趋化因子CCL3在病理性疼痛和阿片耐受中的作用

李凤娇 史永慧 王冬梅*

(福建师范大学生命科学学院, 福建省发育与神经生物学重点实验室, 福州 350108)

摘要 趋化因子配体3[chemokine (C-C motif) ligand 3, CCL3]是趋化因子家族的一员, 广泛表达于神经系统和免疫系统中。研究表明, CCL3可通过募集免疫细胞、激活细胞内的信号通路以及介导神经元与神经胶质细胞间的相互作用, 从而参与神经病理性疼痛、炎性痛的发生及维持。此外, CCL3还可引起μ型阿片肽受体(mu opioid receptor, MOR)脱敏, 从而影响吗啡等的镇痛作用, 并参与阿片耐受的形成过程。该文综述了CCL3及其受体在病理性疼痛和阿片耐受中的作用。

关键词 病理性疼痛; 趋化因子; CCL3; 阿片耐受

Roles of Chemokine CCL3 in Pathologic Pain and Opioid Tolerance

LI Fengjiao, SHI Yonghui, WANG Dongmei*

(*Fujian Key Laboratory of Developmental and Neurobiology, College of Life Science, Fujian Normal University, Fuzhou 350108, China*)

Abstract CCL3 [chemokine (C-C motif) ligand 3] is a member of the chemokine family and is widely expressed in the nervous and immune systems. Studies have shown that CCL3 plays a role in the occurrence and maintenance of neuropathic and inflammatory pain by recruiting immune cells, activating intracellular signaling pathways and mediating the interaction between neurons and glial cells. In addition, CCL3 can also cause MOR (μ opioid receptor) desensitization, thus affecting the analgesic effects of morphine and participating in the formation of opioid tolerance. This paper reviews the roles of CCL3 and its receptor in pathological pain and opioid tolerance.

Keywords pathological pain; chemokine; CCL3; opioid tolerance

病理性疼痛主要包括神经病理性疼痛(neuropathic pain, NP)和炎性痛(inflammatory pain), 常伴有自发性疼痛、异常性疼痛和痛觉过敏等临床表征[1]。病理性疼痛的治疗非常困难, 临床上一般以药物治疗(如阿片类药物)为主; 然而, 长期使用阿片类药物易引起患者产生药物耐受等严重的不良反应[2]。因此, 通过探究疼痛的发病机制来寻找新的镇痛药物或镇痛手段成为目前疼痛相关研究领域的热点。

趋化因子是一类具有细胞趋化功能的低分子量蛋白, 通过与趋化因子受体结合而发挥生物学功能。越来越多的研究表明, 外周和中枢神经系统中的趋化因子可通过其对应受体介导神经炎症的发生进而参与病理性疼痛的发展过程[3-5]。目前, 已发现50余种趋化因子, 根据其氨基酸序列中前2个保守的半胱氨酸(cysteine, Cys)的相对位置将趋化因子分为CC、CXC、XC和CX3C 4个亚族, 并将趋化因子受体对应地划分为CCR、CXCR、XCR、CX3CR 4类[6]。近年来, CC亚族中的CCL3及其受体趋化因子受体1[chemokine (C-C motif) receptor 1, CCR1]和趋化因子受体5[chemokine (C-C motif) receptor 1, CCR5]被证明

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*通讯作者。 Tel: 0591-22868211, E-mail: dmwang@fjnu.edu.cn

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*Corresponding author. Tel: +86-591-22868211, E-mail: dmwang@fjnu.edu.cn

参与了病理性疼痛的发生过程, 有研究表明鞘内给予外源CCL3可引发大鼠机械性异常性疼痛, 而给予CCL3中和抗体或其受体CCR5的拮抗剂对脊髓CCL3信号进行药理阻断, 可缓解大鼠的痛觉过敏现象[7-8]。因此, 本文就趋化因子CCL3及其受体CCR1、CCR5在神经病理性疼痛、炎性痛及阿片耐受中的作用进行综述, 为寻找新的镇痛靶点提供一定的研究基础。

