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巨噬细胞极化在骨关节炎中的作用

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摘要：骨关节炎(osteoarthritis，OA)是一种以软骨退变、滑膜炎症和软骨下骨重塑等为特征的慢性退行性关节疾病。巨噬细胞广泛存在于关节滑膜组织中，并与滑膜炎症反应密切相关。巨噬细胞在多种细胞因子或微生物代谢产物等物质的刺激后，可向促炎M1型或抗炎M2型极化，从而调控软骨细胞外基质的微环境，对OA的发生发展产生一定影响。因此，靶向诱导巨噬细胞极化可能是缓解OA的有效手段，但是巨噬细胞极化过程在OA中的具体调控作用尚不完全清楚。该文通过综述巨噬细胞极化与OA的相关文献，总结外泌体、NF-κB、MAPK、STATs、caspases等关键分子在OA巨噬细胞极化过程中的具体调控作用，从而确定滑膜液微环境中巨噬细胞极化对OA中软骨损伤修复的作用，为进一步探究巨噬细胞极化对OA靶向治疗的作用机制提供理论依据。

关键词：骨关节炎；巨噬细胞极化；关节软骨；滑膜炎

Role of macrophage polarization in osteoarthritis

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Abstract: Osteoarthritis (OA) is a chronic degenerative joint disease characterized by cartilage degeneration, synovial inflammation, and subchondral bone remodeling. Macrophages are widely found in articular synovial tissue and are strongly associated with the synovitis response. It has been found that macrophages can be polarized to pro-inflammatory M1 or anti-inflammatory M2 when stimulated by various cytokines or microbial metabolites so as to regulate the microenvironment of the cartilage extracellular matrix and have an impact on the development of OA. Therefore, there may be an effective means of alleviating OA by targeting the induction of macrophage polarization. However, it is not completely clear that the concrete regulatory effect of the macrophage polarization process in OA. In this paper, we summarize the specific regulatory effect of exosome, NF-κB, MAPK, STATs, caspases and other key molecules in the process of macrophage polarization in OA by reviewing the relevant literature of macrophage polarization and OA, so as to determine the role of macrophage polarization in the synovial fluid microenvironment on the repair of cartilage damage in OA, and provide a theoretical basis for further exploring the mechanism of action of macrophage polarization on the targeted therapy of OA.

Key Words: osteoarthritis; macrophage polarization; articular cartilage; synovitis

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骨关节炎(osteoarthritis，OA)是一种好发于中老年人的慢性退行性关节疾病，全球发病率逐年增加[1]，其主要特征包括关节软骨破坏、关节间隙狭窄、滑膜炎症、软骨下骨重塑和骨赘形成等。OA患者通常出现关节疼痛、畸形和功能障碍等一系列临床症状[2]。目前尚无完全逆转OA病程的治疗方法，主要的临床策略包括手术治疗和非手术治疗。其中，非手术治疗主要用于OA早期治疗，以药物治疗和运动疗法为主；手术治疗主要用于OA晚期，包括关节镜清理、单髁置换术和全膝关节置换术等[3]。研究发现，在OA的发生发展中，许多基质降解酶显著上调，例如基质金属蛋白酶(matrix metalloproteinases，MMPs)等，促炎细胞因子分泌增多，滑膜发生炎症反应，使软骨基质稳态失衡，软骨降解[4]。关节软骨是一种无血管组织，损伤后的自愈合能力非常有限[5]。越来越多的证据表明，持续低度的滑膜炎症会加剧软骨损伤[6,7]，而滑膜巨噬细胞在其中发挥了至关重要的作用[8]。因此，精准调控滑膜巨噬细胞促炎作用的经典活化型(classically activated，M1)/抗炎作用的替代活化型(alternatively activated，M2)的极化能够调节软骨细胞外基质的组成，促进软骨修复，从而改善OA患者的关节功能障碍和日常生活活动受限[9-12]。

滑膜巨噬细胞可以被激活、聚集并极化成不同的亚型，主要分为有M1和M2[13,14]。大量研究证据表明，通过干预滑膜巨噬细胞的极化状态，可调节滑膜液免疫微环境，其中M1型巨噬细胞促进炎症反应，破坏软骨组织修复，加速OA进展；而M2型的功能则相反，M2型巨噬细胞能够释放抗炎因子，这在OA软骨损伤修复中发挥至关重要的作用[15-19]。但是滑膜巨噬细胞调控OA的具体分子机制尚不明确。因此，本文就滑膜巨噬细胞极化和OA发生发展关系进行了总结，OA相关的分子机制进行了阐述，为进一步研究滑膜巨噬细胞极化靶向治疗OA提供理论参考。

