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成年哺乳类中枢神经系统内源性神经发生——新的希望

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摘要: 过去的几十年里, 研究人员在成年哺乳类的脑中观察到了新生的神经元及神经发生的过程, 在破译成年神经发生的机制方面取得了巨大进步。阐明涉及成年神经发生的过程及其调节机制可进一步了解成年神经发生与神经和精神疾病以及脑或脊髓损伤之间的关系。因此, 深度解析神经干细胞特性及其活动方式的调节规律, 将有助于揭示影响成年神经发生的内因和外部小生态。该文综述了成人内源性神经发生的最新进展, 神经干细胞的异质性, 神经干细胞的静止和激活状态之间的平衡, 影响神经干细胞命运的内外因素, 神经干细胞的老化和复壮, 以及激活成年内源性神经发生修复脊髓损伤的最新进展。

关键词: 成年哺乳类; 内源性神经发生; 中枢神经系统; 脊髓损伤; 脑损伤

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Adult mammalian CNS endogenous neurogenesis – new hope

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Abstract: In the past few decades, researchers have observed newborn neurons and neurogenesis in the brains of adult mammals, and have made great progress in deciphering the mechanisms of adult neurogenesis. Elucidating the processes involved in adult neurogenesis and their regulatory mechanisms can further understand the relationship between adult neurogenesis and neurological and psychiatric disorders as well as brain or spinal cord injury. Therefore, an in-depth analysis of the characteristics of neural stem cells and the regulation of their activities will help reveal the internal and external niches that affect adult neurogenesis. This article reviews recent advances in adult endogenous neurogenesis, the heterogeneity of neural stem cells, the balance between dormant and activated

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states of neural stem cells, internal and external factors affecting the fate of neural stem cells, the aging and rehabilitation of neural stem cells, and the recent advances in endogenous neurogenesis to repair adult spinal cord injury.

Key words: adult mammals; endogenous neurogenesis; central nervous system; spinal cord injury; brain injury

1998年, 研究人员通过对癌症患者进行5-溴-2'-脱氧尿苷(BrdU)标记, 观察到成人海马齿状回中有新生神经元的存在^[1]。随后, 很多有关成年神经发生机制方面的研究集中在基因及环境对其产生的影响方面。许多内在和外在因素影响成年神经发生的过程, 包括神经祖细胞的增殖、神经祖细胞后代的命运决定以及成体神经元的迁移和成熟^[2-5]。2018年两项著名的截然相反的研究结论的公开发表再次点燃了成年人类是否存在神经发生这一科学争论^[6-7]。本文总结了该领域的一些研究进展和争议, 并认为目前没有理由否认在整个生命周期中, 成年哺乳类新生神经元对中枢神经系统功能可塑性的贡献。

1 成年神经发生的概念

成年内源性的神经发生这个词最早曾被用于产生神经系统的细胞(neurons and glia), 随后又被用于内源性神经干细胞的激活, 直至被限定于产生新的神经元^[8-11]。李晓光团队在2015年又重新补充了该概念^[12-13], 认为成年内源性神经发生是指: 成年哺乳类中枢神经系统中的神经干细胞(neural stem cells, NSCs)可被激活, 被募集迁移至病损部位分化为成熟的神经元, 新生的神经元与宿主细胞形成功能性的神经环路, 最终导致功能恢复。内源性神经发生的主体是神经干细胞, 它是可以自我更新和多潜能的, 这也意味着它们可以自我复制, 并可产生不同的成熟的细胞类型。在中枢神经系统的很多区域如脑室下区、齿状回颗粒层和脊髓中央管的室管膜及室下区等部位都存在着神经干细胞^[14-16], 这些神经干细胞在正常、损伤或应激情况下可被活化, 进行增殖与分化, 但这种活化的程度较低, 活化的神经干细胞数量有限且其分化方向不可控, 因此成年中枢神经系统损伤或疾病不能自发恢复。

