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·综述·

趋化因子CX3CL1和受体CX3CR1及其相关的信号通路在神经性疼痛发生发展中的作用研究进展*

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神经性疼痛(neuropathic pain,NP)是指由躯体感觉系统的病变或疾病引起的疼痛,包含多种外周或中枢性疾病的疼痛综合征[1]。表现为自发性疼痛、痛觉过敏以及痛觉超敏,发病率约为6.9%—10%[2]。NP的病因包括代谢障碍(如糖尿病周围神经病变)、病毒感染、自身免疫疾病(如多发性硬化症,格林-巴利综合征)、创伤性神经系统损伤(如脊髓损伤,截肢)、炎症性疾病、遗传性神经病变和通道病变[3]。临床上常用的治疗方法包括药物治疗、康复训练、针灸、按摩等,但效果欠佳,患者对治疗效果满意度低。NP影响日常生活的许多方面,影响患者的健康状况、生存质量和睡眠质量,并可导致焦虑和抑郁。

NP的发生机制非常复杂,其中神经炎症在NP的建立和维持中起着重要作用,主要由促炎细胞因子和趋化因子介导。神经损伤可诱导脊髓内小胶质细胞和星形胶质细胞激活,释放促炎细胞因子(如肿瘤坏死因子和白细胞介素-1β,IL-1β)、生长因子和趋化因子(如C-C趋化因子配体2,CCL2

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和CXC家族趋化因子1,CXCL1)。趋化因子是低分子量蛋白,参与调节白细胞和其他细胞的迁移,影响炎症过程[4]。CX3C趋化因子配体1(C-X3-C motif chemokine ligand 1,CX3CL1)是一种独特的趋化因子,既能以可溶性形式存在,发挥趋化作用,也可作为结合分子以膜附着形式存在。CX3CL1及CX3C趋化因子受体1(C-X3-C motif chemokine receptor 1,CX3CR1)参与多种疾病的病理过程,如肿瘤、关节炎、神经系统疾病,以及NP[5—8]。

本文主要综述CX3CL1和CX3CR1的分布和功能,通过分析其参与调控的信号通路,探讨CX3CL1/CX3CR1在NP发生中对神经元,免疫细胞的影响,以及如何调节神经元-胶质细胞相互作用,以期更深入了解神经炎症对NP的影响。

1 CX3CL1和CX3CR1的分布和形态

趋化性细胞因子根据其氨基端(N端)半胱氨酸的排列方式,可分为CXC、CC、C和CX3C四个亚族[9]。然而,与其他由多个成员组成的子组不同,CX3C子组只由一个已知的成员组成,即CX3CL1。CX3CL1分布于背根神经节和脊髓神经元[10—11],是一种结构独特的趋化因子,既可以作为静态膜结合糖蛋白介导细胞粘附,也可以作为可溶性亚型存在,即具有膜结合性和可溶性两种形式。

可溶性亚型是去整合素和金属蛋白酶(ADAM10和ADAM17)的蛋白水解裂解产物,并表现出趋化特性[12—14]。神经损伤后脊髓神经元中CX3CL1 mRNA的总表达量不变,但膜结合态CX3CL1蛋白表达降低[10,15]。说明神经损伤后与膜结合的CX3CL1发生裂解,从背根神经节(dorsal root ganglion,DRG)和脊髓神经元分泌[11],使可溶性态CX3CL1升高,激活脊髓小胶质细胞[16]。

CX3CR1是CX3CL1的唯一受体,分布于中枢神经的小胶质细胞,DRG中的卫星细胞和周围神经的巨噬细胞[17—18]。由于CX3CR1的胞外区含有大量带负电荷的侧链,在生理和病理条件下,CX3CL1中的带正电荷氨基酸可以捕获和粘附表达CX3CR1的细胞。

2 CX3CL1和CX3CR1的功能

CX3CL1主要表达于神经元[19],CX3CL1/CX3CR1轴通过单核/巨噬细胞浸润、神经元-小胶质细胞的相互作用和神经元兴奋性等多个病理过程,参与NP的产生和维持。

