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·牙周医学专栏　综述·

细胞程序性死亡在牙周炎与类风湿性关节炎关联中的桥梁作用

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【摘要】　牙周炎与类风湿性关节炎（rheumatoid arthritis，RA）是两种具有相似炎症机制和特征的慢性炎症性疾病。近年来，细胞程序性死亡（programmed cell death，PCD）作为调节炎症和维持组织稳态的重要机制，在牙周炎和RA的发生发展及二者关联中的作用备受关注。PCD包括细胞凋亡、焦亡和坏死性凋亡等不同形式，通过Toll样受体4（Toll-like receptor 4，TLR4）/NF-κB、MAPK等多条信号通路精细调控，决定免疫细胞及组织细胞的命运，从而影响炎症反应、组织破坏及重建。在牙周炎和RA的发病过程中同样发挥重要作用。牙周炎中，牙龈卟啉单胞菌（*Porphyromonas gingivalis*，*P. gingivalis*）等牙周致病菌及其分泌的脂多糖（lipopolysaccharide，LPS）等毒力因子，通过TLR4/NF-κB等通路诱导巨噬细胞等免疫细胞发生焦亡、坏死性凋亡等PCD过程，释放大量白细胞介素（interleukin，IL）-1β、肿瘤坏死因子（tumor necrosis factor，TNF）-α等炎症因子，同时抑制中性粒细胞的正常凋亡，延长细胞生存时间，加剧免疫失衡和牙周组织破坏。而在RA中，滑膜组织的滑膜成纤维细胞（fibroblast-like synoviocytes，FLS）通过Bcl-2家族、JAK/STAT、NF-κB等信号途径获得凋亡抵抗，持续增殖并分泌基质金属蛋白酶和促炎因子，持续激活中性粒细胞和巨噬细胞焦亡，释放IL-1β等炎症因子，加剧关节滑膜炎症和骨破坏。失衡的PCD过程通过炎症因子和代谢网络的交互作用形成跨器官的影响，牙周炎部位产生的炎症因子和损伤相关分子模式（damage-associated molecular pattern，DAMP）可通过血液循环影响关节滑膜细胞及免疫细胞的死亡过程，导致关节炎症和骨破坏进一步加重；而RA的全身性炎症状态，则可通过TNF-α、IL-6等途径反过来上调牙周局部破骨细胞活性或干扰牙周细胞正常凋亡，加重牙周组织的免疫失衡。本文旨在对PCD在两者相关关系中可能的桥梁作用进行综述，以期为未来通过靶向调控PCD治疗牙周炎及RA提供参考。

【关键词】　牙周炎；　类风湿性关节炎；　免疫失衡；　细胞程序性死亡；　凋亡；　坏死性凋亡；　焦亡
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The bridging role of programmed cell death in association between periodontitis and rheumatoid arthritis

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【Abstract】　Periodontitis and rheumatoid arthritis (RA) are chronic inflammatory diseases that share similar inflammatory mechanisms and characteristics. Programmed cell death (PCD) has recently garnered attention for its crucial role in regulating inflammation and maintaining tissue homeostasis, as well as for its potential to link these two diseases. The

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various forms of PCD--including apoptosis, pyroptosis, and necroptosis--are closely controlled by signaling pathways such as Toll-like receptor 4 (TLR4) /NF-κB and MAPK. These pathways determine cell fate and influence inflammatory responses, tissue destruction, and repair, and they both play important roles in the pathogenesis of RA and periodontitis. In periodontitis, periodontal pathogens such as *Porphyromonas gingivalis* (*P. gingivalis*) and its virulence factors, including lipopolysaccharide (LPS), induce pyroptosis and necroptosis in immune cells such as macrophages *via* the TLR4/NF-κB pathway, which leads to an excessive release of pro-inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α. Concurrently, these pathogens inhibit the normal apoptotic process of immune cells, such as neutrophils, prolonging their survival, exacerbating immune imbalance, and aggravating periodontal tissue destruction. Similarly, in RA synovial tissue, fibroblast-like synoviocytes (FLS) acquire apoptosis resistance through signaling pathways such as the Bcl-2 family, JAK/STAT, and NF-κB, allowing for the consistent proliferation and secretion of matrix metalloproteinases and pro-inflammatory cytokines. Meanwhile, the continuous activation of pyroptotic pathways in neutrophils and macrophages results in the sustained release of IL-1β, further exacerbating synovial inflammation and bone destruction. Notably, dysregulated PCD fosters inter-organ crosstalk through shared inflammatory mediators and metabolic networks. Damage-associated molecular patterns (DAMPs) and cytokines that originate from periodontal lesions can spread systemically, influencing cell death processes in synovial and immune cells, thereby aggravating joint inflammation and bone erosion. By contrast, systemic inflammation in RA can upregulate osteoclastic activity or interfere with the normal apoptosis of periodontal cells via TNF-α and IL-6, ultimately intensifying periodontal immune imbalance. This review highlights the pivotal bridging role of PCD in the pathogenesis of both periodontitis and RA, providing a reference for therapeutic strategies that target cell death pathways to manage and potentially mitigate these diseases.