1　巨噬细胞概述

1.1 巨噬细胞

巨噬细胞来源于骨髓中的祖细胞，是机体重要的免疫细胞，可分为定居和游走两类。定居在不同组织中的巨噬细胞有不同的命名，如骨组织中的破骨细胞和关节中的滑膜A型细胞即滑膜巨噬细胞等。游走的巨噬细胞广泛分布于结缔组织中，寿命较长，胞质内富含溶酶体颗粒及其相关的酶类物质，具有很强的变形运动及吞噬杀伤和清除病原体等抗原性异物的能力[20]，参与调控机体病理状态时炎症的进程[21]。炎症部位产生的粒细胞-巨噬细胞集落刺激因子(granulocyte-macrophage colony stimulating factor，GM-CSF)和干扰素-γ(interferon-γ，IFN-γ)等细胞因子可募集和活化巨噬细胞[22]；活化的巨噬细胞又可通过分泌单核细胞趋化蛋白-1(monocyte chemoattractant protein-1，MCP-1)、白细胞介素-8(interleukin-8，IL-8)等趋化因子及IL-1等促炎细胞因子或其他炎性介质来参与和促进炎症反应[23]。

1.2 巨噬细胞极化

成熟巨噬细胞能在多种细胞因子、生长因子和微生物代谢产物的诱导下，出现表型(M1和M2)和功能的分化，呈现明显的异质性，即极化现象[24]。M1巨噬细胞可由IFN-γ、脂多糖(lipopolysaccharide，LPS)或Toll样受体(Toll-like receptors，TLRs)诱导而来，通过产生活性氧中间体(reactive oxygen intermediates，ROI)、NO以及释放溶酶体酶等途径杀伤清除病原体，同时分泌多种趋化因子和IL-1β、IL-6和肿瘤坏死因子-alpha(tumor necrosis factor-α，TNF-α)等促炎细胞因子参与炎症反应，损害组织和细胞的修复[15-18]。M2巨噬细胞由IL-4和IL-13诱导而来，能够释放转化生长因子-β(transforming growth factor-β，TGF-β)和IL-10等抗炎细胞因子，抑制炎症并促进损伤组织重塑[15,17,19]。

此外，有报道称M2巨噬细胞可分为4个亚群：IL-4和IL-13诱导的M2a巨噬细胞，表达甘露糖受体C1(mannose receptor C-type 1，MRC1)和IL-10；免疫复合物信号诱导的M2b巨噬细胞，表达IL-10和主要组织相容性复合体Ⅱ类；IL-10和糖皮质激素诱导的M2c巨噬细胞，表达MRC1、IL-10和TGF-β[25-27]；M2d巨噬细胞可高表达血管内皮生长因子以及诱导型一氧化氮合酶(inducible nitric

oxides synthase，iNOS)等，或低表达TNF-α和精氨酸酶1(Arginase 1，Arg1)等[28]，在血管生成和伤口愈合中发挥作用[29]。其中M2a巨噬细胞主要与抗炎活性有关，M2c巨噬细胞主要与组织修复相关[30,31]。

综上所述，巨噬细胞在炎症反应中起到重要作用。炎症初期M1型巨噬细胞吞噬病原体；炎症后期，M2型巨噬细胞通过分泌IL-10等抗炎细胞因子来调节组织炎症微环境，有利于软骨组织的再生和修复。因此，巨噬细胞极化状态的及时改变对于炎症的消退至关重要。临床治疗OA的目的是尽可能减轻患者的疼痛[32]，而不是修复受损的软骨组织，这主要是因为缺乏有效的药物[33,34]。因此，深入探究巨噬细胞极化的分子机制，实现靶向诱导抗炎M2巨噬细胞极化具有重要的临床意义。