2.1 CX3CL1、CX3CR1对神经元的影响

NP参与调节突触可塑性和神经元兴奋性变化。外周异位冲动长期、持续兴奋所触发的神经元活动可特异性地持续改变突触的结构和功能,这种神经活动依赖的突触结构和功能的变化称之为长时程突触可塑性,是神经病理性疼痛产生和维持的主要机制之一。突触传递长时程增强(long-term potentiation,LTP)是突触可塑性的主要模式,疼痛相关中枢(脊髓背角、前扣带回、海马、杏仁核等)均可出现突触可塑性现象。

CX3CL1/CX3CR1可使突触结构和功能发生改变,继而使周围神经、DRG的初级感觉神元以及脊髓的中枢神经元发生敏化,神经兴奋性增强,在神经痛的发展和维持中起重要作用[20—22]。当神经损伤后,CX3CL1激活CX3CR1受体,诱导小胶质细胞释放白细胞介素-1β(interleukin-1 β,IL-1β),调节突触后神经元的N-甲基-D-天冬氨酸(N-methyl-D-aspartic acid receptor,NMDA)信号,导致一种二十烷类信使的释放,最终增加突触前神经递质的释放,从而产生痛觉过敏[23]。坐骨神经强直刺激(tetanic stimulation of the sciatic nerve,TSS)可使大鼠产生痛觉过敏,并在脊髓背角产生持续3h以上的LTP。使用CX3CR1中和抗体阻断CX3CL1/CX3CR1信号通路或敲除CX3CR1基因可缓解大鼠TSS诱导的痛觉过敏及LTP。相反,使用外源性CX3CL1可显著增强LTP[24]。Ru等[25—26]研究发现,在HIV-1感染的神经痛小鼠模型中可见CX3CL1上调及神经元变性,导致抑制性神经元上的兴奋性突触的丢失,造成感觉神经元的过度激活,产生神经性疼痛。除此之外,神经元损伤时CX3CL1使脊髓背角神经元及DRG神经元细胞凋亡、兴奋性增加[27—28],从而产生NP。Wang等[29]研究发现,在大鼠神经痛模型中CX3CL1表达增加,DRG小直径神经元的兴奋性显著增加。而鞘内注射CX3CL1中和抗体可减弱DRG神经元增强的兴奋性和痛觉过敏。最后,周围神经损伤后,损伤部位释放CX3CL1,使CX3CR1+巨噬细胞聚集并产生趋化因子,导致局部神经元敏化及炎症反应,改变痛觉轴突的感觉传导特性,导致其兴奋性增高[30]。

CX3CL1/CX3CR1轴还可通过多种途径参与神经元-小胶质细胞的相互作用,在神经病理性疼痛中发挥作用。CX3CL1/CX3CR1可激活小胶质细胞,使其释放多种调节递质,包括神经递质、促炎细胞因子、趋化因子,作用于脊髓背角神经元,诱导神经元活动异常,从而导致痛觉过敏[31]。

另外,神经损伤后小胶质细胞局部增殖部分受CX3CL1信号控制,与单核细胞浸润无关。敲除CX3CR1可见小鼠脊髓小胶质细胞增殖减少,痛觉过敏减轻[32]。CX3CL1/CX3CR1轴在脊髓背角和DRG通过参与多种信号通路促进了NP的产生和维持。

2.2 CX3CL1/CX3CR1对周围神经及DRG单核细胞的影响

最新的研究发现与中枢神经系统和周围神经系统损伤后相关的免疫反应可能导致多种疼痛状态[22]。CX3CL1调节神经痛的能力不仅依赖于其性质,还与其自身对白细胞动态平衡的影响有关,如CX3CL1和CX3CR1表达的上调可加强白细胞在受损区域的聚集。在周围神经,CX3CL1由内皮细

胞表达，CX3CR1是巨噬细胞的高度特异性标志物，是维持固有黏膜层巨噬细胞稳态的关键成分。化疗后周围神经损伤导致CX3CR1+单核细胞/巨噬细胞招募增加，通过释放活性氧激活TRPA1通道，使痛觉神经元敏感，从而引发疼痛反应[33]。

