一些细胞因子对哺乳动物神经干细胞增殖分化的影响

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摘要 神经干细胞(neural stem cells, NSCs)的增殖、分化与中枢神经系统(central nervous system, CNS)的自我更新、神经病理损伤的修复密切相关。细胞因子可以调节NSCs的增殖, 诱导NSCs进行特定分化, 这对于治疗CNS损伤疾病具有重要的临床意义。该文综述了生长因子(growth factor, GF)、白细胞介素(interleukin, IL)、干扰素(interferon, IFN)等常见细胞因子对NSCs增殖和分化的影响及其可能的作用机制。其中, 神经生长因子(nerve growth factor, NGF)、碱性成纤维生长因子(base fibroblast growth factor, bFGF)、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)促进NSCs增殖, IL-1β、IL-17、IFN-α抑制NSCs增殖。IL-1α、血管内皮生长因子(vascular endothelial growth factor, VEGF)、IFN-γ促进NSCs向神经细胞方向分化, TNF-α、IL-1β促进NSCs向神经胶质细胞分化。有些细胞因子仅对增殖或分化有影响, 有些细胞因子对增殖和分化均有影响。此外, 大多数细胞因子的不同亚型产生的效应大致相同, 但少数亚型可能会产生不同甚至相反的效应。

关键词 神经干细胞; 细胞因子; 增殖; 分化; 生长因子; 干扰素; 白细胞介素

Effect of Some Cytokines on the Proliferation and Differentiation of Mammalian Neural Stem Cells

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Abstract The proliferation and differentiation of neural stem cells (NSCs) are closely related to self-renewal and neuropathological lesion repair of the central nervous system (CNS). Cytokines-induced amplification and differentiation of NSCs contribute to the treatment of CNS injury. We here review the impacts of growth factor (GF), interleukin (IL), interferon (IFN) and other cytokines on NSCs proliferation and differentiation and the underlying mechanism. Among them, nerve growth factor (NGF), bFGF, tumor necrosis factor-α (TNF-α) promote NSCs proliferation while IL-1β, IL-17, IFN-α inhibit NSCs proliferation. IL-1α, vascular endothelial growth factor (VEGF), IFN-γ promote neural differentiatiation of NSCs while TNF-α, IL-1β promote glial differentiation. Some cytokines affect either NSCs proliferation or NSCs differentiation, while some have effects on them both. In addition, the effects of different subtypes of most cytokines are roughly the same, but a few may have different and

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even opposite effects.

Keywords neural stem cells; cytokines; proliferation; differentiation; GF; IFN; IL

细胞因子是由免疫细胞(如单核细胞、巨噬细胞、T细胞、B细胞、NK细胞等)和某些非免疫细胞(内皮细胞、表皮细胞、纤维母细胞等)经刺激而合成、分泌的高活性多功能小分子蛋白质。细胞因子参与机体多种重要的生理功能, 如参与免疫应答与免疫调节、刺激造血功能、刺激细胞增殖和分化、诱导或抑制细胞毒作用、诱导凋亡。除此之外, 细胞因子的检测结果常用于解释临床疾病。

神经干细胞(neural stem cells, NSCs)是重要的多能干细胞, 具有强大的分裂潜能和自我更新能力, 在中枢神经系统(central nervous system, CNS)中主要分布于海马齿状回颗粒下层(subgranular zone, SGZ)、侧脑室室下区(subventricular zone, SVZ)以及小脑皮质等处。在成年CNS中, 这些NSCs多处于静息状态, 只有当细胞微环境改变时才能被激活[1]。在不同的微环境中, NSCs可增殖分化为神经细胞和神经胶质细胞, 微环境中不同细胞因子对其增殖能力和分化方向有重要影响。此外, 其他因素如年龄也对NSCs的增殖和分化产生影响[2]。

1 生长因子(growth factor, GF)