2 成年人类的神经发生

持续关注成年哺乳类动物神经发生过程的主要原因是人类大脑有可能发生类似的过程。两个著名的研究团队就成年人类神经发生展开了科学争论。2018年, 加州大学旧金山分校Sorrells等^[6]的研究证明, 人类海马齿状回中神经发生的数量在儿童时

期急剧下降, 到成年以后几乎检测不到, 并且人类的海马与其他物种海马的功能不同, 其成年神经发生是保守的。几周后, 哥伦比亚大学的Boldrini等^[7]得出了相反的结论, 他们证明人类终生都存在神经发生。在短短几周内, 上述截然不同的研究结果的发表引起了神经科学界的广泛关注。后续的分析表明, 造成上述不同结果的原因有以下几点: (1) 没有借助BrdU等胸苷类似物或¹⁴C对分裂细胞的DNA进行标记, 单独使用doublecortin(DCX)或PSA-NCAM等蛋白标记物不足以证明神经发生; (2) 样本后固定的时间(死亡时间到脑进入后固定液的时间要≤48h)及后固定液的种类不同都会造成迥异的研究结果, 因为DCX会在死亡后迅速崩解, 而10%的福尔马林固定液会覆盖样本的一些蛋白标志物的抗原; (3) 荷尔蒙状态、饮食、癫痫、焦虑、成瘾、炎症和压力这些因素都会影响人类的神经发生水平。Sorrells等的研究显然没有考虑和规避上述因素对神经发生的影响^[7]。2019年, 伊利诺伊大学芝加哥分校的Tobin等^[18]在老年人(79~99岁)及老年痴呆患者的脑海马中发现了神经发生, 而且这些神经发生与认知功能有关。

自从Joseph Altman偶然发现成年大鼠的神经发生^[19]及Fernando Nottebohm在鸣禽类发现成年神经发生^[20]以后, 关于“灵长类的神经发生是有限的”这一观点一直引起热议^[21]。这个领域已经走过了漫长的道路, 并积累了很多方面的证据支持成年人类大脑中神经发生的存在。此外, 还需要额外研究证明成年新神经元生成的方法, 如单细胞RNA测序能对细胞表型和潜在分化轨迹提供更完整的分析及更有价值的信息。

3 神经干细胞的异质性及动力学状态

成年哺乳类的脑[脑室下区(SVZ)及齿状回]和脊髓中(中央管及其下区)存在着神经干细胞^[14-16], 它们代表着可以自我更新并能在不同的刺激下分化为神经元、星形胶质细胞及少突胶质细胞的一个细胞池^[14-16]。神经干细胞由极其多样化的细胞群构成, 根据其增殖状态和区域特征, 可表现出不同的特征和功能。在SVZ中, 神经干细胞所处的具体位置

决定了它们在嗅球中最终分化和成熟为何种神经元类型^[17]。依据 SVZ 神经源巢中各自的代表性微区域, 由特定转录因子如 Nkx6.2、Zic^[19]、Gsx2^[20]、Nkx2.1^[21] 或 Pax6^[22-23] 构图, 发现神经干细胞可产生几种不同的调节嗅球的中间神经元亚型^[24], 揭示了神经源巢中细胞类型之间的复杂性和相互调节^[25-26]。

此外, 成人神经干细胞及其胚胎对应物可产生功能不同的多巴胺能神经元亚群^[27], 暴露于奖赏相关气味则特异性地增加成体出生神经元的活性, 而不是先前已存在的神经元^[3]。显著的神经干细胞的可塑性也可通过 SVZ 的神经干细胞在脑损伤后可转化为反应性星形胶质细胞参与瘢痕形成得到证实, 并且这些 SVZ 源性的反应性星形胶质细胞也可以通过 Mash1 转化为神经元^[28]。

