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背根神经节巨噬细胞调节神经病理性疼痛的潜在作用机制

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摘　要

神经病理性疼痛是神经系统损伤导致的慢性疼痛，它伴有持续的痛觉体验严重影响着患者的生活质量。由于神经性疼痛的发病机制十分复杂，而目前的治疗方法远不能令人满意。因此，探索有效的治疗方法是目前临床中急需解决的问题。背根神经节是感觉传导和调节的重要结构，背根神经节内的巨噬细胞作为外周免疫细胞在神经病理性疼痛中的作用越来越受到重视。背根神经节巨噬细胞与神经元存在双相联系，深入研究外周免疫细胞与外周神经系统的联系，可为治疗各种慢性疼痛提供新思路。本文就背根神经节内巨噬细胞参与神经病理性疼痛的相关分子通路研究进展进行综述。

关键词

神经病性疼痛，背根神经节，巨噬细胞，神经炎症，机制

Macrophage Regulates Neuropathic Pain in Dorsal Root Ganglion: Potential Mechanisms

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Abstract

Neuropathic pain is accompanied by persistent nociceptive experience. As a major consequence, a patient's quality of life is deeply affected. Neuropathic pain is a chronic pain syndrome with a complicated mechanism that currently has no effective therapy. Therefore, it is an urgent problem

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to further explore an effective treatment for patients with neuropathic pain. The dorsal root ganglion is an important structure for sensory conduction and regulation. It is suggested that macrophage activation in dorsal root ganglia could be involved in neuropathic pain mechanisms. Neurons of dorsal root ganglia interact with macrophages. The link between the peripheral nervous system and immune cells is under intensive investigation and will provide important insights for plausible treatments. In this review, we summarize the underlying molecular mechanisms of macrophages in the dorsal root ganglia involved in neuropathic pain.

Keywords

Neuropathic Pain, Dorsal Root Ganglion, Macrophage, Neuroinflammation, Mechanism

1. 引言

神经病理性疼痛，是临床中常见的一种慢性疼痛，它是神经系统的原发性病变或功能障碍引发或引起的疼痛[1]，主要是由癌症、糖尿病、感染、自身免疫性疾病、化疗或创伤等因素造成的神经系统损伤[2]，这些情况通常会导致衰弱的慢性疼痛综合征，称为神经病理性疼痛。它主要表现为自发性疼痛，痛觉过敏和异常性疼痛，全球近 10%的人深受其害，严重影响人们的正常生活质量；神经病理性疼痛产生的机制十分复杂，不仅限于神经系统活动的改变，还涉及由炎性细胞因子和趋化因子介导的神经元、免疫细胞之间的相互作用，炎性细胞因子带来的效应其中一部分是细胞因子的自身效应，此外他还可以通过调节炎症反应的其他介质的合成和释放而维持疼痛，这导致了神经性疼痛的发展和慢性化[3]。研究发现由顺铂诱导的细胞损伤通过激活 CD3+T 细胞上的 TIM8，导致 IL-13 的产生增加，进而诱导巨噬细胞 IL-10 的产生和周围神经病变的分离，缓解了神经病理性疼痛[4]。周围神经巨噬细胞和肠道常驻巨噬细胞，除了成体单核细胞来源的浸润巨噬细胞外，还分泌多种介质，如肿瘤坏死因子-α、白细胞介素(IL)-1β、IL-6、高迁移率组框 1 和骨形态发生蛋白 2 (BMP2)，调节初级传入的兴奋性[5]。

最近发现，外周神经系统的巨噬细胞，尤其是在背根神经节，对于神经病理性疼痛起到了非常重要的作用。但由于巨噬细胞改变痛觉敏感性的具体机制尚不明确，本文的主要目的是综述了背根神经节中的巨噬细胞对于神经病理性疼痛可能的产生及发展相关机制，也为其治疗方式提供了新的指导思路。