GF是具有刺激细胞生长的细胞因子, 其通过与特异性、高亲和力细胞膜受体结合, 调节细胞生长及产生其他效应。在NSCs的生长过程中, 多种GF可单独或者联合发挥作用, 促进NSCs增殖及促进其向神经细胞分化。值得注意的是, 不同种类的GF联合使用时, 作用明显强于单一GF。联合使用GF能明显促进NSC向神经细胞方向分化, 其中, 碱性成纤维生长因子(base fibroblast growth factor, bFGF)与胰素岛样生长因子-1(insulin-like growth factor-1, IGF-1)共同作用效果最为显著, 原因可能是bFGF的促有丝分裂作用与IGF-1有丝分裂间期促分化作用有协同效应[3]。

以神经营养因子(neurotrophin, NT)、bFGF、IGF-1、表皮生长因子(epidermal growth factor, EGF)以及血管内皮生长因子(vascular endothelial growth factor, VEGF)为例进行说明。

1.1 NT

NT是一组对神经细胞生长、分化、凋亡等过程起重要调节作用的蛋白质, 由神经细胞所支配的组织(如肌肉)及神经胶质细胞中的星型胶质细胞产生。NT经逆向轴浆运输到达胞体, 促进神经细胞合成相关蛋白质, 从而产生上述作用。NT主要成员有神经生长因子(nerve growth factor, NGF)、脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)和NT-3、NT-4、NT-5、NT-6[4]等。不同NT产生效应的差异与特定的细胞表面受体有关[5]。NGF广泛存在于人和多种动物体内, 是NT中最早被发现、目前研究最为透彻、具有营养神经细胞和促进突起生长双重功能的一种神经细胞生长调节因子。合适浓度的NGF能促进NSCs的增殖, 当浓度继续增加时则能诱导NSCs分化[6], 可能机制为NGF与其受体TrkA结合使其磷酸化, 激活Ras, 进而引起细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)的活化[7]。近来也有研究表明, NGF的前体物质proNGF通过proNGF/p75NTR信号通路抑制NSCs增殖及促进NSCs向少突胶质细胞前体细胞分化[8]。BDNF是体内含量最多的NT, 分布广泛, 主要在CNS表达, 其中海马和皮质的含量最高。在CNS发育过程中, BDNF对神经细胞的存活、分化、生长起重要作用。同NGF一样, BDNF能浓度依赖性的促进NSCs增殖和分化[9], 这种促增殖和分化作用可能是通过激活Wnt/β-catenin信号通路[10], 或t-TRK-B受体(truncated TRK-B receptor)-MAPK(mitogen-activated protein kinases)-AKT(protein kinase B)-STAT-3(signal transducer and activator of transcription-3)信号通路发挥作用[11]。联合应用NGF和BDNF能显著促进NSCs向神经细胞分化[12]。

1.2 bFGF

bFGF是重要的有丝分裂原, 在CNS中有广泛的生物学效应, 能够参与脑内不同区域神经细胞的生长发育和损伤组织的修复再生, 对神经细胞有重要的营养作用[3,13]。实验表明, bFGF具有强大的促NSCs增殖作用, 可激活CNS不同区域的神经前体细胞(neural precursor cells, NPCs)潜在的再生能力, 并且明显促进内源性NSCs向神经细胞分化。bFGF对NSCs增殖和分化的影响呈浓度依赖性[14-15]。联合应

用NGF、bFGF、BDNF可显著促进体外培养NSCs的增殖和分化[16]。

1.3 EGF

EGF是一种广泛存在于人或动物体内的小分子多肽, 是最早发现的GF, 因其能加速皮肤和黏膜创伤愈合、修补增生皮肤表层细胞而得名。EGF既能显著促进NSCs的增殖, 也能促进其分化为神经细胞和神经胶质细胞[17-18]。现在大多数NSC培养都联合运用bFGF与EGF来提高NSC增殖与分化的效率。另外, 有实验发现, FGF-2和EGF是促进NSCs表达与细胞存活、代谢、黏附、分化等相关的分子标志[19]。