2 间充质干细胞来源的外泌体调控巨噬细胞向抗炎M2极化以减缓OA进展

研究发现，从脂肪、脐带和骨髓等多种组织中分离出来的间充质干细胞(mesenchymal stem cells，MSCs)具有向脂肪细胞、成骨细胞、心肌细胞和软骨细胞分化的潜能[35,36]。研究显示，MSCs能够通过旁分泌方式产生的外泌体(exosome，Exos)来调节各种疾病的微环境，抑制疾病的发展，促进组织修复和再生[37-40]。Exos是一组直径为30 nm~150 nm的细胞外囊泡，携带蛋白质、微小RNAs(microRNAs，miRNAs)、长链非编码RNA(longnon-codingRNA，lncRNAs)或其他信号分子，是细胞间传递生物信号的重要载体[41]，与各种疾病的发病机理密切相关[42,43]。

有研究证明，间充质干细胞来源的Exos能够促进软骨细胞增殖，诱导巨噬细胞向M2表型极化[44]，从而调节炎症反应，起到缓解OA的作用[45,46]。各种干细胞来源的Exos能够诱导巨噬细胞向抗炎M2极化，促进软骨细胞增殖(如图1所示)。Jiang等[44]使用接受足月剖宫产孕妇的新鲜脐带，剥离出沃顿胶并进行细胞培养后差速离心提取Exos，注射入兔膝关节骨软骨缺损模型发现MSCs和软骨细胞增殖，脱细胞软骨细胞外基质(acellular cartilage extracellular matrix，ACECM)支架作用增强，同时M2巨噬细胞标记物CD206的基因表达上调，表明人脐带沃顿胶间充质干细胞来源的外泌体(human umbilical cord Wharton's jelly MSC-Exos，hWJMSC-Exos)可以促进骨软骨再生，并诱导巨噬细胞向抗炎M2极化。骨髓间充质干细胞(bone marrow mesenchymal stem cells，BMSCs)是MSCs最常见的来源之一，具有多向分化和自我更新的潜力。因此，有研究使用骨髓间充质干细胞来源的外泌体(BMSC-derived exosome，BMSCs-Exo)对OA大鼠进行关节内注射，同样发现软骨降解程度较少，且软骨生成基因Ⅱ型胶原蛋白(collagen-Ⅱ，COL-Ⅱ)和转录因子SOX9的表达增加，国际骨关节炎研究协会(Osteoarthritis Research Society International，OARSI)评分显著较低；滑膜中M1/M2巨噬细胞极化的表型也一致，即iNOS

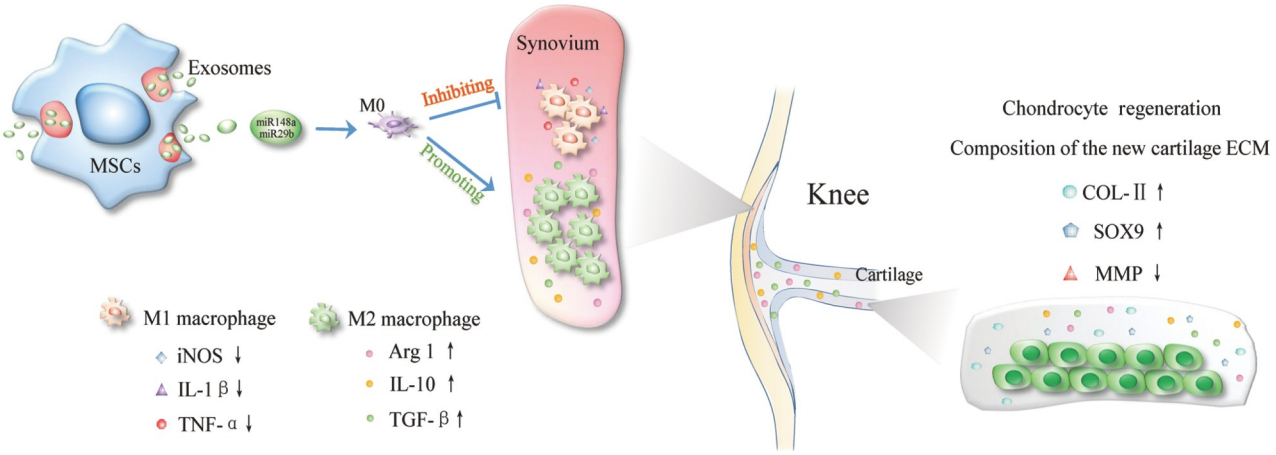

图1 间充质干细胞来源的外泌体调控巨噬细胞向抗炎M2极化

+(M1型巨噬细胞标记物)阳性细胞比例明显降低，Arg1+(M2型巨噬细胞标记物)阳性细胞比例增加；促炎细胞因子IL-1β、TNF-α水平明显降低，而抗炎细胞因子IL-10水平升高[47]。上述结果均表明，BMSCs-Exo促进滑膜巨噬细胞由促炎M1向抗炎M2极化，降低了滑膜炎症水平。这与Kamada等[48]的结果相一致。此研究发现，为OA小鼠移植关节内脂肪来源的再生细胞(human adipose-derived regenerative cells，ADRCs)，可减少软骨细胞中分解代谢因子并调节巨噬细胞极化，从而减轻OA进展。