1 CCL3及其受体CCR1、CCR5

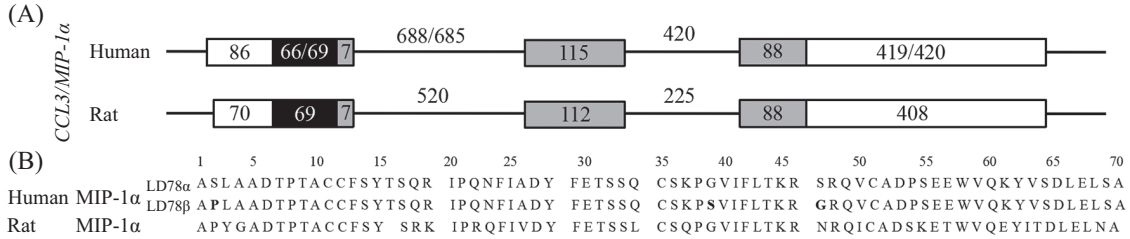
CCL3又名巨噬细胞炎性蛋白-1α(macrophage inflammatory protein-1 alpha, MIP-1α), 属于CC亚族。1988年, 学者们从内毒素诱导的小鼠巨噬细胞的上清液中分离纯化出一种肝素结合蛋白, 并将其命名为MIP-1α[9]。 随后, 科研人员于2000年根据新命名法按照配体结构将MIP-1α命名为CCL3[6]。CCL3由包含3个外显子和2个内含子的基因编码而成, 该基因位于人体第17号染色体、小鼠第11号染色体上[10](图1)。CCL3前体蛋白含有92个氨基酸, 成熟蛋白含有69个氨基酸, 其相对分子质量约为8 kDa[9]。在正常条件下, CCL3在体内的合成水平较低, 其主要在中性粒细胞中表达。在受到促炎因子或细胞因子如脂多糖(lipopolysaccharide, LPS)、P物质、肿瘤坏死因子-α(tumor necrosis factor-alpha, TNF-α)、白细胞介素-1β(interleukin-1 beta, IL-1β)等的诱导时, 成熟造血细胞、巨噬细胞、淋巴细胞、中性粒细胞、自然杀伤细胞等直接参与免疫反应的细胞以及成骨细胞、小胶质细胞和星形胶质细胞均可产生大量CCL3[10-11]。

CCR1和CCR5是CCL3的主要作用受体, 均为G蛋白耦联受体家族成员, 分布广泛, 在神经元、小胶质细胞、星形胶质细胞以及中性粒细胞等免疫细胞中均有表达[12-13]。当机体受到神经损伤或发生炎症时, CCL3被大量释放并作用于促炎细胞和免疫细胞表面的CCR1和CCR5, 将其中的G蛋白分解为Gα和Gβγ亚基。Gα可诱导磷脂酰肌醇3激酶(phosphatidylinositide 3-kinase, PI3K)途径活化, 而Gβγ亚基可活化磷脂酶C(phospholipase C, PLC)并诱导胞外Ca^{2+}大量涌入, 导致蛋白激酶C(protein kinase C, PKC)活化[10]。

2 CCL3及其受体CCR1、CCR5在神经病理性疼痛中的作用

2.1 外周神经损伤引起的神经病理性疼痛

坐骨神经慢性压迫性损伤(chronic constriction injury, CCI)是常见的神经病理性疼痛模型之一。在CCI小鼠脊髓中, 小胶质细胞来源的CCL3/CCR5通过上调TNF-α、IL-1β以及激活p38丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase, p38 MAPK)信号, 进而参与小鼠神经病理性疼痛的发生, 且该过程可被CCL3中和抗体所逆转[14]。敲除CCR5抑制了CCI引起的神经病理性疼痛; 鞘内注射CCR5选择性拮抗剂MVC(maraviroc)下调了CCI诱导的大鼠脊髓背角和背根神经节(dorsal root ganglia, DRG)中CCR5以及离子钙结合衔接分子-1(ionized calcium binding adapter molecule-1, Iba-1)和胶质纤维酸性蛋白(glial fibrillary acidic protein, GFAP)的表达[15]。此外, MVC还可下调CCI大鼠脊髓背角中p38 MAPK、细胞外调节蛋白激酶1/2(extracellular regulated protein kinases 1/2, ERK1/2)、核因子-κB(nuclear factor kappa-B, NF-κB)的磷酸化水平以及IL-1β、IL-18、IL-6和诱导型一氧化氮合酶(inducible