【Key words】 periodontitis; rheumatoid arthritis; immune imbalance; programmed cell death; apoptosis; necroptosis; pyroptosis

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1　牙周炎与类风湿性关节炎的关系

牙周病是危害口腔健康最常见的疾病之一,在世界流行病中位列第六,全球范围内约有10%的成年人患有重度牙周炎[1]。牙周炎已成为成年人失牙的主要原因。然而,牙周炎不仅影响口腔健康,还可通过多种途径影响系统性疾病的发生发展,其中就包括RA[2-3]。

RA是一种会影响关节内膜,引起疼痛肿胀,最终导致骨破坏和关节畸形的慢性自身免疫性疾病,以滑膜炎症、肿胀,抗瓜氨酸蛋白抗体(anti-citrullinated protein antibody,ACPA)等自身抗体的产生,多关节软骨及骨破坏和全身并发症为特征,是最常见的慢性炎症性疾病之一[4-5]。牙周炎与RA都是慢性炎症性疾病,且具有诸多共同特征,包括共同的炎症机制、免疫异常及微生态变化。具体而言,牙周炎与RA均可出现固有免疫与适应性免疫的协同失衡,尤其是中性粒细胞与巨噬细胞过度激活[6-7],不仅促进自身抗体与免疫复合物的形成,还可导致高水平的TNF-α、IL-1β等促炎细胞因子与NF-κB、MAPK等炎症相关信号通路的过度激活,加之牙周组织和关节滑膜在慢性炎症环境下均可出现血管通透性增加、免疫细胞浸润及诱导更多炎性因子的释放[8-9],形成持续性炎症正

反馈；此外，两种疾病都涉及不同程度的微生态失衡，牙周炎患者出现以牙龈卟啉单胞菌（*Porphyromonas gingivalis*，*P.gingivalis*）等致病菌占比增高为特征的口腔菌群紊乱[10]，而RA患者的肠道、口腔微生态亦可能出现类似的失衡[11]。

目前已有大量研究发现两者之间存在一定相互作用关系[12-19]。Schmickler等[12]通过对168例RA患者的牙周健康状况进行调查发现，RA患者的临床探诊深度、附着丧失水平及失牙数目显著高于对照组。de Smit等[13]发现，患重度牙周炎的RA患者28个关节疾病活动度评分及CRP水平均显著高于未患牙周炎的RA患者。此外，牙周炎与RA间还存在直接的生物学交叉。ACPA作为RA的重要标志之一，在RA的发生发展过程中发挥重要作用，可通过破坏瓜氨酸的耐受性来诱导自身免疫的发生，而牙周炎的主要致病菌*P.gingivalis*可通过分泌肽酰基精氨酸脱亚胺酶（peptidyl arginine deiminase，PAD）来促进蛋白质的瓜氨酸化[4]，进而导致ACPA升高。值得注意的是，*P.gingivalis*在牙周局部诱导的细胞程序性死亡（PCD）过程，尤其是焦亡和坏死性凋亡等炎症性死亡形式[20-21]，可能通过释放被瓜氨酸化的蛋白以及大量炎症因子[22]，进一步增加免疫系统对这些新抗原的识别机会，从而打破机体对瓜氨酸化蛋白的耐受，促进ACPA水平的持续升高。

近年来，PCD作为调控炎症与组织稳态的重要生物过程，在牙周炎和RA中的作用逐渐受到关注。其中，细胞凋亡（apoptosis）、焦亡（pyroptosis）及坏死性凋亡（necroptosis）等PCD形式在两种疾病的发病过程中可能起着关键作用，且可能作为两者关联的桥梁机制。

2　牙周炎与PCD

牙周炎作为一种由菌斑微生物始动、宿主自身免疫反应介导的慢性炎症性疾病，可致牙周支持组织的炎症性破坏[23]。在牙周炎发生发展中，牙周致病菌可通过激活Toll样受体4（Toll-like receptor 4，TLR4）/NF-κB和JAK/STAT等信号通路，诱导中性粒细胞、巨噬细胞等免疫细胞PCD失控，导致释放大量白细胞介素（interleukin，IL）-1β、肿瘤坏死因子（tumor necrosis factor，TNF）-α等炎症因子，从而放大牙周局部炎症失衡。失衡的PCD是介导炎症放大与组织破坏加剧的重要环节，由微生物刺激、宿主免疫反应以及炎症通路的异常激活所共同驱动。

2.1　凋亡与牙周稳态的失衡

1972年，Kerr等[24]首次提出“凋亡”这一术语，并通过电子显微镜观察记录了凋亡全过程，是最早被系统研究的程序性死亡形式。除了清除衰老或受损细胞维持组织正常功能外，胸腺中T细胞的阴性选择通过凋亡去除识别自身抗原的T细胞，避免自身免疫反应[25-26]。同时，凋亡还负责清除感染后活化的免疫细胞，以避免过度的炎症反应，是机体维持免疫平衡的重要生理过程之一[27]。通常情况下，在健康牙周组织中，成纤维细胞、成骨细胞以及免疫细胞的凋亡水平受到严格调控，以维持牙周微环境的稳态[28-30]。但有研究发现[31-34]，牙周致病菌可导致细胞的死亡模式发生改变，如*P.gingivalis*入侵时，其脂多糖（lipopolysaccharide，LPS）、精氨酸牙龈蛋白酶和PAD等毒力因子可干扰宿主细胞正常凋亡过程。其中，*P.gingivalis*来源的LPS和PAD可共同作用，并与TLR4结合，激活NF-κB、JAK/STAT信号通路，抑制中性粒细胞凋亡从而延长其存在时间；LPS还可能通过调控MicroRNA（miR）-499/NRIP1轴，激活JAK/STAT信号通路，抑制巨噬细胞凋亡，从而延缓这些免疫细胞的清除，促进它们持续释放促炎因子，加剧局部组织破坏。牙周炎中，NF-κB、MAPK、JAK/STAT和PI3K/AKT等多种信号通路与转录因子参与PCD过程的调控[35-37]。其中，NF-κB的持续激活不仅能促进IL-1β、TNF-α等促炎因子释放，也可上调凋亡相关蛋白Bcl-2的表达并调控Caspase家族的转录与翻译[38]，从而决定细胞的生存与死亡倾向。