以上研究仅初步证明MSCs-Exo通过调节巨噬细胞极化来延缓OA，但Exos作为关键的细胞间通讯器，能将不同类型的分子转移到受体细胞中，包括lncRNAs、miRNAs、信使RNAs(mRNAs)和蛋白质[49]等。有研究发现，hWJMSC-Exos内miR148a和miR29b表达增高[44]，在转录后调控编码基因，使M2巨噬细胞数量增加，并促进软骨再生和软骨基质合成[50,51]，对OA有潜在的抑制作用。这为临床实现软骨再生修复明确了一个分子靶点。然而，目前对间充质干细胞来源的外泌体所携带的分子调控巨噬细胞极化的通路知之甚少，仍有待进一步研究。

3　NF-κB信号通路调控M1巨噬细胞极化以加速OA进展

核转录因子-κB(nuclear transcription factor kappa-B，NF-κB)是一种可以调控基因转录的核因子，对于诱导各种炎症相关的细胞因子和介质至关重要，包括iNOS、MMP、TNF-α和IL-1β等[52,53]，同时也是巨噬细胞极化的重要调控因子[54,55]。磷酸化是NF-κB激活的关键步骤。Lu等[56]用胶原酶诱导C57BL/6小鼠OA模型注射Fargesin与Zhou等[57]对前交叉韧带横断的OA小鼠腹腔注射金线莲苷(kinsenoside，Kin)均发现，Fargesin和Kin能抑制由LPS和IFN-γ激活的NF-κB上游信号通路丝裂原活化蛋白激酶(mitogen-activated protein kinases，MAPK)信号分子p-P38，从而阻断巨噬细胞向促炎M1极化，在一定程度上缓解软骨退变，改善OA。此外，Kin除了通过抑制NF-κB上游MAPK的激活，还可以通过抑制IκBα的磷酸化，进一步降低下游NF-κB信号通路中p-P65的水平，从而使M1巨噬细胞向M2表型极化[57]。也有研究使用土荆皮乙酸(pseudolaric acid B，PAB)靶向稳定过氧化物酶体增生物激活受体γ(peroxisome proliferator-activated receptor γ，PPARγ)，抑制滑膜组织中的NF-κB信号传导，减少促炎细胞因子的产生，从而进一步减少M1巨噬细胞的浸润，达到改善OA软骨退变的作用[58]。综上所述，Fargesin、PAB和Kin等化合物均通过抑制NF-κB信号的激活，使其停留于胞质内而无法转移入核，进而不能阻断M1巨噬细胞极化为M2，以此来改善OA进展。

有研究表明，miRNAs可能通过抑制NF-κB的信号通路来抑制滑膜炎症和软骨损伤，从而参与调控OA病变[59,60]。Lu等[61]为内侧半月板不稳定术(destabilize the medial meniscus，DMM)造模的OA小鼠关节内注射能够恢复软骨细胞稳态的乳脂球表皮生长因子8(milk fat globule-epidermal growth factor 8，MFG-E8)，结果发现miR-99b-5p在OA软骨中表达显著上调并抑制MFG-E8的功能，使软骨细胞中NF-κB p65信号通路被磷酸化激活，释放的NF-κB转移入核，进一步阻止巨噬细胞向M2亚型极化，加剧了软骨退变，导致OA加重。然而，有研究结果与之相矛盾，该研究发现IL-4诱导M2巨噬细胞极化，未能激活NF-κB/MAPK信号中激酶的磷酸化，这说明NF-κB/MAPK信号通路并未参与M2巨噬细胞极化[57]。这有可能是由于NF-κB/MAPK属于促炎通路，诱导巨噬细胞向促炎M1极化，若抑制NF-κB的激活，就能减少M1巨噬细胞的浸润；而M2型巨噬细胞主要发挥抗炎作用，可能有其他通路调控其极化。