1.4 IGF-1

IGF-1是一种在分子结构上与胰岛素类似的蛋白质, 也被称为“生长激素介质”, 是介导生长激素作用的一种活性蛋白质。在胚胎发生过程中, IGF-1和IGF-1受体在整个CNS均有表达, 它们的mRNAs分布于特定的神经细胞群体[20-21]。胚胎脑组织中IGF-1含量很高, 随着年龄的增长, 除了神经发生活跃的区域(如海马、脑室下层等), 成年脑组织IGF-1含量急剧下降, 与之相反, IGF-1R含量一直保持在高水平, 年龄对其影响不大[22]。以上证据提示, IGF-1在NSCs增殖分化中起到了重要作用。实验表明, IGF-1影响神经细胞增殖。缺乏IGF-1时, 用EGF或FGF-2培养NSCs不能使其形成克隆球; 而在EGF和(或)FGF-2存在的条件下, IGF-1能浓度依赖性的促进CNS增殖, 并且这种促增殖作用与接触IGF-1的时间长短有关。与IGF-1持续性作用相比, 短时间接触更能有效发挥其促增殖作用[23]。此外, 当IGF-1被抗体中和之后, 体内神经细胞形成数目明显减少[24], 表明IGF-1对NSC向神经细胞方向分化有重要作用, 并且这种促分化作用与BDNF有协同作用[25]。

1.5 VEGF

VEGF是胎儿和成人血管发生和血管生成过程中重要的调控因子, FGF、EGF、IL-1、TNF-α等均能使VEGF及其受体表达上调, 提高其生物学活性[26]。VEGF最主要的生物学作用是促进血管和淋巴管来源的内皮细胞生长[27]。在CNS中, VEGF也发挥着神经营养和神经保护的重要作用。它可以刺激神经细胞轴突生长[28], 促进培养的中脑神经细胞存活[29]等。研究发现, VEGF既能在体外, 也能在体内实验中促进大鼠NSCs增殖, 这种促进作用是通过VEGFR2/Flk-1受体完成的, 使用VEGFR2/Flk-1受体抑制剂SU1498能明显阻断VEGF对神经发生的诱导作用。同时, VEGF也能促进大鼠NSCs向神经细胞方向分化以及促进非神经细胞(如内皮细胞)的分化[30]。VEGF在CNS中促进神经发生和血管再生的作用能有效促进脑损伤的修复再生, 具有巨大的应用前景。

2 白细胞介素(interleukin, IL)

IL是一组由多种细胞产生的细胞因子, 因最早在白细胞中发现, 作为细胞间信号传递的分子而得名。IL家族庞大, 目前已经至少发现有38种。IL功能众多, 包括诱导细胞间的相互作用、促进免疫细胞的成熟等。在CNS, 近年来发现, 部分IL可作为促炎细胞因子参与到神经发生的调节, 对NSC的增殖与分化有重要作用。脑部损伤、感染时, 这些促炎细胞因子可促进神经发生, 修复、再生神经细胞。在神经炎症反应达到峰值时, 还起到清除损伤、死亡细胞和恢复神经细胞正常功能的重要作用[31]。在神经炎症反应过程中, 小胶质细胞的激活是重要的一环。颅内发生缺氧、缺血、细菌或病毒感染等情况会诱发相应的神经炎症反应, 激活小胶质细胞, 后者会产生IL-α、IL-1β、IL-6等促炎细胞因子, 参与神经发生的调节[31-34]。

IL-1又称淋巴细胞刺激因子, 是由单核细胞产生的一种多肽。IL-1参与免疫反应、炎症、发热、急性期蛋白质合成等过程, 全身或局部诱发的IL-1可有力地启动、加强、延长CNS疾病的炎症反应。IL-1有IL-1α和IL-1β两种不同亚型。应用放射免疫学技术发现, 人脑海马区的神经纤维及大鼠大脑前皮质、海马、嗅球、小脑脉络丛、下丘脑、纹状体及延髓存在高水平的IL-1β及IL-1受体(IL-1 receptor, IL-1R)[35]。体外实验表明, IL-1α能通过与IL-1R1结合, 激活下游IκB(inhibitor of NFκB)/NFκB1(nuclear factor-κ-gene binding)信号通路, 促进CD1小鼠(一种来自费城癌症研究所的实验小鼠)NSCs增殖[36]。值得注意的是, IL-1R1通路对NSCs的影响与实验动物的年龄密切相关, 5个月龄的IL-1Ra转基因小鼠海马区NPCs的增殖受到显著抑制, 而22个月龄的1L-1Ra转基因小鼠NPCs的增殖未受到明显影响[37]。IL-1β则抑制NSCs增殖, 实验表明, 与对照组相比, 经IL-1β处理过的神