A: *CCL3*的基因结构。水平线代表内含子序列, 方框代表外显子序列, 其中白色代表未翻译序列, 灰色代表已翻译的前导序列, 黑色代表已翻译的成熟蛋白, 方框内数字为该段序列长度。B: CCL3的氨基酸序列。人类CCL3/MIP-1α分为LD78α和LD78β两种亚型。序列上方的编号每隔5个氨基酸标注一次, 以便于阅读。

A: gene structure of *CCL3*. The horizontal lines represent intron sequences, and the boxes represent exon sequences. White box represents untranslated sequences, gray box represents translated precursor sequences, and black box represents translated mature proteins. The number in the box is the length of the sequence. B: amino acid sequence of CCL3. Human CCL3/MIP-1α is divided into two subtypes, LD78α and LD78β. The numbers above the amino acid sequences are annotated every 5 amino acids for easy reading.

图1 CCL3/MIP-1α的基因结构及氨基酸序列(根据参考文献[10-11]修改)

Fig.1 Gene structure and amino acid sequence of CCL3/MIP-1α (modified from the references [10-11])

nitric oxide synthase, iNOS)等伤害感受性因子的水平，上调脊髓中IL-1RA、IL-18BP和IL-10等抗伤害感受性因子以及DRG中的信号转换器和转录激活因子3(signal transducer and activator of transcription 3, STAT3)的水平，其中STAT3是IL-6和IL-10的关键调节因子[16]。以上结果均表明，CCL3可能通过受体CCR5介导小胶质细胞和星形胶质细胞的活化，激活NF-κB或抑制STAT3影响多种炎性因子的表达，CCL3还通过激活p38 MAPK、ERK1/2信号通路参与CCI诱导的神经病理性疼痛。

感觉神经组织释放高迁移率族蛋白B1(high mobility group box 1, HMGB1)可诱发神经性疼痛。在选择性神经损伤(spared nerve injury, SNI)模型大鼠脊髓背角中，HMGB1、CCL3、CCR1、CCR5表达上调，鞘内注射CCL3中和抗体和CCR1、CCR5抑制剂可缓解神经病理性疼痛和神经炎症；鞘内注射HMGB1中和抗体可抑制CCL3和CCR5的表达水平，说明发生SNI后，HMGB1促进神经元上CCL3的表达，CCL3作用于小胶质细胞上的CCR1、CCR5，进而介导SNI引发的大鼠神经炎症和神经病理性疼痛[17]。