有研究证明, 整个中枢神经系统 (CNS) 中的一部分 CD133⁺ 室管膜细胞可以在特定信号 (如 VEGF 和 bFGF) 存在的情况下, 重新激活分化为神经元, 表明这些细胞是休眠的室管膜神经干细胞^[29], 更可靠地证实了室管膜细胞的干细胞特性^[25,30-32]。

上述研究结果表明, 区域和发育身份特点对神经干细胞谱系进展起着关键作用。单细胞转录组分析证明, 成年神经干细胞与放射状神经胶质祖细胞共享核心转录表型, 在神经发生过程晚期, 其向成年神经干细胞状态过渡^[33]。基于神经干细胞的激活或静息状态, 可以将其分为不同的亚型: 静息状态的神经干细胞 (quiescence neural stem cells, qNSCs) 和激活状态的神经干细胞 (activation neural stem cells, aNSCs)^[34-35]。急性纯化分离的 SVZ 源性的神经干细胞可分为四种类型: 休眠的神经干细胞 (dormant NSCs)、静息的神经干细胞 (qNSCs)、活化的神经干细胞 (aNSCs) 和祖细胞^[36-37]。单细胞转录组的伪时序分析显示, aNSCs 也具有三个亚群 (早期、中期和晚期激活状态), 它们表现出细胞周期时间和进程的变化, 以及特定基因的差异表达。一个针对海马齿状回的渐进连续的转录动力学分析证明, 海马的 NSCs 也是异质性的, 存在着自静息到神经元分化不同的状态^[38]。

4 影响NSCs状态的外在调节因素

神经源巢 (又称神经源小生态) 是可提供结构支架、局部分泌因子和氧气来支持和营养神经干细胞的广泛的微环境。它由不同类型的相互作用的神经细胞和非神经细胞组成: 室管膜细胞 (SVZ 区)、星形胶质细胞、周细胞、小胶质细胞和血管, 以及

神经干细胞的子代 (短暂扩增的神经祖细胞和成神经细胞)。来自神经源巢的局部刺激, 以及来自远端器官的循环血液因子, 都可正面或负面影响神经干细胞的状态和分化潜能, 从而调控成年大脑的神经发生。

星形胶质细胞和小胶质细胞可以通过在神经源巢中分泌促炎细胞因子 (如 IL-1) 来影响神经发生和诱导认知功能障碍^[39]。神经源巢中的非神经组成部分主要是交织其中的脉管系统^[40-43]。值得注意的是, 不仅是神经源巢里的脉管系统, 非神经源性区域如皮质里的血管也可分泌扩散信号 (如 PIGF-2) 影响神经干细胞增殖^[44-45]。成年神经干细胞可分泌因子如 VEGF^[46] 或神经血管蛋白 EGFL7 (血管细胞也可分泌) 来调节神经干细胞的静息状态^[47]。另外, 神经干细胞可以减少炎症代谢产物琥珀酸, 从而推动神经源巢中的小胶质细胞向抗炎表型转化^[48]。除局部微环境外, 由脉络丛分泌至脑室及脊髓中央管内循环的脑脊液中的一些因子可调节神经干细胞命运, 影响神经发生。这些因子包括 IGF2、Sonic Hedgehog、Wnts、视黄酸、NT-3 及骨形态发生蛋白^[49-53]。此外, 还可以通过神经元活动来调节神经干细胞的状态, 神经元活动是成人神经发生的标志^[54]。例如, GABA 能神经元可远程将 GABA 去极化信号投射到局部小白蛋白中间神经元上, 而此中间神经元又可使海马神经干细胞保持静息^[55]。值得注意的是, 成年的神经发生可通过下丘脑控制, 依据饥饿或饱腹感状态进行调节。在这种情况下, 前阿片样黑皮素神经元选择性地支配脑室下区前部, 并促进 Nkx2.1⁺ NSCs 的增殖和深层颗粒神经元的产生^[56]。此外, 对红藻氨酸诱发癫痫的小鼠模型的研究证明, 神经元的高度兴奋可诱导神经干细胞的大量活化而加速其耗竭, 将其转化为反应性星形细胞, 从而耗尽成年海马神经发生^[57]。