2.2　焦亡及坏死性凋亡对牙周炎症的放大

焦亡是一种由炎症小体激活的PCD形式，其标志是气孔形成蛋白介导的细胞膜穿孔和IL-1β、IL-18等炎症因子的释放[39-40]。而IL-1β和IL-18则可募集和激活巨噬细胞及中性粒细胞[41]，且焦亡细胞所释放的损伤相关分子模式（damage-associated molecular pattern，DAMP）可增强树突状细胞的抗原递呈能力[42]，因此常伴随强烈的炎症反应。坏死性凋亡是一种具有促炎特性的PCD，由受体相互作用蛋白激酶（receptor interacting protein kinase，RIPK）-1和RIPK-3及混合谱系激酶样蛋白（mixed lineage kinase-like，MLKL）介导。需要注意的是，坏死性凋亡（necroptosis）并非是凋亡（apoptosis）的特殊或病理形式，其因兼具细胞坏死和凋亡的特征，所以得名“坏死性凋亡”，两者具有截然不同的分

子机制和表现。坏死性凋亡在感染及促进炎症反应方面发挥重要作用，并可在凋亡受阻时作为备选细胞死亡方式被激活，发挥“兜底”作用[43]。

牙周炎时，*P.gingivalis* 可通过其LPS等毒力因子与宿主免疫细胞表面的TLR4结合，启动NF-κB信号通路，激活NLRP3炎症小体[44]。同时，由致病菌引起的炎症反应会导致局部氧化应激水平升高，活性氧（reactive oxygen species，ROS）等氧化产物可以直接刺激NLRP3炎症小体的激活[45]。牙周组织中的巨噬细胞可通过NLRP3炎症小体途径发生焦亡，并伴随IL-1β和IL-18等炎症因子的释放[46-47]。此类促炎因子的过量产生将进一步招募中性粒细胞与单核细胞浸润，加剧骨吸收与软组织破坏[48]。类似地，坏死性凋亡在病原刺激下可释放大量DAMPs，并与其他PCD方式联动，形成炎症级联放大效应，使牙周炎症难以消退[49-50]。

3　类风湿性关节炎中的PCD

RA是以滑膜炎症与关节结构破坏为特征的全身性自身免疫病。RA患者的滑膜环境中，滑膜成纤维细胞（fibroblast-like synoviocytes，FLS）、巨噬细胞等多种细胞的PCD过程均出现严重紊乱[51-53]。

3.1　关节滑膜内细胞的凋亡失衡与异常增殖

FLS参与生成关节软骨及透明质酸等滑膜液成分，在健康关节中维持滑膜内稳态，然而，当FLS受到NF-κB、JAK/STAT、PI3K/AKT等多条促炎与增殖信号通路的持续刺激，可诱导FLS过表达Bcl-2、Mcl-1等多种抗凋亡蛋白，并抑制Bax、Bak等促凋亡蛋白的表达，同时，RA患者FLS表面Fas减少，导致Fas/FasL死亡受体通路被抑制，导致内外源性凋亡均受阻[54-55]，使其出现凋亡抵抗并呈现出增殖过度和侵袭性等类肿瘤细胞特征，是RA滑膜增生的关键特征[56]。此外，RA中PCD调控同样也受到表观遗传修饰的影响。Zhang等[57]发现，miR-361-5p通过抑制FLS凋亡，促进其异常增殖，进而加重RA。这种凋亡抵抗使FLS持续存在并持续分泌炎症介质与基质金属蛋白酶（matrix metalloproteinases，MMPs），加剧关节软骨与骨组织的破坏[58]。此外，由于巨噬细胞等免疫细胞的凋亡受阻，免疫细胞在关节滑膜中异常聚集，持续释放TNF-α、IL-1β等炎症因子，刺激自身抗原的递呈及自身抗体的生成，从而不断推动RA的发生与进展[59-60]。

3.2　焦亡、坏死性凋亡与关节慢性炎症循环

RA患者关节滑膜中持续存在高水平的氧化应激，ROS和其他氧化物质通过直接作用于NLRP3，促进其激活[61]。随着NLRP3炎症小体的过度活化，由其介导的经典焦亡途径被激活[62-63]。持续的焦亡失衡与凋亡失衡可导致巨噬细胞、FLS不断释放IL-1β、TNF-α等促炎因子[46]，这些因子不仅直接参与关节软骨与骨质破坏，还可改变关节局部免疫平衡，进一步诱导更多免疫细胞向病灶聚集，使关节滑膜始终处于高炎症状态。同时，TNF-α等促炎因子的大量积累可激活RIPK1，RIPK1与RIPK3结合形成复合物，随后激活MLKL。激活的MLKL通过跨膜作用导致细胞膜穿孔，进而导致巨噬细胞的坏死性凋亡，释放TNF-α等大量促炎因子，进一步加强了自身免疫反应和关节损伤的恶性循环[64]。