KIGUCHI等[18-20]研究发现，CCL3通过上调IL-1β及激活ERK1/2信号通路介导坐骨神经部分结扎(partial sciatic nerve ligation, PSNL)小鼠模型中神经病理性疼痛的发生。PSNL后，受损坐骨神经区的驻留巨噬细胞和施万细胞活化，*Ccl3*的基因启动子区发生组蛋白乙酰化修饰，从而导致CCL3的表达上调[18]。CCL3募集血源巨噬细胞到受损坐骨神经区，使其与驻留巨噬细胞共同维持IL-1β的高表达，该过程可被尼古丁(巨噬细胞抑制剂)、CCL3中和抗体和小干扰RNA(small interfering RNA, siRNA)-CCR1/CCR5抑制，siRNA-CCR1/CCR5也可阻断ERK1/2的磷酸化[20]。研究发现，PSNL小鼠脊髓背角中*CCL3*/*CCR1*的mRNA表达上调；鞘内使用CCL3中和抗体可缓解PSNL引起的机械和热痛觉过敏[8]。在周围神经损伤(peripheral nerve injury, PNI)引起的神经病理性疼痛模型中，大鼠损伤侧脊髓中*CCL3*/*CCR5*的mRNA水平显著增加，且主要由小胶质细胞表达；鞘内注射CCL3中和抗体和MVC显著缓解了PNI引起的机械痛觉过敏[7]。以上实验结果表明，在脊髓中CCL3通过CCR1、CCR5影响周围神经损伤引起的神经病理性疼痛。然而PSNL和PNI模型中CCR1和CCR5表达变化的不一致则可能与模型不同有关，也体现了CCL3结合受体的复杂性，有研究表明CCL3通过CCR1介导早期急性短暂的疼痛效应，而通过CCR5介导长期持续性的疼痛；并且CCR1拮抗剂BX513对晚期异常性疼痛有短暂缓解作用，表明CCR5触发的晚期机械异常性痛是由CCR1诱导的疼痛信号介导的[7]。

2.2 中枢神经损伤引起的神经病理性疼痛

在脊髓神经损伤(spinal cord injury, SCI)导致的神经病理性疼痛中，大鼠脊髓背角中星形胶质细胞分泌的CCL3/CCR1表达量上调[21]。瞬时受体电位香草酸亚型1(transient receptor potential vanilloid 1, TRPV1)、TRPV2、Toll样受体4(toll like receptor 4, TLR4)被认为是疼痛相关受体，免疫组化结果显示在SCI大鼠的脊髓背角中，CCR1与TRPV1共表达；在脊髓后角中，CCL3/CCR1与TRPV1、TRPV2、TLR4共表达[21]，这些结果证明了CCL3/CCR1参与了神经损伤后疼痛的发展过程。在SCI大鼠大脑中，大麻素受体1(cannabinoid receptor 1, CB1)分别与CCL3、TRPV1部分共定位于导水管周围灰质(periaqueductal gray, PAG)、丘脑和海马区[22]，提示CCL3、CB1和TRPV1可能在SCI诱导中枢神经可塑性变化中起作用。研究发现，用CCL3预处理TRPV1和CCR1共转染的HEK294细胞可大幅增加TRPV1介导的Ca^{2+}内流并激活PLC-PKC信号通路，这种致敏作用可分别被百日咳毒素，以及Gi蛋白、PLC和PKC的抑制剂所拮抗[23]。此外，研究表明SCI小鼠中*Ccl3*基因表达水平和p38 MAPK磷酸化水平均呈上调的趋势[24]。以上结果暗示，CCL3结合CCR1后通过PLC-PKC信号途径直接使与CCR1共表达的TRPV1敏感，导致胞外Ca^{2+}内流，激活一系列细胞内信号如p38 MAPK，进而参与SCI诱导的中枢敏化。

在LPS诱导的脑损伤大鼠[25]和创伤性脑损伤(traumatic brain injury, TBI)小鼠[26]中，CCL3表达显著上调，提示CCL3参与了脑损伤引发的疼痛发病过程。CCL3其及受体CCR1、CCR5在TBI小鼠的大脑皮质、海马区、丘脑和纹状体中高度表达，且中性粒细胞、小胶质细胞和星形胶质细胞是其表达来源[12]。在脑损伤早期，CCL3可以增强免疫细胞向损伤部位的浸润促进脑损伤后的炎症反应。研究发现，LPS[25]和*N*-甲基-*D*-天冬氨酸(*N*-methyl-*D*-aspartic acid, NMDA)[27]诱导的脑损伤分别通过MAPK、NF-κB和c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)信号通路介导小胶质细胞中CCL3的上调。CCL3上调可促进损伤后小胶质细胞的聚集，以及细胞内环氧化酶2(cyclooxygenase 2, COX2)和iNOS的产生。COX2和iNOS分别参与合成前列腺素和一氧化氮，是疼痛和炎症的重要调节因子。