5 神经干细胞的老化和复壮

衰老可对神经发生产生负面影响, 导致脑室下区和海马的神经源巢中的细胞产量急剧且持续地下降^[58-61]。随着年龄的增长, aNSCs 失去了它们的增殖潜能, 变得静息^[62], 但是, 值得注意的是, 在一定程度的刺激下 (例如运动甚至癫痫), 它们可以在一定程度上被重新激活, 这表明神经干细胞的可塑性在一定程度上保留在老龄化的机体中^[60]。例如, 研究表明, 高迁移率 B 族 2 (HMGB2) 与神经干细胞从静止向增殖的转变有关, 衰老对这些细胞群产

生了负面影响, 而运动刺激了 HMGB2⁺ 细胞的增殖^[63]。此外, 对小鼠衰老过程 (2、6、18 和 22 月龄) 中多个时间点的整体脑室下区的转录组分析表明, 脑室下区的转录组不会随着年龄的增长而线性改变, 因为在 18 个月时 Mash1⁺ 祖细胞的增殖等过程会减少, 然后在 22 个月又大幅度增加^[64]。对 2 月龄和 6 月龄小鼠的基因表达谱的分析表明, 在 aNSCs 程序中, 一些分子发生了显著的改变, 细胞周期明显延长^[65]。细胞周期中与年龄相关的变化可能是由于受损蛋白质的积累导致神经干细胞增殖率降低所导致的^[66]。有研究表明, 蛋白质稳态缺陷是由于 qNSCs 中的溶酶体缺陷所致, 但通过在老年 qNSCs 中短暂表达 TFEB 的活性形式或用雷帕霉素全身治疗发现, 溶酶体途径的增强可导致神经干细胞由静止状态逆转为活跃状态^[67]。综上所述, 一个固有的发育程序支配着整个生命周期中神经干细胞的转录动态。

除了固有的老化程序外, 来自邻近巢 (小生态) 的细胞, 甚至是远端器官的环境因素, 也会影响神经干细胞的状态和命运^[68]。海马巢的转录动力学观察揭示了与年龄相关的神经干细胞、祖细胞和小胶质细胞的数量和分布的变化^[69]。随着年龄的增长, 小胶质细胞在脑室下区的神经源巢中逐渐被激活, 分泌促炎细胞因子, 导致神经干细胞处于不利的环境中, 随后减少神经发生^[70]。在脑室下区附近, 脉络丛能严格调节年龄相关行为, 阻断脉络丛的 IFN-I 信号可减轻慢性神经炎症, 恢复认知功能和海马神经发生^[71]。此外, 脉络丛转录组和分泌体 (在脑脊液中循环的蛋白质) 在不同年龄有不同的表达, 这些变化直接影响神经干细胞的行为和命运^[72]。

由于老化对神经干细胞有巨大影响, 许多工作都集中在识别可能重置老化时钟的机制上。运动、热量限制和异种慢性血液置换等系统性操作已经证明, 重新激活内在程序是可能的, 以便使神经干细胞和大脑恢复活力^[73-74]。通过异时异种共生^[75]或年轻的血浆注射^[76], 可以使年老的神经干细胞恢复活力。

在血液发现了如促衰老 (CCL11、b2- 微球蛋白^[77-78]) 或恢复活力 (GDF11、TIMP2^[75,79-81]) 的系统因素, 分别阻断或诱导上述因子会带来令人激动的各种可能, 可对抗与年龄相关的神经发生和认知功能的下降。最近, 病毒介导的齿状回中 10-11 易位 -2 (Tet2) 甲基胞嘧啶双加氧酶的过度表达能够通过增加参与 DNA 甲基化的 5- 羟甲基胞嘧啶的产生,