2. 背根神经节是感觉调控的靶点

背根神经节对于神经病理性疼痛的影响十分重要。一是因为背身神经节的特殊性，它是包括痛觉在内的躯体感觉初级传入神经元细胞体的聚集处[6]，它位于椎间孔附近，它的远端轴突构成初级传入神经，而近端轴突通过背部脊髓与背角细胞相连，可以接受感受器传来的神经冲动并将其传动到脊髓。相对于损伤部位的神经元来讲，它对于感觉得影响更大。其次，它被许多非神经元细胞所包围，形成了物理屏障。但是，当周围神经损伤后，神经元和周围的非神经细胞均被激活，钠离子通道、钾离子通道、钙离子通道、TRP 通道等均被激活，导致了疼痛的持续产生[7]。HCN2 通道也可能与痛觉感受器、炎症和参与神经病理性疼痛的细胞因子相关。所以，背根神经节作为神经调节靶点具有它的独特特性。痛觉的持续敏感，也不单是感觉神经元自身问题，神经损伤后周围的非神经细胞也被激活，通过感觉神经元和非

神经细胞相互作用网络，促进了痛觉敏感的发生与发展。

3. 巨噬细胞影响神经病性疼痛潜在的分子和信号通路

巨噬细胞是人体重要的免疫细胞，外周巨噬细胞主要功能包括：吞噬、抗原提呈和细胞因子的产生，它可以通过清除细胞碎片，激活和化解炎症，在非特异性和特异性免疫中都起到了重要作用。但是在慢性炎症或疼痛中，巨噬细胞可能会产生相反的作用[8]，被激活的巨噬细胞参与炎症反应，通过产生致炎和致痛介质来调节疼痛的产生与发展[5]。实验发现，当周围神经发生损伤后，同侧的背根神经节内的巨噬细胞显著增加[9] [10]，主要原因是周围巨噬细胞的浸润[11] [12]。于等人实验发现，背根神经节内的巨噬细胞对于神经病理性疼痛的产生了重要的影响[13]。因此，背根神经节内巨噬细胞相关的疼痛相关通路以及巨噬细胞－神经元细胞的相互作用，可能是治疗神经病理性疼痛的潜在靶点。

3.1. 多种疼痛相关分子参与神经病理性疼痛产生

神经肽 P 物质是一种主要由神经元分泌的多肽，参与许多生物过程，包括伤害性感受和炎症反应[14]，它是神经免疫调节活动的主要介质，在巨噬细胞中表达[15]，可以调节包括巨噬细胞在内的免疫细胞的各种功能，并且可以通过 ERK/p38MAPK 信号通路，活化小鼠巨噬细胞内 NF-κB 水平，促进巨噬细胞产生炎性趋化因子[16]。在慢性疼痛发展过程中，活化的巨噬细胞分泌趋化因子，不仅可以促进周围巨噬细胞的大量浸润，还可以吸引其他的免疫细胞的浸润，促进炎症的持续发展[17]。而在老年大鼠神经病理性疼痛模型中，损伤神经源性的环氧化酶 2 (COX2)参与慢性疼痛的维持。在神经损伤后，伴随着背根神经节内表达 COX2 的巨噬细胞增多和前列腺素 E2 (PGE2)的水平升高，促进背根神经节神经元的 PGE2 受体和离子通道瞬时受体电位香草酸-1 (TRPV1)表达增加，而背根神经节内 Ca^{2+}浓度的变化对维持神经元兴奋性起到了重要作用[18]。同时，PGE2 对大鼠背根神经节神经元酸敏离子通道(ASICs)活性的增强作用，也促进了慢性疼痛的产生与发展[19]。神经生长因子在巨噬细胞到伤害性感受器的信号转导中也起着重要的中介作用。在损伤或炎症反应后，炎症相关多肽(补体 C5a)迅速产生[20]。最近研究发现，C5a 的受体在巨噬细胞表明高度表达，通过作用于巨噬细胞的 C5aR1，经过级联反应促进巨噬细胞神经生长因子分泌。巨噬细胞产生的神经生长因子与背根神经节神经元的酪氨酸激酶(TrkA)受体结合，并且可以促进神经元 TRPV1 的表达，增加神经元的敏感性[21]。