经球直径与体积均显著缩小。进一步实验发现, 加入内源性IL-1R1受体阻断剂后, 前述IL-1β对神经球的影响作用显著降低。IL-1β抑制NPC增殖的作用可能与诱导p38蛋白激酶的磷酸化, 激活p38丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase, p38MAPK), 信号转导通路有关[35]。在分化方面, IL-1α与IL-1β效应相似, 能促进NSCs向神经胶质细胞分化。其中, IL-1β可能通过激活STAT信号通路来发挥作用, 因为实验转染抑制STATs表达的siRNA后, 上述作用可被明显抑制[38]。

IL-6由活化的T细胞和成纤维细胞产生, 是一种多效能细胞因子, 能调节多种细胞功能。IL-6对不同来源的NSCs有不同的效应。IL-6能通过STAT-3信号和bHLH转录因子(helix-loop-helix transcription factors)调节胚胎期小鼠NSCs的增殖分化, 具体为促进NSCs增殖以及向星型胶质细胞分化, 抑制NSCs向神经细胞分化[39]。也有研究得出相反的结论, 如IL-6能与gp130结合, 激活Ras/MAPK信号通路抑制青春期及成年CD1小鼠NSCs增殖[36]; 此外, IL-6促进成年大鼠海马区NPCs向神经细胞分化, 而对其向神经胶质细胞分化没有影响[40-41]。上述差异形成的原因有待研究。

此外, 调节性T细胞能通过分泌IL-10显著促进NSCs增殖, 有望成为缺血性休克的新疗法[42]。相反, IL-17抑制NSCs增殖及减弱NSCs生长为神经球的能力, 同时抑制NSCs分化为星型胶质细胞和少突胶质细胞前体细胞[43]。

3 干扰素(interferon, IFN)

IFN是细胞在受到某些病毒感染后分泌的宿主特异性糖蛋白, 其主要作用是抗病毒、抗肿瘤、抑制细胞增殖以及免疫调节等。IFN可分为三型, 分别为I型、II型和III型。I型IFN主要由白细胞和成纤维细胞产生, 包括IFN-α和IFN-β等; II型IFN又称免疫IFN, 即IFN-γ, 是由有丝分裂原刺激T淋巴细胞所产生。近几年, 新发现的IFN-λ被称为III型干扰素, 主要表达在免疫细胞、部分肿瘤细胞及上皮细胞表面[44]。IFN在NSCs的增殖分化过程中也发挥着作用。

3.1 IFN-α

IFN-α也属于促炎细胞因子, 具有很强的免疫调节作用, 现已广泛用于慢性病毒性肝炎和恶性肿瘤的治疗中。临床研究表明, 长期大剂量使用IFN-α易导致失眠、抑郁、认知功能障碍、记忆障碍等神经精神方面的负面影响[45-47]。实验表明, IFN-α有明显的抑制NSCs增殖的作用, 而对NSCs的分化影响不大, 这可能是IFN-α作为药物使用时导致抑郁症等疾病的诱因之一[48-49]。

3.2 IFN-β

IFN-β, 又名人成纤维细胞IFN, 是治疗多发性硬化症的首选药物[50]。体外实验表明, 小鼠NPCs表达IFN-α/β受体, 但是IFN-β对NSCs的增殖和分化没有直接的作用, 而是通过直接抑制NPCs凋亡来发挥神经保护作用[51]。此外, IFN-β能减少神经炎症反应过程中抗原呈递, 并且抑制小胶质细胞产生促炎细胞因子[52]。进一步研究表明, IFN-β1b能浓度依赖性的促进人NPCs增殖, 且低浓度的IFN-β1b能促进NSCs向神经细胞和星型胶质细胞分化, 高浓度的IFN-β1b则促进NSCs向前少突胶质细胞分化[53]。