来拯救海马神经发生和增强认知, 提示表观遗传可介导神经干细胞的复状^[82]。此外, 用白藜芦醇 (一种与 Sirtuins 活化和长寿相关的分子) 治疗 6 个月大的小鼠, 可诱导海马神经发生, 以及大脑可塑性和认知的增强^[83]。

6 激活成年内源性神经发生修复脊髓损伤

脊髓损伤具有触发室管膜细胞增殖特性及多向分化潜能的重大变化。不同的脊髓损伤模型如挫裂伤、挤压伤、保存中央管完好的部分切割伤等, 及不同的损伤程度, 均可导致室管膜细胞广泛增殖^[84-87], 这个过程是对损伤的一个根本性的保守反应^[88]。脊髓损伤后室管膜细胞增殖可导致神经干细胞的数量显著增加^[89]。学者们利用谱系追踪技术, 预先分别标记少突胶质细胞的祖细胞、星形胶质细胞和室管膜细胞, 对脊髓损伤后它们的命运进行追踪研究, 结果提示, 在种群水平上, 脊髓损伤后室管膜细胞是唯一具有多潜能性的细胞种群^[84,88-89], 即脊髓损伤后, 室管膜细胞产生了大量组成胶质瘢痕核心区域的星形胶质细胞和分散于白质内的少突胶质细胞, 几乎没有神经元的产生。研究表明, 除了神经干细胞内在的特性, 神经源巢或局部微环境, 如相邻细胞、生长因子、细胞因子、循环信号等, 都协同调节干细胞的存活、增殖、分化^[90]。

脊髓和脑创伤后, 损伤区充满各种炎性因子、抑制因子、缺氧和水肿等, 就像盐碱地, 这种恶劣的微环境抑制了神经发生。

如何调控损伤局部微环境, 激活处于静息状态的内源神经干细胞增殖及定向分化为神经元, 重建受损神经网络, 是修复脑和脊髓损伤亟待解决的关键问题。为了解决上述问题, 李晓光团队经过二十多年的研究, 提出了成年内源性神经干细胞孵化学说: 中枢神经系统损伤局部的微环境 (充满炎性的、缺氧和水肿) 就像土壤 (盐碱地) 一样, 内源性神经干细胞就是蛰伏的种子, 改善损伤或疾病局部微环境土壤 (盐碱地变成黑土地) 可以激活种子内源性神经干细胞, 募集并迁移至病损区域, 增殖分化为神经元并功能性地整合入宿主环路中。在他们的研究中, 经过修饰与表征的生物材料支架不仅起到桥梁的支撑性作用, 还可持续地向损伤区递送神经营养因子, 旨在创造一个有利于再生的微环境。结果证明, 在 NT-3 壳聚糖支架创造的微环境下, 内源性神经干细胞被激活, 迁移至损伤区, 分化且成熟为功能性神经元, 重新与宿主脊髓或脑建立起功

能性神经环路, 最终导致功能障碍恢复^[12,91]。这些研究向成熟神经元不能再生这一传统观点发出了挑战。

7 展望

过去几年对神经干细胞生物学的研究大大增加了人们对在生理和病理环境中控制神经干细胞行为的分子机制的理解。神经干细胞在静息和活化之间的微妙平衡很容易因不同的刺激而改变, 并可用于在体外和体内更好地操纵神经干细胞的命运。在成年哺乳类脊髓内存在内源性神经干细胞, 通过原位调节内源性神经干细胞来修复脊髓损伤并促进功能恢复是最具前景的治疗策略。中枢神经系统损伤后, 诸多不利于神经修复因素的存在使得单一的神经再生策略很难取得显著效果, 这也提示如何通过生物材料支架改善或重塑再生微环境, 安全地激活成年内源性神经发生, 可能才是治疗中枢神经系统损伤的关键。

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