4　STATs信号通路调控M2巨噬细胞极化以缓解OA进展

信号转导和转录激活因子家族(signal transducer and activator of transcription family，STATs)多参与调控体内细胞因子和生长因子的信号转导及基因转录。研究发现，STATs家族成员STAT3和STAT6被磷酸化激活后，在M2巨噬细胞极化中发挥重要作用[62,63]。有研究使用当归素

(angelicin，ANG)通过CD9/gp130激活p-STAT3/STAT3信号转导[64]，另外有学者使用Kin上调p-STAT6/STAT6的表达[57]，二者均可促进M1巨噬细胞向M2巨噬细胞极化，同时下调IL-1β和TNF-α等炎症介质的表达，保护和维持M2巨噬细胞极化，缓解OA进展。Quero等[65]则进一步发现，转染miR-221-3p模拟物的M2巨噬细胞分泌的IL-10和CXCL13减少，而IL-6和IL-8的表达增加，同时下调JAK3蛋白表达并抑制p-STAT3激活，表明miR-221-3p可能通过抑制JAK3/STAT3激活，驱动M2巨噬细胞向促炎功能转变。值得注意的是，除了miRNAs，lncRNA也通过STATs信号通路参与了巨噬细胞极化。有研究表明，lncRNA MM2P阻断了STAT3的去磷酸化，并与RNA结合蛋白FUS(fused in sarcoma)相互作用，诱导M2巨噬细胞极化，促进M2来源的外泌体SOX9进入软骨细胞，使软骨细胞的功能明显增强，减缓了OA的进展[66]。综上所述，巨噬细胞向抗炎M2极化有可能是通过磷酸化激活STATs信号通路来调控的。

5 Caspases信号通路调控巨噬细胞极化以加速OA进展

Caspases是一类半胱氨酸蛋白酶，在细胞凋亡信号转导的级联反应中发挥协同作用，也参与调控一系列传染性、炎症性、恶性、代谢性和神经退行性疾病中功能失调的细胞死亡和炎症通路[67,68]。根据结构和功能上的差异可分为凋亡相关caspase(caspase-3、caspase-6等)和炎症相关caspase(caspase-1、caspase-4等)[69,70]。已有研究发现，在前交叉韧带横断的兔OA模型关节腔内注射caspase抑制剂Z-VAD-FMK，能显著抑制软骨降解，同时减少软骨细胞中caspase-3的表达[71]。Caspases抑制剂可能对仅限于细胞死亡的组织损伤疾病有效，如创伤后关节炎，在损伤后有一个时间窗，可以挽救受损伤的软骨细胞，使其免于细胞死亡的进展[72]。有学者发现，caspases不仅与软骨凋亡有关，也参与调控巨噬细胞极化[73]。研究表明，膝关节骨性关节炎滑膜液的促炎微环境通过上调miR-155-5p/caspase-3的表达，抑制M1巨噬细胞凋亡，使巨噬细胞向促炎M1极化[73]。该结果为OA期