3.3 IFN-γ

IFN-γ主要由T淋巴细胞产生。$CD8^+$T细胞能分泌IFN-γ, 以配体–受体特异性结合方式抑制NSCs的增殖[54-55]。同时, IFN-γ能显著促进NSCs的分化[56], 可能与激活JNK信号通路有关[57]。使用不同浓度的IFN-γ处理由胚胎干细胞分化而来的NSCs的实验发现, 与正常分化的对照组相比, 适宜浓度的IFN-γ能改变分化细胞比例, 使神经细胞和少突胶质细胞比例增加, 而星型胶质细胞的比例明显减少[58]。此外, IFN-γ和IFN-β均能抑制神经球增殖, 但是两者中只有IFN-γ可以促进NSCs向神经细胞分化, 而且其抗增殖效应不一定与其促分化效应相关联[59]。

3.4 IFN-λ

IFN-λ由IFN-λ1、IFN-λ2、IFN-λ3和最新发现的IFN-λ4[60]组成。我们的研究发现, 人脑能表达内源性IFN-λ及其受体, IFN-λ的表达水平随神经细胞的分化程度增高而增强[61], 提示IFN-λ可能参与NSCs的增殖、分化。

4 集落刺激因子(colony stimulating factor, CSF)

CSF是一组促进不同发育阶段造血干细胞起增殖、分化的细胞因子, 是血细胞发生过程中必不可少的刺激因子。有研究发现, CSF家族中的部分成员对NSCs的增殖与分化也有一定的刺激作用。下

面就几个相关的CSF加以说明。

4.1 G-CSF

G-CSF能促进NSCs的增殖、增加NSCs的细胞活力[62]。有实验发现, G-CSF在促进NSCs增殖的过程中, 增强了STAT-3磷酸化水平, 从而激活STAT-3的下游通路, 调节NSCs的增殖[62]。此外, G-CSF可通过血脑脊液屏障, 直接抑制NSCs的凋亡, 减少内源性NSCs死亡[63]。G-CSF还能动员骨髓中的$CD34^+$T细胞至外周血[64], 这些细胞能刺激星形胶质细胞分泌VEGF[65], 进一步促进血管生成、改善微循环、发挥神经保护作用[66]。G-CSF还可以通过bHLH转录因子调节NSCs分化[67], 促进NSCs分化成神经细胞和神经胶质细胞。但是在无血清的条件下, G-CSF无法独立启动NSCs的分化[62]。

4.2 促红细胞生成素(erythropoietin, EPO)

EPO是由肾小管周围间质细胞和肝脏分泌的一种细胞因子, 能够促进红细胞生成。体外实验表明, EPO可促进NSCs增殖[68]、抑制NSCs凋亡[69]、促进NSCs向神经细胞方向分化[70]。目前研究较深入的是, EPO对神经发生的促进作用和对神经的保护作用[71]。其促进神经发生的可能机制是通过上调NSPCs(neural stem/precursor cells)中的SOCS-2(suppressor of cytokine signaling-2)水平[72]。SOCS-2是一种细胞因子信号的调节剂。它不仅促进胚胎SVZ神经发生[73], 还能促进海马区神经细胞的轴突生长[74], 这可能是EPO能在神经损伤后增强神经保护作用的一个重要机制。此外, Shingo等[75]还提出, EPO可能通过NF-κB通路促进神经的发生。但EPO对NSCs增殖分化影响的机制还有待于进一步研究。

5 肿瘤坏死因子(tumor necrosis factor, TNF)

TNF主要由活化的巨噬细胞、NK细胞及T淋巴细胞产生, 因其能使多种肿瘤发生出血性坏死而得名。TNF-α的生物学活性占TNF总活性的70%~95%, 因此, 目前常说的TNF多指TNF-α。TNF-α兼具神经保护和神经毒性的双重作用。高浓度的TNF-α对于NSCs具有细胞毒性作用, 甚至会导致NSC的凋亡[76]。较低浓度的TNF-α对NSCs的作用则较为复杂。