3.2. 血管紧张素 2 受体(AT2R)和趋化因子 CCL2 受体

小鼠和人类的巨噬细胞可以表达肾素和血管紧张素(AngII) [22]，当外周有大量巨噬细胞浸润，这可能促进 AngII 浓度升高，促使疼痛过敏[23]。研究显示，AngII 可以直接作用于背根神经节神经元，通过 G 蛋白偶联 AT2R 诱导轴突生长和蛋白激酶 A 介导的 TRPV1 调节，从而导致外周敏化[24] [25]。但，Shepherd 等人发现，背根神经节神经元并不表达 AT2R，而是激活的巨噬细胞上的 AT2R 参与病理性疼痛信号的传递，他们还发现 TRPA1 参与 AT2R 依赖的神经病变、机械性和冷痛过敏[23]。由于巨噬细胞浸润外周神经病变部位，巨噬细胞中 AT2R 的激活可能作为细胞损伤信号，通过激活巨噬细胞 AT2R，然后产生活性氧(ROS)，作用于感觉神经元上的 TRPA1 通道，进而引发持续的伤害性感受器兴奋[26]。又有实验发现，在周围神经损伤后，表达 NADPH 氧化酶 2 (NOX2)的巨噬细胞在背根神经节内大量浸润，并通过 NOX2 依赖的方式增加 ROS 的产生，诱导背根神经节内炎性介质 TNF-α 的表达上调[27]。同时局部的神经损伤释放的趋化因子 CCL2，通过作用于巨噬细胞的 CCR2 受体，使巨噬细胞产生氧化应激，促进 TRPA1 作用伤害性神经元，导致痛觉过敏[28]。在巨噬细胞通过释放炎症介质直接刺激伤害性感受器诱发痛觉的同时，伤害性感受器可以通过释放神经肽和趋化因子反向激活巨噬细胞。在背根神经节伤

害性感受器上 sigma-1 受体激活，产生趋化因子 CCL2 [29]，随后出现大量的巨噬细胞浸润，它们主要聚集在感觉神经元的周围，产生的 CCL2 作用于周围巨噬细胞的 CCR2 受体，促进了 IL-6 释放增加，进而机械性疼痛的产生[30]。

3.3. Toll 样受体

Toll 样受体(TLR)是模式识别受体的一个家族，可在先天和适应性免疫途径中启动信号传导。高度保守的跨膜蛋白家族包括识别外源和内源危险分子的细胞外结构域和激活下游通路的胞外域[31] [32]。越来越多的研究发现，TLRs 通过 NF-κB 通路调节神经炎性反应，损伤刺激作用于巨噬细胞上的 TLRs，通过髓样分化因子(MyD88)依赖的信号通路，激活 NF-κB 基因，促进 TNF-α 等炎性因子的释放，所以，在神经病理性疼痛中起到了重要的作用[31] [33]。更细化的研究发现，在慢性疼痛的刺激下，可以诱发巨噬细胞活化，通过 TLR2 介导炎性反应，进而引起神经病理性疼痛，Shi 等人在 TLR2 缺陷型小鼠中发现，巨噬细胞的活化明显减少外周受伤的神经中 TNF-α 的表达降低，而在小胶质细胞中并未发现相关 mRNA 的表达[34]。而 TLR9 通路可以促进巨噬细胞的在背根神经节的浸润，但对于疼痛的调节，却存在性别差异[35]。TLR9 通路可以促进巨噬细胞释放肿瘤坏死因子 α (TNF-α)和趋化因子 CXCL1，并与感觉神经元上的 TNFR1/TNFR2 和 CXCR2 结合，导致痛觉过敏[35]。紫杉醇诱导外周神经病变导致巨噬细胞浸润至背根神经节，这种浸润不受 TLR9 突变的影响。紫杉醇治疗还上调了巨噬细胞培养和背根神经节组织中肿瘤坏死因子和 CXCL1 mRNA 的表达，但这些变化在雄性动物中受到 TLR9 mRNA 突变的影响[35]。巨噬细胞上 TLR4 介导的双通路参与慢性疼痛的维持[36]，当刺激巨噬细胞上的 TLR4，不仅可以通过 MyD88 通路，诱导 NF-κB 易位和促炎细胞因子(如 TNF-α、IL-1、IL-2、IL-6)的表达[37]，同时还可以通过干扰素调节因子 3 激活 1 型 IFN 基因和 TLR4 信号传导通路[38]。巨噬细胞 Toll 样受体途径介导了细胞的活化和炎症因子的产生与释放，在疼痛的产生和维持中体现了重要的作用。