脱髓鞘是神经病理性疼痛中枢敏化的重要过程。上调的CCL3通过募集炎性细胞如巨噬细胞等到损伤区而调控SCI后的炎症反应, 参与脊髓损伤后的继发性变性[28]。继发性变性包括轴突及其损伤部位远端髓鞘的降解和吞噬作用, CCL3和IL-1β作为巨噬细胞反应的重要因子, 它们可相互作用并诱导中枢神经系统和外周神经系统的沃勒变性中髓磷脂的快速分解和清除[29]。在溶血磷脂酰胆碱(lysophosphatidylcholine, LPC)诱导的脊髓脱髓鞘中, CCL3迅速上调, 促进T细胞、中性粒细胞和单核细胞进入脊髓, 并显著增加吞噬巨噬细胞的数量和促进LPC诱导的脱髓鞘[30]。在其他脱髓鞘疾病如多发性硬化症[31]和实验性自身免疫性脑脊髓炎[32]中, $CCR1^+/CCR5^+$单核细胞的聚集和CCL3的显著上调也证明了CCL3其及受体CCR1、CCR5在中枢神经系统病变过程中具有重要意义。

2.3 疾病引起的神经病理性疼痛

糖尿病周围神经病变是临床典型的诱发神经病理性疼痛的疾病之一。在链脲佐菌素(streptozotocin, STZ)诱导的1型糖尿病(type 1 diabetes mellitus, T1DM)大鼠模型[33]和2型糖尿病(T2DM)猴模型[34]中, 学者们发现了动物脊髓背角中小胶质细胞和星形胶质细胞的显著激活以及*CCL3*、*CCR1*、*CCR5* mRNA的表达上调。但在T1DM小鼠脊髓背角中, 只发现CCL3蛋白上调, 而CCR1、CCR5蛋白水平不变[35]。但鞘内给予CCL3中和抗体和CCR1拮抗剂J113863有助于逆转STZ引起的小鼠机械和热痛觉过敏。因此, 我们推测CCL3可能通过CCR1和CCR5参与糖尿病神经病理性疼痛的发展过程, 但其中的具体机制尚未可知, 有待进一步研究。

2.4 药物引起的神经病理性疼痛

紫杉醇(paclitaxel, PTX)是常见的化疗药物, 具有特殊的抗肿瘤机制, 然而PTX的使用常引起患者发生周围神经病变同时伴有神经病理性疼痛[36]。PTX可引起大鼠和小鼠脊髓背角中小胶质细胞的激活, 导致嘌呤能离子通道型受体7(purinergic ligand-gated ion channel 7 receptor, P2X7R)和CCL3及其受体CCR5表达量有所上升。PTX治疗亦会引起大鼠脊髓背角中TNF-α、γ-干扰素(interferon-γ, IFN-γ)和粒细胞–巨噬细胞集落刺激因子(granulocyte-macrophage colony stimulating factor, GM-CSF)显著上调[37]。鞘内注射选择性P2X7R拮抗剂和CCL3中和抗体可以逆转PTX引起的大鼠机械异常性疼痛[38]。研究表明, P2X7R参与小胶质细胞中CCL3的释放[39], 推测P2X7R在被细胞外腺嘌呤核苷三磷酸(adenosine triphosphate, ATP)激活后, 促进小胶质细胞释放CCL3和CCR5, CCL3和CCR5结合进一步激活小胶质细胞, 释放TNF-α、IFN-γ等炎性因子从而参与PTX诱导的大鼠神经病理性疼痛。在外周中, PTX处理引起神经元损伤以及CCL2、CCL3表达增加[37], 然而在化疗药物引起的周围神经病变中没有白细胞浸润或常驻巨噬细胞激活, 这表明DRG中CCL2、CCL3的表达变化可能来自于激活的卫星胶质细胞[40-41]。