有证据表明, TNF-α是体内诱导NSCs的增殖和迁移的重要信号分子, 能促进成人NSCs的增殖。TNF-α促增殖的机理是通过活化IKK/NF-κB信号通路促进NSCs神经球的形成。而活化的NF-κB正反馈细胞产生TNF-α, 二者相互作用, 共同促进NSCs的增殖[77]。除此之外, TNF-α还可以通过调节内源性大麻素信号通路刺激体内NSCs的增殖[78]。关于TNF-α对NSCs分化的影响, 有研究者发现, 小剂量TNF-α可提高人胚胎NSCs分化成少突胶质细胞的能力, 减少NSCs分化为神经细胞的比例[79]。

6 转化生长因子-β(transforming growth factor-β, TGF-β)家族

TGF-β家族由一类结构、功能相关的多肽生长因子组成, 发挥促进或抑制肿瘤细胞的作用。TGF-β家族包括TGF-β、活化素(activin)、骨形态发生蛋白(bone morphogenetic protein, BMP)、生长分化因子(growth differentiation factor, GDF)等。

6.1 TGF-β

TGF-β不仅是一种抗炎细胞因子, 也是调控细胞发育和细胞周期的关键分子[80]。TGF-β对于NSCs增殖的作用目前有争议。有报道发现, TGF-β在体外可以减弱NSCs的增殖[81]。但在体内实验中, TGF-β阻断对NSC增殖没有影响[80]。造成体内外实验结果差异的原因, 可能是体内有其他因子调节NSCs的增殖, 使TGF-β对于NSCs增殖的调节作用无法显现。除此之外, IL-1β可以刺激TGF-β的产生, 且可以激活TGF-β, 故TGF-β也被认为是其他细胞因子影响NPC增殖的下游调节因子之一[82]。TGF-β促进原代培养NSCs的分化[81]。体内实验也证实, TGF-β促进神经的发生, 促进NSCs向神经细胞及神经胶质细胞的转化[81]。TGF-β还可以通过诱导VEGF产生促进神经的发生[83]。而完全激活的小胶质细胞可以分泌IL-6, 通过抑制TGF-β从而抑制神经发生, 但其具体的机制有待进一步的研究[84]。

6.2 BMP

BMP是TGF-β家族的最大亚群, 包括至少20种生长因子, 能够调节神经系统的生长发育。一般来讲, BMP信号能抑制NPC向神经细胞和少突胶质细胞分化, 并促进星形胶质细胞的发生[85]。比如BMP4对于NSCs增殖具有抑制作用, 同时能够促进体外培养的NSCs向星形胶质转化[86], 这种调节作用主要是通过激活Smad(drosophila mothers against decapentaplegic protein)1/5/8信号通路实现的。BMP4以剂量依赖的

方式, 通过BMP-Smad信号诱导新生鼠皮质下双潜能少突胶质细胞–星形胶质细胞祖细胞分化为星形胶质细胞, 抑制少突胶质细胞的分化[87]。也有研究发现, BMP6对NSCs的增殖有抑制作用, 且BMP6能触发NSCs向星形胶质细胞的分化[88]。

7 趋化因子家族(chemokine family)

趋化因子家族是指具有吸引白细胞移行到感染部位的一些具有趋化作用的低分子量(多为8~10 kDa)的蛋白质, 包括IL-8、MCP-1(monocyte chemotactic protein-1)等, 其主要作用是诱导细胞迁移、刺激发育中新血管形成并提供促使细胞成熟的关键信号分子。趋化因子家族对NSCs的主要作用是促进其增殖并诱导分化。一些炎性细胞因子可以诱导某些趋化因子及其受体的表达[89]。比如用IFN-γ和TNF-α分别或联合处理可显著增加特定的趋化因子, 如CXCL1(the chemokine C-X-C ligand 1)、CXCL9和CCL2(C-C chemokine ligand 2)的表达[90]。IL-10和IL-4能上调NPC上一些趋化因子受体如CXCR4(C-X-C chemokine receptor type 4)和CCR5(C-C chemokine receptor type 5)的表达[91]。下面就以CCL2/MCP-1和CXCL12/CXCR4为例进行具体的说明。