RA关节微环境高水平的炎症因子和氧化应激可引发炎症性PCD，如焦亡与坏死性凋亡，而巨噬细胞及其他免疫细胞焦亡则进一步导致IL-1β等促炎因子的持续释放，再度放大炎症反应。而坏死性凋亡释放的DAMPs进一步刺激免疫反应，形成恶性循环，使关节滑膜中始终处于高炎症状态。

4　PCD的桥梁作用

牙周炎与RA在病理改变以及免疫学特征上存在诸多相似之处。近年来的研究进一步聚焦于两者共同病理过程中PCD的作用机制。这些细胞死亡过程可能并非孤立事件，而是通过改变微环境、影响免疫应答及组织稳态，从而在牙周炎与RA两者的发生与进展过程中起到“桥梁”作用。

4.1　局部与全身炎症的相互强化：PCD在双向影响中的关键地位

牙周炎的局部炎症始于牙周致病菌与牙周软、硬组织的复杂相互作用，当牙周组织中的中性粒细胞和巨噬细胞等免疫细胞受到持续刺激时，其凋亡与焦亡等PCD过程的平衡被打破，免疫细胞分泌的IL-1β、TNF-α、IL-6等炎症因子可通过血液循环，使机体处于低度炎症状态[65-66]。IL-1β、TNF-α等因子可上调细胞间黏附分子-1和单核细胞趋化蛋白-1等血管内皮细胞表面黏附分子及趋化因子，使更多免疫细胞迁移并黏附至血管内皮，随后渗出至关节滑膜[5]。持续的炎症刺激会导致关节滑膜内免疫细胞聚集，加剧局部炎症，同时还可促进关节滑膜中免疫细胞的活化与异常细胞死亡的出现，加剧关节破坏[67]。

同时，RA患者滑膜中的免疫细胞发生异常

PCD过程，并释放多种促炎分子，这些促炎分子会在牙周局部诱导血管内皮细胞表达黏附分子，促进免疫细胞向牙周组织浸润[68]；同时上调RANKL、IL-17等介质，刺激破骨细胞活化，导致牙槽骨吸收，最终对牙周免疫微环境及软硬组织产生负面影响[69-70]。

PCD不仅是衰老或受损细胞的单纯清除，更是将微环境的信号传递至组织器官导致结构与功能变化的重要环节[71-72]。当PCD通路在牙周组织中被致病菌与免疫失衡因素反复激活时，其后果不仅表现为炎症介质的释放和免疫细胞的聚集，更关键的是通过调控软硬组织的破坏与修复，最终导致器官形态与功能的病理性重塑。这种从分子到组织的深层次影响可通过全身信号网络实现跨器官联动。牙周组织中由PCD驱动的基质分解产物、骨吸收信号以及DAMPs等分子可以通过血液循环影响远端器官[73-74]，对关节微环境下成骨细胞、软骨细胞及免疫细胞的反应模式施加影响。反之，RA关节中由PCD紊乱触发的骨质破坏信号与免疫失衡产物同样可影响牙周组织，进一步导致牙周结构破坏。

4.2　表观遗传调控与环境因素参与牙周炎与RA的相互作用

PCD过程的调控与表观遗传学修饰密切相关[75]。研究发现，miR-155、miR-146a在两种疾病中均出现异常表达，进而影响多条细胞死亡与炎症信号通路[76-78]，从而在全身层面将口腔和关节的慢性炎症连接起来。提示在牙周炎和RA患者中，免疫细胞及成纤维细胞的表观遗传学特征存在相似变化，这些变化影响了细胞对促炎和死亡信号的响应。

此外，环境因素也可能通过影响PCD的表观遗传调控与代谢通路[79]，从而增加个体同时患牙周炎与RA的风险。吸烟作为两者的共同危险因素[80-81]，不仅可加重牙周组织中炎症和PCD失调，也能在RA中促进异常的自身免疫反应与炎症损伤。

4.3　其他PCD的作用

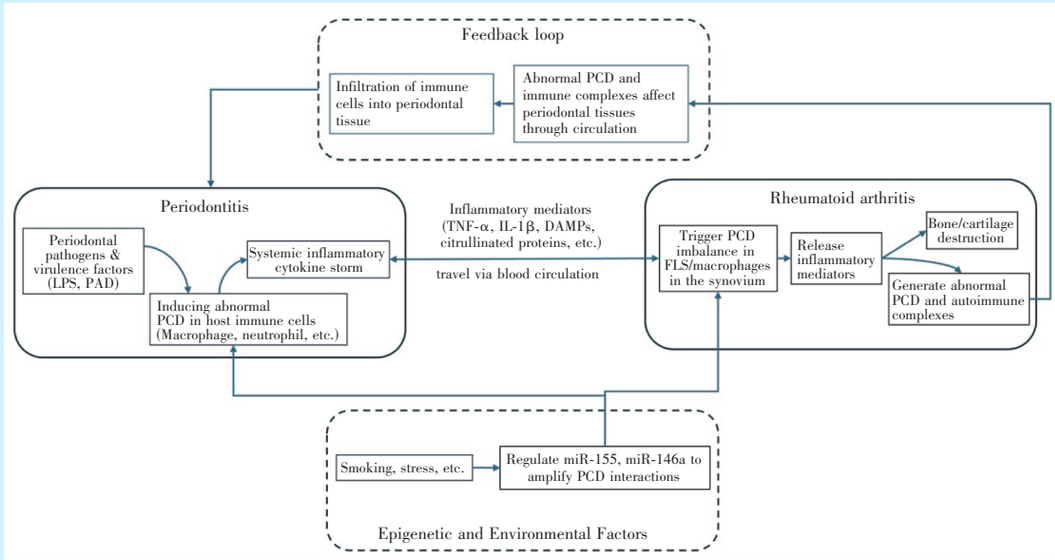
在牙周炎和RA中均存在中性粒细胞的病理性存活（正常凋亡被抑制），而中性粒细胞有一特有的PCD形式，即NETosis，该PCD伴随中性粒细胞胞外陷阱（neutrophil extracellular traps，NETs）的释放，具有促炎特性[82]。在牙周炎中，TNF-α等炎症因子的积累以及*P.gingivalis*、伴放线聚集杆菌等致病菌的毒性产物可诱导NETosis，释放瓜氨酸化蛋白，激发RA自身免疫反应[83]。而RA则通过全身性炎症与自身抗体增强牙周局部的NETosis，形成炎症的双向促进[84]。