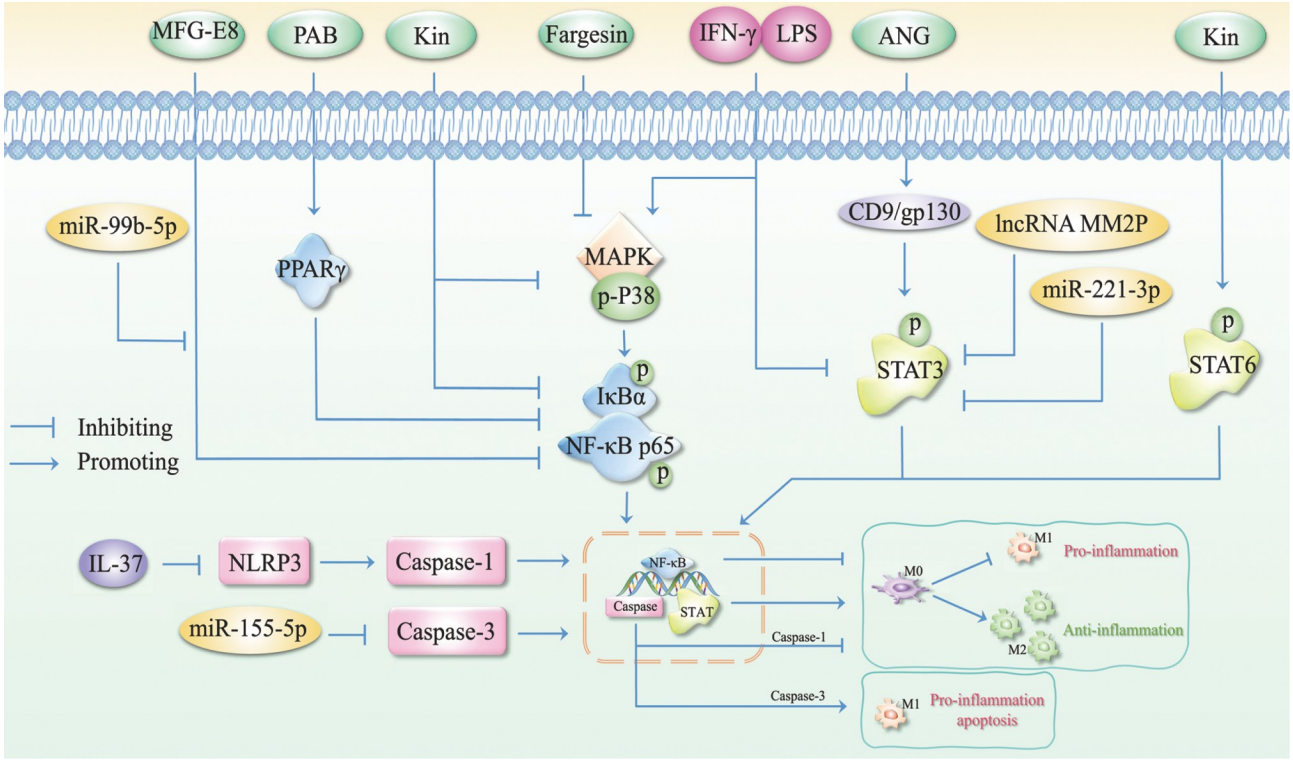

图2 NF-κB、MAPK、STATs和Caspases信号通路参与调控巨噬细胞极化的模式图

间M1巨噬细胞数量的增加提供了一个新的解释。此外，有研究发现，IL-37通过核苷酸结合寡聚化结构域样受体蛋白3(nucleotide-binding oligomerization domain-like receptor protein 3, NLRP3)通路抑制炎症相关caspase-1的活性，促炎细胞因子的分泌减少，并使巨噬细胞从促炎M1向抗炎M2极化，从而改善颞下颌关节骨性关节炎[74]。因此，无论是凋亡相关还是炎症相关的caspase均参与调控巨噬细胞极化，其中凋亡相关caspase-3可抑制促炎M1巨噬细胞凋亡，促进炎症反应；而炎症相关caspase-1则是分泌更多炎症因子，抑制促炎M1向抗炎M2极化(图2)。

6　小结与展望

巨噬细胞对于有效控制和清除感染、促进组织修复和伤口愈合至关重要，但M1巨噬细胞也可通过介导活性氧诱导组织损伤、损害组织再生和伤口愈合。为防止过度的组织损伤和慢性炎症反应，抗炎M2巨噬细胞参与调节控制。因此，诱导巨噬细胞由促炎M1向抗炎M2极化就成为愈合受损组织和治疗慢性疾病的一个巨大的潜在靶点。而调控巨噬细胞极化改善OA可能有2种不同的途径：(1)脊髓、脂肪或者脐带来源的MSCs分泌的Exos，调控滑膜巨噬细胞向抗炎M2表型极化，改善软骨细胞外基质的炎症反应，同时增加软骨生成基因COL-Ⅱ和SOX9的表达，促进软骨再生与修复，缓解OA的发展，这是治疗OA的一种安全有效的策略(图1)；(2)靶向诱导巨噬细胞极化的化合物可有效抑制关节炎症中释放的微生物产物和细胞因子，再经过NF-κB、MAPK、STATs、caspases等关键信号分子调控，减少促炎M1型巨噬细胞浸润，并向抗炎M2型巨噬细胞极化，促进软骨修复，最终缓解OA症状(图2)。随着对巨噬细胞极化研究的不断深入，有更多的研究报道影响巨噬细胞极化的相关信号通路，这也促进以调控巨噬细胞极化为靶点的临床抗OA药物的研发。除此之外，调控巨噬细胞M1/M2表型、数量和分布的平衡，可以抑制有害炎症并增强组织修复，为其他慢性炎症的治疗提供新的研究思路。

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