CXCL12/CXCR4能促进NSCs的体外增殖[92]。CXCL12可以通过bFGF/EGF信号通路调节趋化因子受体CXCR4的表达。CXCR4通过调节相应的生长因子, 诱导NPC的增殖。但是CXCL12本身无法直接使NPC产生增殖效应[93]。体外实验表明, CXCL12促进了某些NPC的增殖, 就可能是因为CXCR4增强了一些促NPC增殖的生长因子所导致[93]。

NSCs的有效分化被认为依赖于趋化因子CCL2/MCP-1。NPC能在趋化因子CCL2/MCP-1的影响下, 特异性地与血脑屏障内皮相互作用, 在内皮下间隙分化为星形胶质细胞、神经细胞和少突胶质细胞[94]。CCL2对NSCs分化成星形胶质细胞和少突胶质细胞的数量没有太大的影响, 其主要的作用是促进少突胶质细胞的成熟, 特别是在与IFN-γ联合使用时的效果较为明显[90]。除此之外, 趋化因子CXCL9和CCL21也可以促进神经细胞的分化[90]。

8 结语与展望

本文综述一些常见的细胞因子, 如GF、IL、IFN、CSF等对NSCs增殖与分化的影响(表1)。其中, 促进NSCs增殖的细胞因子有NGF、bFGF、VEGF、G-CSF、EGF、TNF-α和EPO等。需要注意的是, EGF与TNF-α促进增殖的作用有明显的浓度依赖性。抑制NSCs增殖的细胞因子有IL-1β、IL-17、IFN-α和BMP等。在促进NSCs分化的细胞因子中, VEGF、bFGF和IL-6主要促进NSCs向神经细胞方向分化, IL-1β主要促进NSCs向神经胶质方向分化。而EGF、G-CSF、TGF-β和CCL2等, 既可以促进NSCs向神经细胞的分化, 也可以促进NSCs向神经胶质细胞的分化。一些细胞因子对于NSCs的增殖和分化均有明显作用, 比如EGF、EPO和TGF-β等。而一些细胞因子只对NSCs的增殖或者只对NSCs的分化有明显的作用, 如IFN-α对NSCs的增殖有明显的抑制作用, 而对NSCs的分化作用不明显。同一类细胞因子一般对NSCs有相似的生理作用, 比如大多数生长因子对NSCs的增殖和(或)分化起促进作用。而某些细胞因子或同一细胞因子的不同亚型可能会产生不同甚至相反的效应, 比如IFN-α有明显的抑制NSCs增殖的作用, 而IFN-β对NSCs增殖作用效果却并不明显。不同细胞因子可能通过同一信号通路产生作用, 如G-CSF和IL-6都可以通过STAT-3信号通路促进NSCs的增殖。而相同效应却不一定通过同一通路产生, 比如都是促进NSCs增殖的效应, TNF-α和EPO可能都是通过NF-κB信号通路促进NSCs的增殖, 而G-CSF和IL-6的促增殖效应可能是由STAT-3产生。除此之外, 同一通路不一定只产生同一种效应。比如IL-1β可以通过STAT-3信号通路促进星形胶质的分化, 而G-CSF可以通过STAT-3促进NSCs的增殖。

干细胞定向诱导分化技术对于治疗某些中枢神经系统疾病具有重要的临床意义[95]。NSCs的体外诱导分化技术已用于多种中枢神经系统疾病动物模型的研究, 如亨廷顿舞蹈症[96]、帕金森病[97-98]、马查多–约瑟夫病[99]、阿尔兹海默症[100]等。田增明等[101]报道, 用人胚胎来源的NSCs移植治疗21例小脑萎缩患者后发现, NSCs移植后患者临床症状有改善。Lindvall等[97]报道, 用人胚中脑组织对帕金森病患者进行的试验性治疗, 观察到移植的神经细胞能在受体大脑内存活并形成功能的联系, 显著而持久地改善帕金森病的临床症状。以上实验均利用了bFGF、EGF等对NSCs进行体外扩增技术以及利用各种细胞因子促使NSCs向多巴胺能神经细胞、胆