3.4. 高迁移率族蛋白 B1 及下游通路

背根神经节巨噬细胞上其他的受体也参与慢性疼痛的维持。最近发现，背根神经节的巨噬细胞可以通过高迁移率族蛋白 B1 (HMGB1)/晚期糖基化终末产物受体(RAGE)通路作用于背根神经节上的 Ca v3.2 T 型钙离子通道，对神经病理性疼痛产生重要的作用[39] [40]。Ca v3.2 T 型钙通道可以分别调节初级传入神经末梢的神经元兴奋性和神经递质释放[41] [42] [43]。在神经病理性疼痛模型中，大量巨噬细胞聚集在背根神经节周围，释放的 HMGB1，通过 HMGB1/RAGE 通路促进背根神经节内早期生长反应 1 (EGR-1)的转录，进而上调 Ca v3.2 T 型钙通道在背根神经节的表达，并增加了初级传入神经元的兴奋，从而导致痛觉过敏[39]。同时，HMGB1 还可以与感觉神经元和免疫相关细胞(树突状细胞、巨噬细胞等)上的 TLR5 特异性结合，以 MyD88 依赖的方式启动 NF-κB 信号通路的激活，导致体内促炎细胞因子的产生，促进感觉神经元的痛觉敏感[44] [45]。

3.5. 信号脂质受体和烟碱型乙酰胆碱受体

信号脂质受体(G2A)是 G 蛋白偶联受体，对神经病理性疼痛产生很大的影响。在感觉神经元上，亚油酸代谢产物与 G 蛋白偶联受体特异性结合，通过蛋白激酶 C (PKC)的激活使 TRPV1 增敏，导致机械性疼痛超敏反应增加[46] [47]；而且，在巨噬细胞等免疫细胞中大量表达[47] [48]。最近研究发现，巨噬细胞中的 G2A 激活启动了 MyD88-PI3K-AKT 信号和瞬时基质金属蛋白酶-9 的释放，从而触发细胞骨架的重塑和迁移；在 G2A 缺乏的小鼠，体内机械疼痛反应降低，同时减少神经损伤部位免疫细胞的激活和细胞炎性因子的释放[49]，这说明 G2A 受体在神经损伤诱导的神经病理性疼痛的发生和发展中起着关键作

用。烟碱型乙酰胆碱受体(NAChRs)是一种配体门控阳离子通道，表达于外周巨噬细胞上，应用该受体的选择性激动剂 TC-2559，可以通过抑制信号转导和转录激活因子 3 (STAT3)，降低了炎症介质(IL-1β 和 CCL3)的释放，可改善啮齿动物神经病理性疼痛[50] [51]。实验还发现，在周围神经损伤后，在背根神经节的巨噬细胞上的 NOD 样受体 2 上调，通过激活丝氨酸/苏氨酸蛋白激酶 2，促进 NF-κB 的激活和促炎基因的转录，使 TNF-α 和 IL-1β 分泌增多，诱导周围神经损伤后神经病理性疼痛的产生和维持，也为预防和治疗神经病理性疼痛提供新的潜在靶点[52]。

此外，炎症的消退需要促消炎介质(SPM)发挥作用。由巨噬细胞表达的 G 蛋白偶联受体 GPR37 是 SPM 受体，它可以调节吞噬作用和炎症消退。神经保护素 D1 (NPD1)可以特异性作用于巨噬细胞的 GPR37 受体，主要是影响巨噬细胞内的钙离子水平和吞噬作用，并诱导巨噬细胞向抗炎的 M2 转化并释放抗炎介质，从而缓解疼痛持续发生[53]。以上说明背根神经节内巨噬细胞是神经病理性疼痛重要的参与者。

4. 展望

在背根神经节周围的感觉传导微环境中，不管是神经元细胞的损伤，还是周围的免疫细胞(巨噬细胞、小胶质细胞等)浸润增生，都会改变神经微环境的平衡，感觉异常会随之出现，轻微的触碰可能就会产生剧烈且持续性的疼痛。神经病性疼痛是在临床中常见的慢性疼痛，严重影响患者的生活质量。因此，深入研究神经病理性疼痛可能存在的细胞分子机制有着重要意义。近期的研究发现背根神经节内的巨噬细胞参与神经病理性疼痛的产生与维持。其主要原因，一是因为巨噬细胞的浸润与增殖。神经损伤后，背根神经节内巨噬细胞局部浸润和增殖，参与多种炎症信号通路，导致背根神经节感觉神经元电位的改变，最终产生持续的异常疼痛信号。二是因为位置的特殊性，背根神经节是感觉初级传入神经元细胞体的聚集处，局部神经微环境的平衡失调，严重影响感觉从外周向中枢神经系统的传导。这说明了背根神经节内巨噬细胞活化与增殖在神经病理性疼痛的重要作用，巨噬细胞相关信号通路将为神经病理性疼痛的治疗提供新的思考。

利益冲突

所有作者声明无利益冲突。

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