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## 胞外基质对神经干细胞增殖和分化的调控作用

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**摘要:**胞外基质(ECM)作为细胞微环境的关键组分,通过物理机械特性与生化信号传导协同影响神经干细胞的行为,而神经干细胞(NSCs)的增殖与分化调控稳态是神经发育、损伤修复及神经退行性疾病治疗的核心问题。文章系统综述了ECM主要成分及其降解产物对NSCs增殖、分化和迁移的调控机制,重点分析其通过物理支架功能、与细胞表面受体相互作用调节信号传导、机械特性影响以及释放结合生长因子等方式,精准调控NSCs增殖、分化与迁移,以助推ECM调控NSCs行为进而影响神经发育、损伤修复及神经退行性疾病的新理解,为ECM应用于神经修复与再生医学领域提供更多理论基础。

**关键词:**神经干细胞;胞外基质;神经退行性疾病;细胞治疗

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神经系统疾病包括一系列影响中枢和外周神经系统的衰弱状态,导致神经组织的进行性损伤和丧失<sup>[1]</sup>。这些疾病包括神经退行性疾病,其典型特征是异常蛋白质聚集体的积累和特定神经元群体的逐渐丧失<sup>[2]</sup>。目前治疗神经系统疾病的方法主要集中在管理症状和减缓疾病进展上,而不是解决潜在病理<sup>[3]</sup>。药物治疗可缓解部分症状,但往往疗效有限并存在副作用,如治疗帕金森病(PD)的多巴胺能药物、治疗阿尔茨海默病(AD)的胆碱酯酶抑制剂和治疗多发性硬化症(MS)的免疫调节药物<sup>[4-6]</sup>。综上,目前神经系统疾病治疗方案因病因尚未完全明确且现有疗法存在局限性,难以实现神经再生和功能的全面恢复,因此,迫切需要开发能够促进神经再生的创新治疗方法。

利用干细胞的自我更新和分化成不同类型细胞的能力,以干细胞为基础的治疗策略已成为治疗

神经系统疾病潜在病理生理学的可行选择。其中神经干细胞(Neural stem cell, NSCs)在神经系统的发育、维持和修复中扮演着至关重要的角色,在胚胎发育阶段,它们是生成大脑和脊髓神经细胞的源头<sup>[7]</sup>。成年后的NSCs主要存在于海马齿状回(Dentate gyrus, DG)、嗅球(Olfactory bulb, OB)和侧脑室下区(Subventricular zone, SVZ),参与组织再生和修复,对学习、记忆等认知功能至关重要<sup>[8-9]</sup>。它们在治疗神经退行性疾病和损伤方面具有潜力,并可用于建立疾病模型和药物筛选,同时也是细胞治疗和基因治疗的重要工具<sup>[10-11]</sup>。NSCs命运的调控是一个精细控制的过程,依赖于一个复杂的调控网络,从表观遗传延伸到翻译水平,并涉及细胞外基质(Extracellular matrix, ECM)成分。随着研究的持续深入,研究人员发现ECM在神经发育和疾病中的作用远比预期的要复杂。ECM的特定组分能够通

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过与细胞表面受体结合,激活或抑制信号传导途径,进而影响NSCs的行为<sup>[12]</sup>。此外,ECM的动态变化对NSCs的微环境有着显著的影响,这些变化可能与神经系统的发育阶段、年龄以及疾病状态有关<sup>[13]</sup>。如在AD病理状态下,ECM的变化包括硫酸软骨素蛋白多糖(CSPGs)表达增加且与A $\beta$ 斑块和神经原纤维缠结密切相关,胶原蛋白(Collagen)的表达和交联发生变化影响神经元存活和功能并参与神经炎症反应,以及纤连蛋白和层粘连蛋白出现异常表达和分布影响细胞黏附、迁移和信号传导,进而影响神经元功能和神经网络稳定性<sup>[14]</sup>。可见,NSCs命运受ECM多成分交互作用及机械/生化信号整合调控,ECM组分的动态变化与神经发育阶段、年龄及疾病状态紧密相关,并在神经系统发育、维持及修复中扮演重要角色。