铜死亡是过量的铜结合到三羧酸循环的脂酰化蛋白上，导致蛋白质聚集并引发细胞毒性压力，最终导致细胞死亡[85]。牙周致病菌LPS可导致巨噬细胞内铜的过度积累，进而出现铜死亡，导致溶酶体和线粒体结构受损，从而出现自噬和线粒体自噬异常，导致受损细胞器无法及时清除，进一步导致了胞内炎症因子的堆积[86]。而在RA中，由于滑膜低氧环境以及FLS类肿瘤细胞特征所致的Warburg效应，使谷氨酰胺被快速消耗，从而抑制铜死亡的发生。铜死亡的抑制则可导致FLS和T细胞等免疫细胞的病理性存活，进一步加重关节炎症和破坏[87]。RA中Warburg效应使能量代谢以糖酵解、谷氨酰胺代谢为主，是否可推测其可能通过血液中谷氨酰胺等代谢产物水平反馈调节牙周巨噬细胞的铜离子稳态和线粒体功能，进而影响铜死亡的发生？目前针对铜死亡在RA与牙周炎关系中的作用研究尚少，其具体调控机制以及与其他PCD的交互亟待进一步研究揭示。

随着研究深入，诸如铜死亡、泛凋亡（PANoptosis）和双硫死亡等越来越多的新型PCD形式逐渐浮现，但其在牙周炎与RA中的作用研究尚在起步阶段，进一步增加对这些PCD的研究，对丰富二者关联的理解并开辟更多研究思路有深远意义。

5　展　望

PCD为牙周炎与RA之间的关联提供了一个重要的病理与免疫学层面上的桥梁（图1）。如果在牙周炎治疗中，有效控制致病菌及其诱导的细胞凋亡、焦亡等PCD失衡，不仅能减少牙周组织破坏程度，还可能降低全身炎症水平，从而对RA的关节破坏进程产生抑制作用。同样，对于RA患者，调控PCD的动态平衡，不仅有助于缓解关节炎症，也可能改善牙周健康。此外，通过干预表观遗传修饰，也显示出对口腔与关节微环境中PCD平衡的调控潜力，从而对牙周炎与RA产生协同保护作用[88-89]。将PCD作为研究和治疗的切入点，不仅能够揭示牙周炎与RA背后的共病机制，还为临床治疗提供了新思路和多样化的选择。未来的研究有望通过进一步探索PCD调控策略，开发出更精准、联合效应更显著的治疗方案，助力两种疾病的



The schematic diagram illustrates the correlation between periodontitis and rheumatoid arthritis, emphasizing the "bridging role" of PCD in tissue damage and immune responses, as well as the potential regulatory influence of environmental and epigenetic factors in this process. LPS: lipopolysaccharide; PAD: peptidyl arginine deiminase; IL: interleukin; TNF: tumor necrosis factor; FLS: fibroblast-like synoviocytes; miR: microRNA; PCD: programmed cell death

Figure 1　Schematic diagram showing the "bridging role" of programmed cell death in periodontitis and rheumatoid arthritis

图1　牙周炎与类风湿关节炎中细胞程序性死亡的"桥梁作用"示意图

综合管理。

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参考文献

[1] Hajishengallis G. Interconnection of periodontal disease and comorbidities: evidence, mechanisms, and implications[J]. Periodontol 2000, 2022, 89(1): 9-18. doi: 10.1111/prd.12430.

[2] González-Febles J, Sanz M. Periodontitis and rheumatoid arthritis: what have we learned about their connection and their treatment? [J]. Periodontol 2000, 2021, 87(1): 181 - 203. doi: 10.1111/prd.12385.

[3] Lopez-Oliva I, Malcolm J, Culshaw S. Periodontitis and rheumatoid arthritis: global efforts to untangle two complex diseases[J]. Periodontol 2000, 2024. doi: 10.1111/prd.12530.

[4] McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis[J]. N Engl J Med, 2011, 365(23): 2205 - 2219. doi: 10.1056/NEJMra1004965.

[5] Di Matteo A, Bathon JM, Emery P. Rheumatoid arthritis[J]. Lancet, 2023, 402(10416): 2019-2033. doi: 10.1016/S0140-6736(23)01525-8.

[6] Hashai K, Abadi F, Clyman D, et al. Macrophages polarize to the pro-inflammatory phenotype and delay neutrophil efferocytosis to augment *Aggregatibacter actinomycetemcomitance* JP2 clearance [J]. J Periodontal Res, 2023, 58(5): 997 - 1005. doi: 10.1111/jre.13160.