阿片类药物是目前临床上常用的有效镇痛药物, 然而它也可导致外周神经系统和中枢神经系统伤害感受通路敏化, 造成阿片类药物诱导的痛觉过敏(opioid-induced hyperalgesia, OIH)的产生。瑞芬太尼是一种超短效MOR激动剂, 在瑞芬太尼诱发的大鼠痛觉过敏中, 脊髓[42]和DRG[43]中CCL3/CCR5 mRNA和蛋白水平上调, 在DRG中CCL3/CCR5与小胶质细胞、星形胶质细胞共定位, CCR5还与神经元共表达, 表明CCL3可能是连接神经胶质细胞和神经元的介质。鞘内给予CCL3中和抗体和CCR5拮抗剂MVC可以逆转瑞芬太尼诱导的痛觉过敏。NMDA受体的激活是瑞芬太尼诱导痛觉过敏的机制之一。有研究表明, CCL3可提高大鼠海马神经元中NMDA诱发的Ca^{2+}和NMDAR的水平, 慢性CCL3处理还改变了参与递质释放的突触前蛋白突触素I和抑制中间神经元所用的抑制性递质γ-氨基丁酸的合成酶谷氨酸脱羧酶65/67的水平, 从而影响突触活性以及与突触活性相关的Ca^{2+}信号[44]。推测CCL3/CCR5可能通过激活NMDA受体影响神经元兴奋性以及调控胶质细胞–神经元之间的相互作用从而参与OIH的维持与中枢敏化。

3 CCL3及其受体CCR1、CCR5在炎性痛中的作用

关节炎是常见的炎性痛模型之一, *Ccl3*被鉴定为类风湿性关节炎(rheumatoid arthritis, RA)的风险基因座[45]。研究发现, 关节炎患者滑液和滑膜组织以及外周血清中CCL3表达显著上调, CCL3/CCR1主要由浸润的巨噬细胞、内衬细胞、淋巴细胞和单核细胞分泌, 可促进淋巴细胞、单核细胞和巨噬细胞向关节部位的迁移和聚集, 加重局部炎性反应[46-48]。CCL3还可通过激活PI3K/AKT[AKT又称蛋白激酶B(protein kinase B, PKB)]信号通路提高促炎性因子如IL-6、IL-1β、TNF-α和核因子κB受体活化因子配体(receptor activa-

tor of nuclear factor-κB ligand, RANKL)的表达水平, 并促进CD4$^+$T细胞介导的RA的炎症反应[46]。

在大鼠实验性自身免疫性前列腺炎中, CCL3、IL-1β上调和ERK1/2磷酸化诱导脊髓小胶质细胞增殖激活以及脊髓炎症, 活化的小胶质细胞表达嘌呤能离子通道型受体4(purinergic ligand-gated ion channel 4 receptor, P2X4R)并释放脑源性神经营养因子(brain-derived neurotrophic factor, BDNF), 进而参与周围疼痛诱导机制[49]。足底注射角叉菜胶或完全弗氏佐剂(complete Freund's adjuvant, CFA)可诱发小鼠急性或慢性炎性痛, 在发炎侧的足底中CCL3的表达显著上调, 主要表达于巨噬细胞和嗜中性粒细胞中; CCL3通过CCR1发挥过度伤害感受作用, CCL3中和抗体和CCR1拮抗剂J113863可阻断角叉菜胶和CFA引起的热痛觉过敏和CFA引起的机械异常性疼痛[50]。在中暑发热反应[51]和急性胰腺炎[52]模型中, CCL3通过CCR1、CCR5激活JNK和p38 MAPK信号通路进而诱导细胞炎症反应, 促进TNF-α、IL-6和IL-1β的分泌, 而该过程可被siRNA-CCL3抑制。