本文梳理整合了研究人员关于ECM多组分交互作用影响NSCs行为的文献,阐明ECM在NSCs命运调控中的关键作用机制,为ECM应用于神经发育与再生领域提供细胞机制支撑。

## 1 胞外基质的组分与作用

ECM是细胞外微环境的关键组成部分,在细胞形态、增殖、分化及组织稳态中发挥重要作用。在哺乳动物体内,ECM约占蛋白质组的1.0%~1.5%,主要包含三大类成分:Collagen、弹性蛋白(Elastin, ELN)等结构蛋白;非胶原糖蛋白如层粘连蛋白(Laminin, LN)和纤连蛋白(Fibronectin, FN);以及糖胺聚糖(Glycosaminoglycan, GAG)与蛋白聚糖(Proteoglycans, PGs)<sup>[15-16]</sup>。其中,Collagen和ELN等结构蛋白与PGs共同构成ECM的基本骨架,并形成纤维网状复合物;而非胶原糖蛋白则通过直接或间接与细胞表面受体(如整合素)结合,将ECM与细胞内外连接成有机整体<sup>[17]</sup>。此外,ECM蛋白通过糖基化、共价交联和蛋白酶解等翻译后修饰,并结合大量细胞因子和生长因子,不仅为细胞提供物理支撑,还作为信号分子激活下游通路调节细胞生存、增殖、分化及迁移等行为<sup>[18-20]</sup>。因此,ECM通过其复杂的空间结构和动态信号调控,在细胞发育、组织稳态维持及病理过程中扮演核心角色。

## 2 ECM通过PI3K/Akt等信号通路调控NSCs的增殖

ECM在NSCs的增殖过程中发挥着至关重要的

作用,ECM不仅为NSCs提供了物理支架,还通过与细胞表面受体的相互作用,调节细胞生长因子信号传导和细胞行为。ECM的机械特性,如刚度和弹性,也显著影响NSCs的增殖能力,较高的基质刚度通常与细胞增殖和生存率相关<sup>[21]</sup>。在成年海马区,整合素 $\beta$ 1通过FAK/Src通路维持NSCs的静止状态;而在损伤后,FAK过度激活会导致NSCs异常增殖。ECM中的LN与整合素结合,促使磷脂酰肌醇3-激酶p85和黏着斑激酶发生磷酸化,促进NSCs的增殖<sup>[22]</sup>。研究人员开发了一种多功能脱细胞脊髓源性细胞外基质(dSECM),从dSECM中持续释放的胶质细胞源性神经营养因子(GDNF)通过激活PI3K/Akt和MEK/Erk通路促进轴突发生和髓鞘再生<sup>[23]</sup>。综上所述,ECM通过提供物理支持、调节信号传导、响应机械特性以及释放生物活性因子等多种方式,全面调控NSCs的增殖过程,为神经再生医学提供了重要的理论基础和潜在的应用策略。

## 3 YAP/FGF/BDNF等细胞因子多维度调控NSCs的分化

ECM对NSCs的分化起着至关重要的作用,它不仅提供了一个物理支撑框架,还通过与细胞表面受体如整合素相互作用,激活特定的信号传导途径,从而影响NSCs的分化。在胚胎发育早期,脊髓ECM的纤维直径较粗、溶胀率较高,通过整合素 $\alpha$ 6 $\beta$ 1与LN的结合,激活FAK/Src通路,促进NSCs向神经元分化<sup>[24]</sup>。在基因表达层面,Matrigel增强ECM-受体相互作用和YAP转录因子的活性,促进糖脂代谢,进而增强NSCs增殖和神经分化;Poly-L-lysine(PLL)则上调胶质细胞分化和氨基酸代谢相关基因,促进星形胶质细胞分化<sup>[25]</sup>。ECM的物理特性,如刚度和弹性,能够指导NSCs向特定细胞系分化,较软的ECM促进向神经元的分化,而较硬的ECM促进向胶质细胞的分化<sup>[26]</sup>。此外,ECM还能够结合和释放生长因子,如纤维生长因子(FGF)和脑源性神经营养因子(BDNF),这些因子对NSCs的分化方向具有决定性影响<sup>[27-28]</sup>。ECM中的特定成分,如LN和Collagen,也直接参与调节NSCs的分化过程,通过影响基因表达和细胞内分子网络来控制神经干细胞的命运<sup>[29]</sup>。因此,ECM是神经发育和再生过程中的一个关键调节因素,其对NSCs分化的影响是多方面的,涉及从细胞黏附到细胞信号传导,再到细胞命运决定的各个层面。