另外，CX3CL1作为一种粘附分子，可在神经损伤后使内皮细胞粘附特性发生改变，促进免疫细胞通过血管内皮细胞在炎症部位的快速积累，并使CX3CR1+单核/巨噬细胞浸润到坐骨神经，通过促进单核/巨噬细胞浸润神经以及局部小胶质细胞增殖诱发NP[34]。啮齿类动物中，长春新碱治疗后产生的痛觉过敏被证明与坐骨神经巨噬细胞浸润有关[33,35]。在巨噬细胞中，CX3CL1以CX3CR1依赖的方式促进活性氧(ROS)的形成，激活感觉神经元上的TRPA1受体（瞬时受体电位A1，transient receptor potential A1)，诱发神经痛[33]。使用CX3CL1/ CX3CR1抗体可有效抑制单核细胞在DRG聚集，减少DRG神经元凋亡，缓解痛觉过敏[36—37]。

3 CX3CL1/CX3CR1在神经性疼痛调控中参与的信号通路

3.1 P2X7R/CatS通路

神经损伤后，小胶质细胞嘌呤受体P2X配体门控性离子通道7（P2X ligand-gated ion channel 7 receptor，P2X7R）被三磷酸腺苷（ATP）激活后启动NF-κB信号转导，释放组织蛋白酶S（cathepsin S，CatS），裂解神经元膜结合的CX3CL1趋化因子结构域，释放可溶性CX3CL1。而后，CX3CL1通过与小胶质细胞膜上CX3CR1结合，进一步激活NF-κB信号转导，促进其释放炎症介质，使脊髓背角神经元兴奋性增高，从而产生NP[38]。可见，P2X7R/CatS/CX3CL1在周围神经损伤后形成正反馈回路诱发NP。鞘内注射CX3CR1中和抗体能够抑制CX3CL1诱发的小胶质细胞激活，缓解NP[39]。阻断P2X7R或CX3CR1可通过阻止脊髓背角神经元释放趋化因子CX3CL1或小胶质细胞释放炎性介质，缓解NP[40—41]。

3.2 p38 MAPK通路

p38 丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）是CX3CL1/CX3CR1信号转导过程中重要的激酶，通过调节脊髓小胶质细胞的活性在NP中发挥作用。神经损伤后，脊髓背角神经元释放的CX3CL1与小胶质细胞的CX3CR1结合后，启动p38 MAPK通路，促进小胶质细胞释放促炎因子，如TNF-α，IL-1β和IL-6，调节脊髓背角突触的传递[42—43]。在脊神经结扎（spinal nerve ligation，SNL）大鼠模型中鞘内注射CX3CR1中和抗体，降低了脊髓小胶质细胞中p38 MAPK的激活水平，同时抑制痛觉过敏[44]。相反，鞘内注射CX3CL1则可激活p38 MAPK通路，诱发正常大鼠出现痛觉过敏。另外，Lee等[45]研究表明，在坐骨神经慢性压迫模型（chronic sciatic nerve constriction model，CCI）中IL-6通过p38 MAPK通路增加脊髓内小胶质细胞CX3CR1表达，使其对CX3CL1的反应增强。阻断CX3CR1或抑制p38 MAPK的激活均可预防CCI或外源性IL-6诱发痛觉过敏。因此可见，阻断脊髓小胶质细胞的CX3CR1或抑制p38 MAPK的激活可缓解NP。

CX3CL1还可以通过调节DRG中巨噬细胞的p38 MAPK通路参与NP的形成。在化疗药物诱发的周围神经痛模型中，紫杉醇可上调DRG中CX3CL1，激活CX3CL1/CX3CR1轴，使CX3CR1+巨噬细胞聚集并启动p38 MAPK信号通路，导致DRG内caspase-3(半胱氨酸天冬氨酸酶3)激活及神经元凋亡[37]，从而诱发化疗后的周围神经痛。鞘内注射CX3CL1中和抗体能够抑制长春新碱诱发的DRG单核细胞聚集以及神经元凋亡，缓解疼痛。