[7] Zhang X, Zhao W, Zhao Y, et al. Inflammatory macrophages exacerbate neutrophil-driven joint damage through ADP/P2Y(1) signaling in rheumatoid arthritis[J]. Sci China Life Sci, 2022, 65(5): 953-968. doi: 10.1007/s11427-020-1957-8.

[8] Hao T, Zhang R, Zhao T, et al. *Porphyromonas gingivalis* infection promotes inflammation *via* inhibition of the AhR signalling pathway in periodontitis[J]. Cell Prolif, 2023, 56(2): e13364. doi: 10.1111/cpr.13364.

[9] Deng R, Bu Y, Li F, et al. The interplay between fibroblast-like synovial and vascular endothelial cells leads to angiogenesis *via* the sphingosine-1-phosphate-induced RhoA-F-actin and Ras-Erk1/2 pathways and the intervention of geniposide[J]. Phytother Res, 2021, 35(9): 5305-5317. doi: 10.1002/ptr.7211.

[10] Chigasaki O, Aoyama N, Sasaki Y, et al. *Porphyromonas gingivalis*, the most influential pathogen in red-complex bacteria: a cross-sectional study on the relationship between bacterial count and clinical periodontal status in Japan[J]. J Periodontol, 2021, 92(12): 1719-1729. doi: 10.1002/JPER.21-0011.

[11] García S. Microbiome status as a predictive tool for response to therapy in rheumatoid arthritis[J]. Rheumatology(Oxford), 2024, 63(12): 3199-3200. doi: 10.1093/rheumatology/keae292.

[12] Schmickler J, Rupprecht A, Patschan S, et al. Cross-sectional evaluation of periodontal status and microbiologic and rheumatoid parameters in a large cohort of patients with rheumatoid arthritis [J]. J Periodontol, 2017, 88(4): 368 - 379. doi: 10.1902/

jop.2016.160355.

[13] de Smit M, Westra J, Vissink A, et al. Periodontitis in established rheumatoid arthritis patients: a cross-sectional clinical, microbiological and serological study[J]. Arthritis Res Ther, 2012, 14(5): R222. doi: 10.1186/ar4061.

[14] Massarenti L, Enevold C, Damgaard D, et al. Peptidylarginine deiminase 2 gene polymorphisms in subjects with periodontitis predispose to rheumatoid arthritis[J]. Int J Mol Sci, 2022, 23(17): 9536. doi: 10.3390/ijms23179536.

[15] Bolstad AI, Fevang BS, Lie SA. Increased risk of periodontitis in patients with rheumatoid arthritis: a nationwide register study in Norway[J]. J Clin Periodontol, 2023, 50(8): 1022 - 1032. doi: 10.1111/jcpe.13826.

[16] Nik-Azis NM, Mohd N, Mohd Fadzilah F, et al. Rheumatoid arthritis serotype and synthetic disease-modifying anti-rheumatic drugs in patients with periodontitis: a case-control study[J]. PLoS One, 2021, 16(6): e0252859. doi: 10.1371/journal.pone.0252859.

[17] Svärd A, Kastbom A, Ljungberg KR, et al. Antibodies against *Porphyromonas gingivalis* in serum and saliva and their association with rheumatoid arthritis and periodontitis. Data from two rheumatoid arthritis cohorts in Sweden[J]. Front Immunol, 2023, 14: 1183194. doi: 10.3389/fimmu.2023.1183194.

[18] Hashimoto H, Hashimoto S, Shimazaki Y. Functional impairment and periodontitis in rheumatoid arthritis[J]. Int Dent J, 2022, 72(5): 641-647. doi: 10.1016/j.identj.2022.01.002.

[19] de Pablo P, Serban S, Lopez-Oliva I, et al. Outcomes of periodontal therapy in rheumatoid arthritis: the OPERA feasibility randomized trial[J]. J Clin Periodontol, 2023, 50(3): 295 - 306. doi: 10.1111/jcpe.13756.

[20] Li Y, Li B, Liu Y, et al. *Porphyromonas gingivalis* lipopolysaccharide affects oral epithelial connections *via* pyroptosis[J]. J Dent Sci, 2021, 16(4): 1255-1263. doi: 10.1016/j.jds.2021.01.003.

[21] Li YY, Cai Q, Li BS, et al. The effect of *Porphyromonas gingivalis* lipopolysaccharide on the pyroptosis of gingival fibroblasts[J]. Inflammation, 2021, 44(3): 846 - 858. doi: 10.1007/s10753 - 020 - 01379-7.

[22] Moadab F, Wang X, Le E, et al. Evidence of membranolytic targeting and intracellular citrullination in neutrophils isolated from patients with rheumatoid arthritis[J]. Sci Rep, 2024, 14(1): 15511. doi: 10.1038/s41598-024-66516-w.

[23] 张倩, 陈斌, 闫福华. 牙周基础治疗后龈沟液中4种生物标志物水平变化及临床意义[J]. 口腔疾病防治, 2021, 29(12): 828-835. doi: 10.12016/j.issn.2096-1456.2021.12.005.
Zhang Q, Chen B, Yan FH. Changes and clinical significance of four biomarkers in gingival crevicular fluid after nonsurgical periodontal therapy[J]. J Prev Treat Stomatol Dis, 2021, 29(12): 828-835. doi: 10.12016/j.issn.2096-1456.2021.12.005.