#### 4 ECM通过PI3K/Akt和Wnt等信号通路调控 NSCs 迁移

细胞通过调节与基质膜(BM)结合的相关蛋白如LN的量和分布来响应ECM的变化起到重塑细胞骨架的作用<sup>[30]</sup>。LN作为基底层的主要成分,与细胞表面受体如整合素和突触蛋白相互作用,其中LN的短臂参与形成分子网络,而长臂的球状结构域介导与整合素受体的相互作用,这对于NSCs在神经发生过程中的正确定位和迁移至关重要<sup>[31-35]</sup>。络丝蛋白(Reelin)通过与VLDLR和ApoER2受体结合激活PI3K/Akt信号通路,促进NSCs的迁移和成熟<sup>[36]</sup>;ECM通过HSPGs稳定Wnt配体,激活 $\beta$ -catenin核转位,在低氧条件下,HIF-1 $\alpha$ 诱导Wnt3a表达,上调MMP-9,促进NSCs迁移<sup>[37]</sup>。透明质酸(hyaluronan, HA)与CD44受体结合,可能通过调节ECM的物理性质影响NSCs的迁移<sup>[38]</sup>。ECM的孔隙率和三维结构可调控NSCs的迁移路径,在中风模型中,ECM降解酶MMP-9通过重塑基质孔隙,促进NSCs向损伤区迁移。这些信号分子通过对ECM理化性质的调节进而实现与NSCs表面的特定受体结合,激活或抑制一系列细胞内信号通路,从而作用于NSCs的迁移和成熟发育过程。

#### 5 ECM调控NSCs修复神经损伤

NSCs的微环境对细胞命运决定起着关键作用,NSCs启动分化后,会迁移到需要的区域与ECM相互作用。近年来,干细胞治疗作为神经损伤治疗的前沿策略备受关注。研究者们通过同轴3D打印技术,开发出由不同水凝胶材料构成的新型支架,内层是HA衍生物和N-钙粘蛋白修饰的海藻酸钠双重网络水凝胶,外层是温度敏感明胶和纤维素纳米纤维混合水凝胶,该支架可调控微环境、优化细胞行为,促进大鼠脊髓损伤运动功能恢复<sup>[39]</sup>。还有研究利用低温3D打印Collagen/壳聚糖支架装载胰岛素生长因子-1预处理的NSCs的外泌体,增强创伤性脑损伤后的神经再生<sup>[40]</sup>。此外,从传统脱细胞支架到现代高性能水凝胶等多种模型被用于NSCs移植支架以修复受损的神经系统。早期研究基于壳聚糖/丝素蛋白、神经膜细胞来源的ECM修饰支架,用于弥合大鼠坐骨神经间隙,效果与脱细胞神经移植相似<sup>[40]</sup>。近年来,研究人员开始利用生物技术手段来调控NSCs的增殖和分化,LIN等<sup>[41]</sup>从猪坐骨

神经制备脱细胞神经基质水凝胶(pDNM-G),其支持神经膜细胞增殖,不诱导强烈宿主免疫反应,促进M2型巨噬细胞活化及持续重塑反应,促进神经再生、髓鞘化和功能恢复。还有研究发现新生兔比成年兔更有效地促进神经祖细胞增殖、迁移和神经元分化,促进轴突生长和脊髓类器官再生<sup>[42]</sup>。BARTLETT等<sup>[43]</sup>通过动态机械分析验证,临床级胶原蛋白(3-6 mg/mL)和纤维蛋白(10%-20% v/v)水凝胶可通过调整浓度与中枢神经系统组织的刚度和粘弹性精确匹配,为脊髓损伤修复、脑组织再生及减少植入后炎症反应提供了力学适配的ECM解决方案。近年来,研究者通过开发基于水凝胶、脱细胞基质等生物材料的3D打印支架和生物调控技术,优化NSCs微环境以促进其增殖、迁移、分化和神经再生,并在脊髓损伤、脑损伤中实现了功能恢复。然而免疫原性、规模化生产、功能整合等挑战仍需通过材料创新与技术突破来解决。

