	缓解代谢相关认知损伤	代谢干预
间充质干细胞（MSCs）移植	神经保护	细胞治疗
MSCs来源外泌体（MSCs-Exos）	神经保护	细胞衍生物
体能与脑力结合活动	延缓认知衰退	行为干预
集成VR/IADL训练	通过环境刺激改善认知功能	行为干预
神经刺激	增强认知功能	神经调控
去甲肾上腺素增强	协同延长寿命	分子通路
抵抗ROS诱导的损伤	抑制凋亡与氧化应激	分子通路
PI3K/AKT/mTOR/SIRT通路调控	调控细胞存活与代谢	分子通路
促进端粒合成	减轻神经炎症	分子通路
心理风险因素	增加神经退行性疾病的易感性	风险因素

注：本表整合分子/细胞治疗、社会心理-生物干预及生活方式/药物策略，通过多通路协同改善帕金森病症状、认知障碍及衰老相关问题。MSCs，间充质干细胞；VR，虚拟现实；IADL，工具性日常生活活动；PD，帕金森病。

Note: This table integrates molecular/cell-based therapies, socio-psycho-biological interventions, and lifestyle/pharmacological strategies to synergistically improve PD symptoms, cognitive impairment, and aging-related conditions. MSCs, mesenchymal stem cells; VR, virtual reality; IADL, instrumental activities of daily living; PD, Parkinson′s disease.

大脑衰老的理解,从传统宏观研究的“模糊图景”,迈向以细胞类型为基础、分子网络为核心的精准探索阶段。现有成果已初步绘制出大脑衰老的多维图谱,揭示了不同细胞类型的衰老轨迹,并催生了“单细胞衰老时钟”等量化工具。这些进展不仅推动了分子机制的解析,也为干预策略制定提供了理论依据和技术支撑。

然而,该领域仍存在诸多挑战:在分子层面,多组学数据的异质性与批次效应限制了不同研究间的横向整合;在细胞层面,稀有细胞群体及区域特异性衰老机制仍未被充分解析;在空间层面,组织解离导致细胞-微环境互作信息丢失;在因果层面,多数研究仍停留在描述性图谱构建,缺乏CRISPR-perturb-seq、谱系追踪等手段对关键分子的因果验证。

围绕这些问题,未来的研究方向可从以下三方面展开,以进一步探索衰老相关机制及潜在调控策略。在分子靶点干预层面,可聚焦多巴胺受体(如D3R/D4R)、GLP-1受体、SIRT家族等与衰老进程密切相关的关键分子靶点,结合小分子药物研发及多模态生物标志物预测模型构建,有望为精准药物设计及机制性验证提供支撑。在细胞干预策略方面,MSCs及其Exos、可清除衰老细胞的Senolytics药物等细胞层级干预手段已显示出一定的神经保护与抗炎作用;若能结合单细胞多组学技术绘制的细胞“衰老图谱”,或可进一步发展细胞类型特异性的靶向清除与修复策略。在生活方式与系统性干预维度,热量限制、运动及心理社会干预是维持神经-免疫-血管单元稳态的重要外部调控变量;将这类干预方式与分子或细胞疗法协同整合,以探索“多维度联合干预”的有效路径。

在技术前沿方面,AI与多模态大模型为衰老研究的突破提供了新契机。通过整合scRNA-seq、scATAC-seq、ST、蛋白质组学及影像学数据,GNNs、多模态大模型可重建跨尺度的细胞互作网络,并在因果层面结合CRISPR-perturb-seq等实验手段,实现“AI推断-实验验证”的双轮驱动,推动从描述性图谱迈向因果机制解析。

AI使用声明

在本研究的写作过程中,作者仅使用人工智能辅助工具对部分语句进行了翻译、语言润色及表述优化。人工智能工具未参与研究设计、数据收集、统计分析、结果解读及结论形成,也未生成任何学术性内容。本研究全部科学思想、研究方法、数据处理与逻辑推断均由作者独立完成,并经作者逐字审校,以确保内容的真实性、准确性与学术规范性。本研究的撰写和提交符合期刊关于人工智能辅助工具使用的相关规定,不存在任何形式的学术不端行为。

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