[24] Kerr JF, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics[J]. Br J Cancer, 1972, 26(4): 239-257. doi: 10.1038/bjc.1972.33.

[25] Givony T, Leshkowitz D, Del Castillo D, et al. Thymic mimetic cells function beyond self-tolerance[J]. Nature, 2023, 622(7981): 164-172. doi: 10.1038/s41586-023-06512-8.

[26] Boulet S, Odagiu L, Dong M, et al. NR4A3 mediates thymic negative selection[J]. J Immunol, 2021, 207(4): 1055 - 1064. doi: 10.4049/jimmunol.1901228.

[27] Hove-Skovsgaard M, Zhao Y, Tingstedt JL, et al. Impact of age and HIV status on immune activation, senescence and apoptosis [J]. Front Immunol, 2020, 11: 583569. doi: 10.3389/fimmu.2020.583569.

[28] Guo S, Fu L, Yin C, et al. ROS-induced gingival fibroblast senescence: implications in exacerbating inflammatory responses in periodontal disease[J]. Inflammation, 2024, 47(6): 1918-1935. doi: 10.1007/s10753-024-02014-5.

[29] Huang Y, Zhang L, Tan L, et al. Interleukin-22 inhibits apoptosis of gingival epithelial cells through TGF-β signaling pathway during periodontitis[J]. Inflammation, 2023, 46(5): 1871 - 1886. doi: 10.1007/s10753-023-01847-w.

[30] Batoon L, Koh AJ, Millard SM, et al. Induction of osteoblast apoptosis stimulates macrophage efferocytosis and paradoxical bone formation[J]. Bone Res, 2024, 12(1): 43. doi: 10.1038/s41413-024-00341-9.

[31] Prucsi Z, Zimny A, Płonczyńska A, et al. *Porphyromonas gingivalis* peptidyl arginine deiminase (PPAD) in the context of the feed-forward loop of inflammation in periodontitis[J]. Int J Mol Sci, 2023, 24(16): 12922. doi: 10.3390/ijms241612922.

[32] Wang C, Li X. MiR-499 enhances *Porphyromonas gingivalis* LPS-induced inflammatory response in macrophages by targeting NRIP1 *via* JAK/STAT pathway[J]. J Biosci, 2023, 48: 51.

[33] Castro SA, Collighan R, Lambert PA, et al. *Porphyromonas gingivalis* gingipains cause defective macrophage migration towards apoptotic cells and inhibit phagocytosis of primary apoptotic neutrophils[J]. Cell Death Dis, 2017, 8(3): e2644. doi: 10.1038/cddis.2016.481.

[34] Sochalska M, Stańczyk MB, Użarowska M, et al. Application of the *in vitro* Ho_xB8 model system to characterize the contributions of neutrophil-LPS interaction to periodontal disease[J]. Pathogens, 2020, 9(7): 530. doi: 10.3390/pathogens9070530.

[35] Lü L, Yakoumatos L, Ren J, et al. JAK3 restrains inflammatory responses and protects against periodontal disease through Wnt3a signaling[J]. FASEB J, 2020, 34(7): 9120 - 9140. doi: 10.1096/fj.201902697RR.

[36] Yu T, Mi N, Song Y, et al. Exosomes miR-92a-3p from human exfoliated deciduous teeth inhibits periodontitis progression *via* the KLF4/PI3K/AKT pathway[J]. J Periodontal Res, 2024, 59(4): 771-782. doi: 10.1111/jre.13262.

[37] Sun M, Ji Y, Li Z, et al. Ginsenoside Rb3 inhibits pro-inflammatory cytokines *via* MAPK/AKT/NF-κB pathways and attenuates rat alveolar bone resorption in response to *Porphyromonas gingivalis* LPS[J]. Molecules, 2020, 25(20): 4815. doi: 10.3390/molecules25204815.

[38] Long M, Wang Z, Shao L, et al. Electroacupuncture pretreatment attenuates cerebral ischemia-reperfusion injury in rats through transient receptor potential vanilloid 1-mediated anti-apoptosis *via*

inhibiting NF-κB signaling pathway[J]. Neuroscience, 2022, 482: 100-115. doi: 10.1016/j.neuroscience.2021.12.017.

[39] Shi J, Zhao Y, Wang K, et al. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death[J]. Nature, 2015, 526(7575): 660-665. doi: 10.1038/nature15514.

[40] Ding J, Wang K, Liu W, et al. Pore-forming activity and structural autoinhibition of the gasdermin family[J]. Nature, 2016, 535 (7610): 111-116. doi: 10.1038/nature18590.

[41] Babcock IW, Sibley LA, Labuzan SA, et al. Caspase-1 in Cx3cr1-expressing cells drives an IL-18-dependent T cell response that promotes parasite control during acute toxoplasma gondii infection [J]. PLoS Pathog, 2024, 20(10): e1012006. doi: 10.1371/journal.ppat.1012006.

[42] Zhou Z, He H, Wang K, et al. Granzyme A from cytotoxic lymphocytes cleaves GSDMB to trigger pyroptosis in target cells[J]. Science, 2020, 368(6494): eaaz7548. doi: 10.1126/science.aaz7548.

[43] Gong YN, Guy C, Olauson H, et al. ESCRT-III acts downstream of MLKL to regulate necroptotic cell death and its consequences[J]. Cell, 2017, 169(2): 286-300.e16. doi: 10.1016/j.cell.2017.03.020.