#### 6 总结与展望

ECM在NSCs的增殖、分化、迁移及命运重编程中发挥核心作用,既为NSCs提供物理支持,又通过响应机械特性、与细胞表面受体相互作用激活特定信号通路以及释放生物活性因子等多种机制精细调控NSCs的行为,其中ECM的生化信号对NSCs的发育和自我更新等过程至关重要,在神经发育、损伤修复及退行性疾病中均具有不可替代的作用。同时,NSCs通过调节基质膜结合蛋白的表达和分布来响应ECM的变化,因此,ECM与NSCs之间的作用是相互的。在干细胞治疗和生物材料支架的发展中,如3D打印水凝胶支架、pDNM-G和ECM衍生支架有效调控NSCs的发育和行为,可以看到修复受损神经系统的新策略,这些策略有效促进了神经再生和功能恢复。这些生物材料不仅提供了ECM的主要成分,还通过模拟天然组织的超微结构提供了拓扑指导,加深了研究者对NSCs微环境的理解,也为未来的神经再生和功能恢复治疗策略提供了新的基础研究与实践探索方向。

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## Regulation of extracellular matrix on proliferation and differentiation of neural stem cells

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**Abstract:** Extracellular matrix (ECM), as a key component of the cell microenvironment, affects the behavior of neural stem cells through physical and mechanical properties and biochemical signal transduction. The regulation of proliferation and differentiation of neural stem cells (NSCs) is the core issue of neural development, injury repair and treatment of neurodegenerative diseases. This article systematically reviews the regulatory mechanisms of the main components of ECM and its degradation products on the proliferation, differentiation and migration of NSCs. It focuses on the analysis of its precise regulation of NSCs proliferation, differentiation and migration through physical scaffold function, interaction with cell surface receptors to regulate signal transduction, mechanical properties, and release of binding growth factors, so as to promote the new understanding of ECM regulating NSCs behavior and affecting nerve development, injury repair and neurodegenerative diseases, and provide more theoretical basis for the application of ECM in the field of nerve repair and regenerative medicine.

**Key words:** neural stem cells; extracellular matrix; neurodegenerative diseases; cell therapy



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## Study on the inhibitory effect of melatonin and its homologs on *Rhizoctonia solani*

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**Abstract:** Soreshin blight is an important soilborne disease caused by *Rhizoctonia solani*, which causes significant economic losses. In this study, the inhibitory effects of melatonin, 5-methoxytryptamine and 5-methoxyindole on the growth of *R. solani* were detected by the hyphal growth rate assay, the growth of hyphal were observed under an optical microscope, and the hyphal cell apoptosis and death as well as reactive oxygen species were observed. The hyphal cells were stained with the fluorescent dye dichlorofluorescein yellow acetate (DCFH-DA). The changes in reactive oxygen species inside the *R. solani* cells and the apoptosis of mycelial cells and reactive oxygen species in *R. solani* were observed under a fluorescence microscope. Using Hoechst33342/PI fluorescence double staining method to detect the changes in cell viability of *R. solani* after treatment with melatonin and its homologs. The results showed that certain concentrations of melatonin, 5-methoxytryptamine and 5-methoxyindole inhibited the growth of *R. solani* significantly and caused abnormal expansion of hyphal end and localized deformation. The certain concentrations of melatonin, 5-methoxytryptamine and 5-methoxyindole induced apoptosis in the hyphae of *R. solani*, and the apoptosis increases with increasing concentration. Additionally, they induced the accumulation of reactive oxygen species to inhibit the growth of *R. solani*. Therefore, 5-methoxytryptamine and 5-methoxyindole can be selected as functional alternatives to melatonin for plant disease control.

**Key words:** melatonin; 5-methoxytryptamine; 5-methoxyindole; *Rhizoctonia solani*; reactive oxygen species; apoptosis