另外，NP病理过程中，单核细胞CCR2与CX3CR1两个受体之间可能通过p38 MAPK通路存在相互作用。在长春新碱诱发的神经痛模型中，CCR2的拮抗剂可在CX3CR1基因敲除小鼠中发挥缓解神经痛的作用，而对正常小鼠无明显止痛作用。并且在CX3CR1基因敲除小鼠坐骨神经中发现，单核细胞CX3CR1下调会通过p38 MAPK通路上调CCR2的表达[35]。

3.3 NF-κB通路

NF-κB（nuclear factor kappa-B，NF-κB）是调节免疫基因和炎症基因的关键信号转导分子，通常在NP的早期被激活[46]。CX3CL1/CX3CR1轴与NF-κB通路的相互作用在神经痛的形成和发展中起关键作用。NF-κB通路的激活可引起脊髓小胶质细胞的激活和其受体CX3CR1上调[47]。Wang等[48]研究表明，在TSS诱发的痛觉过敏模型中，双侧背角NF-κB和CX3CR1表达水平显著增高。而抑制NF-κB或阻断CX3CR1可防止NP的发展。在腰椎间盘突出（lumbar disc herniation，LDH）模型中，LDH压迫神经根引起使DRG中CX3CL1表达增多，使DRG神经元NF-κB通路激活，诱导NP[49]，抑制NF-κB通路可显著减轻LDH诱导的痛觉过敏。

目前认为，NF-κB与CX3CL1/CX3CR1轴的调节作用是相互的。一方面，NP可增加NF-κB p65在CX3CL1启动子区域的招募，使H4的乙酰化水平升高[29]，增强CX3CL1的作用，阻断NF-κB可下调CX3CL1/CX3CR1信号通路的表达；另一方面，CX3CL1/CX3CR1轴可增强NF-κB水平，从而持续上调CX3CL1-CX3CR1轴的作用，使用中和抗体阻断CX3CR1可导致NF-κB表达下降[48]。

3.4 其他通路

3.4.1 MMP通路：在SNL模型中，脊髓NF-κB/基质金属蛋白酶9（matrix metalloproteinase 9，MMP-9）通路激活，促进促炎细胞因子的释放，参与了SNL诱导的NP[50]。在CCI模型中，DRG中MMP-9及CX3CL1蛋白表达显著升高。使用

基质金属蛋白酶抑制剂-1(TIMP-1)或MMP-9 siRNA抑制MMP-9可降低CX3CL1的表达[51]。

3.4.2 Wnt/β-catenin通路:神经损伤可引起Wnts的快速、持久的上调,并激活Wnt/β-catenin信号通路[52]。Wnt/β-catenin通路是典型的Wnt通路[53],在脊髓背角神经元中启动时使CX3CL1在脊髓的水平显著升高,激活小胶质细胞,导致神经炎症和慢性疼痛敏化[54]。使用WNT激动剂可上调大鼠脊髓CX3CL1/CX3CR1水平,诱发痛觉过敏。CX3CR1中和抗体可预防WNT激动剂引起的痛觉过敏[55]。

3.4.3 ERK通路:Sun等[56]研究表明,在大鼠SNL模型中,阻断CX3CR1可显著降低ERK5蛋白激酶5(extracellular regulated protein kinases 5,ERK5)激活水平,敲除ERK5基因可抑制SNL及外源性CX3CL1诱导的痛觉过敏和脊髓小胶质细胞激活,证明CX3CL1/CX3CR1轴可启动ERK通路的激活,参与NP的形成。另外,ERK抑制剂可抑制奥沙利铂诱导的ERK磷酸化和周围神经痛。在大鼠CCI模型中,抑制脊髓P2X7R的表达可使CX3CL1/CX3CR1活动减弱,进而抑制ERK通路的启动,缓解NP。