表1 一些细胞因子对NSCs增殖分化的影响

Table 1 Effect of some cytokines on the proliferation and differentiation of neural stem cells

细胞因子 Cytokines	实验细胞 Experimental cells	影响 Influence			可能信号通路 Possible signal pathways	参考文献 References
		增殖 Proliferation	向神经细胞分化 Differentiation into neurons	向神经胶质细胞分化 Differentiation into glial cells		
NGF	Pregnant rat NSCs	↑	↑	↑	NGF-TrkA-Ras-ERK	[7,12]
BDNF	CD1 mouse NSCs	↑	↑	↑	Wnt/beta-catenin	[9]
bFGF	Early embryonic mouse NSCs	↑	↑	_		[15]
EGF	CD1 albino mouse NSCs	↑	↑	↑		[17]
IGF-1	BALB/c embryonic mouse NSCs	↑	↑	_		[23]
VEGF	CD1 embryonic mouse NSCs	↑	↑	_	VEGFR2/Flk-1	[30]
IL-1α	Adolescent CD1 mouse NPCs	↑	_	↑	IκB/NFκB1	[36]
IL-1β	Embryonic rat NPCs	↓	↓	↑	p38-MAPK kinase	[35]
	Embryonic mice NSCs	↑	↓	↑	STAT-3 signaling &bHLH transcription factors	[39]
IL-6	Adolescent CD1 mouse NPCs	↓				[36]
	Rat adult hippocampal progenitor cells		↑	_		[41]
IL-17	Embryonic C57Bl/6 mice NSCs	↓	_	↑	p38-MAPK kinase	[43]
IL-10	Adult C57BL/6 mice NPCs	↑				[42]
IFN-α	Male wistar rats NSCs	↓	_	_		[48]
IFN-β	Adult mice NPCs	_	_	_		[51]
IFN-β1b	Human neural precursor cells NSCs	↑	↑	↑		[53]
IFN-γ	Luciferase-expressing transgenic Balb/c mice NSCs	↓	↑	Oligodendrocytes ↑ astrocytes ↓	IFN/IFNR-JNK	[54,56]
G-CSF	Embryonic mice NSCs	↑	↑	↑	STAT-3 signaling pathway	[62]
EPO	Embryonic rats NSCs	↑	↑		Wnt/β-catenin signaling pathway	[68,70]
	Adult mice NPCs	↑			IKK/NF-κB signaling pathway	[77]
TNF-α	Embryonic human NSCs		↓	↑	STAT-3 signaling pathway	[79]
TGF-β	Adult rats NSCs	↓ (*in vitro*)	↑	↑		[81]
BMP4		↓		Oligodendrocytes ↓ astrocytes ↑	Smad 1/5/8 signaling pathway	[86-87]
BMP6	Adult NSCs	↓		↑	REST/BMP6 pathway	[88]
CCL2/MCP-1	Embryonic human NPCs		↑	↑		[94]
CXCL12	Embryonic mice NPCs	↑				[92]

碱能神经细胞、运动神经细胞、γ-氨基丁酸能神经细胞等的分化。此外, 也有学者考虑利用细胞因子刺激内源性NSCs增殖、分化。有研究提示, 哺乳动物中枢神经系统再生能力有限的原因, 并非由于缺乏足够NSCs, 而是由于缺乏刺激NSCs分化所必需的神经因子[102]。许多学者尝试在神经系统损伤局部应用某些刺激因子, 以激活残留于损伤局部内源性的NSCs, 从而完成对神经系统损伤的修复[103]。

总之, 在安全有效的前提下, 如何合理利用细胞因子提高体内外NSCs增殖、分化效率, 使其在基础及临床研究中发挥更大作用, 需要进一步深入探索。

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