4 CCL3在阿片耐受中的作用

阿片类药物常用于临床镇痛治疗, 然而阿片类药物的长期使用会导致机体出现耐受现象, 耐受机制主要包括阿片受体下调、内化、磷酸化和脱敏等, 严重制约了阿片类镇痛药物的临床应用。吗啡是一种常见的镇痛药物, 也是一种MOR激动剂, 鞘内应用CCL3中和抗体和CCR1拮抗剂J113863有助于增强吗啡和丁丙诺啡的镇痛作用[35,53]。鞘内应用CCR5拮抗剂MVC可通过直接影响阿片受体和CCR5的相互作用以及通过减少神经胶质细胞的活化、降低CCL3水平, 从而增强吗啡和丁丙诺啡的镇痛作用[15]。糖尿病猴脊髓背角中CCL3/CCR5上调, 而MOR、κ型阿片肽受体(kappa opioid receptor, KOR)和δ型阿片肽受体(delta opioid receptor, DOR)下调, 表明CCL3/CCR5上调使MOR脱敏, 并且CCR5和MOR可能形成异二聚体并相互交叉脱敏[34,54]。此外, 用CCL3预处理CCR1:MOR/HEK293细胞可诱导MOR内化, 并严重减弱MOR介导的抑制环磷酸腺苷(cyclic adenosine monophosphate, cAMP)积累的作用; CCR1和MOR在大鼠DRG小直径神经元中共表达, CCL3预处理减少了脑啡肽(一种MOR激动剂)引发的神经元钙通量响应, 表明CCL3/CCR1诱导了MOR的异源脱敏[55]。以上结果表明, CCL3及其受体CCR1、CCR5通过诱导阿片受体脱敏内化而参与阿片类药物耐受的发生机制。该过程可能与蛋白激酶A(protein kinase A, PKA)或PKC的激活有关[56]。

5 小结

病理性疼痛的发病机制错综复杂, 每一个作用靶点的发掘都可能为病理性疼痛的治疗带来新的希望。综上所述, CCL3通过其受体CCR1、CCR5在多种神经病理性疼痛、炎性痛以及阿片耐受中发挥重要作用。CCL3可以直接趋化外周免疫细胞参与损伤组织炎症反应, 也可以作为神经元与神经胶质细胞间相互作用的桥梁, 激活多种细胞内信号通路, 还可以影响内源性阿片肽的镇痛作用从而参与疼痛的发生、维持和调节(图2)。多数研究只证实了CCL3

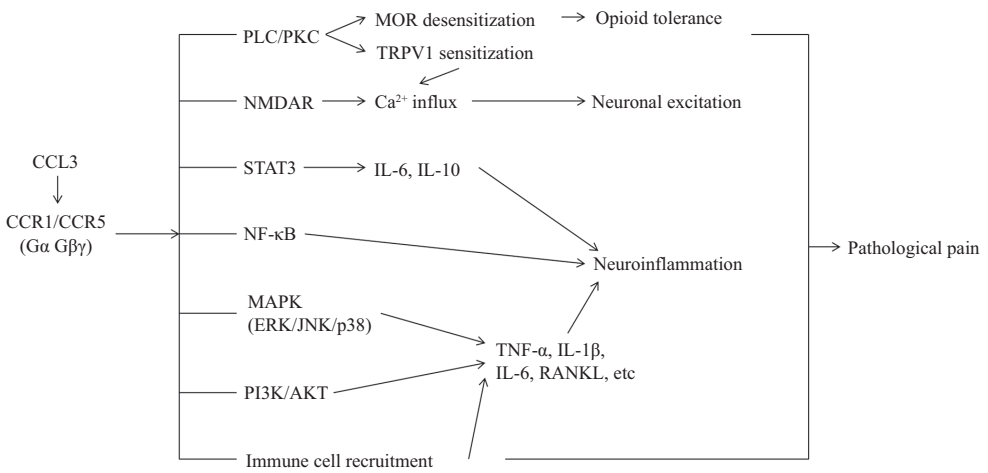


图2 CCL3在病理性疼痛中的作用机制

Fig.2 Mechanisms of CCL3 in pathologic pain

在疼痛中发挥作用, 但其具体的机制仍不清楚, 有待深入研究。

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