3.4.4 Akt1通路:紫杉醇可上调大鼠脊髓背角和DRG的CX3CR1和磷酸化Akt1(丝氨酸-苏氨酸激酶1)的表达,抑制Akt1通路激活可显著减轻紫杉醇诱导的痛觉过敏。CX3CR1中和抗体抑制脊髓背角和DRG中Akt1通路的激活,减轻痛觉过敏[57]。

3.4.5 Notch通路:Notch信号通路通过CX3CL1/CX3CR1激活中枢神经系统的小胶质细胞释放各种促炎细胞因子(TNF-α、IL-1β、IL-6),诱发神经炎症反应及NP。抑制Notch信号通路,能降低小胶质细胞CX3CR1信号通路的激活,减少促炎细胞因子的释放,减轻神经元损伤,减轻化疗药物引起的NP[58]。

4 小结与展望

神经性疼痛作为一种常见多发疾病,准确的诊断和病因研究对神经性疼痛的治疗起着至关重要的作用。综上所述,CX3CL1/CX3CR1通过多种信号通路,影响单核细胞迁移、神经元与小胶质细胞的相互作用及突触可塑性和神经元兴奋性,参与了NP的形成与维持。

除上述关于CX3CL1/CX3CR1轴的基础研究外,目前有相关临床研究[59]表明钙通道拮抗药(加巴喷丁和普瑞巴林)、钠通道阻滞药(奥卡西平)均可以使带状疱疹后遗神经痛患者脑脊液中CX3CL1的水平降低,患者的疼痛程度较前减轻。治疗前患者脑脊液中CX3CL1的水平越高,患者的疼痛程度越重,表明CX3CL1可能参与带状疱疹后遗神经痛的诱导和维持。

研究CX3CL1参与的趋化因子-细胞因子网络参与NP的机制可提供新的治疗策略。如坐骨神经强直刺激后,阻断CX3CL1和IL-18可缓解TSS诱发的痛觉过敏并抑制IL-23和IL-23R上调[60]。其中,CX3CL1主要位于神经元;IL-18和CX3CR1位于小胶质细胞;IL-18R主要位于星形胶质细胞。脊髓中CX3CL1、IL-18和IL-23信号通路的相互作用,促进NP的发生和发展。

对于不同的细胞类型和解剖结构,CX3CL1/CX3CR1在NP发展中发挥的作用可能不同。在选择性神经损伤模型(spared nerve injury,SNI)中,CX3CL1/CX3CR1对NP的影响与其他研究相反。CX3CR1基因敲除小鼠在SNI术后痛觉过敏的持续时间延长,而坐骨神经内注射CX3CL1却延缓SNI术后引起的痛觉过敏[61]。出现该差异的原因尚不明确,可能是因为趋化因子及其受体在中枢和周围神经系统广泛分布于胶质细胞和神经元等不同细胞当中。未来需要使用cre-lox系统进一步确定CX3CL1/CX3CR1在NP中发挥的特定作用。

此外,目前研究较多的针对神经病理性疼痛的干细胞治疗方法也有可能与CX3CL1/CX3CR1相关。干细胞可通过多种途径镇痛,其中一条重要途径为调控炎症微环境,缓解炎症进程,促进组织再生。有研究表明鞘内注射骨髓间充质干细胞(bone marrow mesenchymal stem cells,BMSCs)可导致TNF α、IL 1β等炎症因子的表达下调,减轻神经炎症反应,缓解中枢敏化进而减轻疼痛[62]。同时干细胞移植可明显降低巨噬细胞及局部小胶质细胞内磷酸化-p38 MAPK的表达,并修复损伤的血-脊髓屏障,参与缓解神经痛[63]。本文论述了CX3CL1/CX3CR1参与NP发生的多种可能通路及效应,而干细胞治疗NP的多种机制亦是通过这些通路发挥其相应作用。故研究趋化因子CX3CL1及其受体CX3CR1可能为干细胞治疗及神经再生等方面的研究提供了新的思路。今后可开展此方面研究。

综上所述,研究趋化因子CX3CL1和受体CX3CR1对NP发生的信号通路及其调控作用,有助于为治疗NP寻找新的靶点,未来可发展针对性治疗,对疗效、安全性等进行深入探讨。

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