[44] Kim SY, Son MK, Park JH, et al. The anti-inflammatory effect of SDF-1 derived peptide on *Porphyromonas gingivalis* infection *via* regulation of NLRP3 and AIM2 inflammasome[J]. Pathogens, 2024, 13(6): 474. doi: 10.3390/pathogens13060474.

[45] Jiang X, Ding X, Wei J, et al. Dioscin alleviates periodontitis by inhibiting NLRP3 inflammasome activation *via* regulation of K(+) homeostasis and mitochondrial function[J]. Int J Biol Sci, 2024, 20 (4): 1375-1388. doi: 10.7150/ijbs.85851.

[46] Zhao Z, Ming Y, Li X, et al. Hyperglycemia aggravates periodontitis *via* autophagy impairment and ROS-inflammasome-mediated macrophage pyroptosis[J]. Int J Mol Sci, 2023, 24(7): 6309. doi: 10.3390/ijms24076309.

[47] Wang L, Pu W, Wang C, et al. Microtubule affinity regulating kinase 4 promoted activation of the NLRP3 inflammasome-mediated pyroptosis in periodontitis[J]. J Oral Microbiol, 2021, 14(1): 2015130. doi: 10.1080/20002297.2021.2015130.

[48] Sasaki Y, Otsuka K, Arimochi H, et al. Distinct roles of IL-1β and IL-18 in NLRC4-induced autoinflammation[J]. Front Immunol, 2020, 11: 591713. doi: 10.3389/fimmu.2020.591713.

[49] Gavali N, Chaudhari A, Waghmare P, et al. Role of *Porphyromonas gingivalis* in the downregulation of NLRp3 inflammasome in periodontitis[J]. J Int Clin Dent Res Organ, 2022, 14(2): 91-95. doi: 10.4103/jicdro.jicdro_37_21.

[50] Tweedell RE, Hibler T, Kanneganti TD. Defining PANoptosis: biochemical and mechanistic evaluation of innate immune cell death activation[J]. Curr Protoc, 2024, 4(7): e1112. doi: 10.1002/cpz1.1112.

[51] Abdullah WL, AL-Hashimy AF, Al-Ghurabi BH, et al. Focus on the function and mechanism of pyroptosis in rheumatoid arthritis [J]. Al Salam J Med Sci, 2023, 3(1): 28-36. doi: 10.55145/ajbms.2024.03.01.006.

[52] Wu T, Zhang XP, Zhang Q, et al. Gasdermin-E mediated pyroptosis-a novel mechanism regulating migration, invasion and release of inflammatory cytokines in rheumatoid arthritis fibroblast-like synoviocytes[J]. Front Cell Dev Biol, 2022, 9: 810635. doi: 10.3389/fcell.2021.810635.

[53] Hanlon MM, Canavan M, Barker BE, et al. Metabolites as drivers and targets in rheumatoid arthritis[J]. Clin Exp Immunol, 2022, 208(2): 167-180. doi: 10.1093/cei/uxab021.

[54] Zhang X, Feng H, Du J, et al. Aspirin promotes apoptosis and inhibits proliferation by blocking G0/G1 into S phase in rheumatoid arthritis fibroblast-like synoviocytes *via* downregulation of JAK/STAT3 and NF-κB signaling pathway[J]. Int J Mol Med, 2018, 42 (6): 3135-3148. doi: 10.3892/ijmm.2018.3883.

[55] Cao C, Zhang Y, Cheng J, et al. β-arrestin2 inhibits the apoptosis and facilitates the proliferation of fibroblast-like synoviocytes in diffuse-type tenosynovial giant cell tumor[J]. Cancer Genomics Proteomics, 2021, 18(3 Suppl): 461-470. doi: 10.21873/cgp.20272.

[56] Caire R, Audoux E, Courbon G, et al. YAP/TAZ: key players for rheumatoid arthritis severity by driving fibroblast like synoviocytes phenotype and fibro-inflammatory response[J]. Front Immunol, 2021, 12: 791907. doi: 10.3389/fimmu.2021.791907.

[57] Zhang A, Lu R, Lang H, et al. MiR-361-5p promotes proliferation and inhibits apoptosis of fibroblast-like synoviocytes *via* targeting ZBTB10 in rheumatoid arthritis[J]. Autoimmunity, 2022, 55(5): 310-317. doi: 10.1080/08916934.2022.2073588.

[58] Hu Z, Chen J, Wang M, et al. Rheumatoid arthritis fibroblast-like synoviocytes maintain tumor-like biological characteristics through ciRS-7-dependent regulation of miR-7[J]. Mol Biol Rep, 2022, 49(9): 8473-8483. doi: 10.1007/s11033-022-07666-w.

[59] Li J, Zhang L, Zheng Y, et al. BAD inactivation exacerbates rheumatoid arthritis pathology by promoting survival of sublining macrophages[J]. Elife, 2020, 9: e56309. doi: 10.7554/eLife.56309.

[60] Carmona-Rivera C, Carlucci PM, Goel RR, et al. Neutrophil extracellular traps mediate articular cartilage damage and enhance cartilage component immunogenicity in rheumatoid arthritis[J]. JCI Insight, 2020, 5(13): e139388. doi: 10.1172/jci.insight.139388.

[61] Jing M, Yang J, Zhang L, et al. Celastrol inhibits rheumatoid arthritis through the ROS-NF-κB-NLRP3 inflammasome axis[J]. Int Immunopharmacol, 2021, 98: 107879. doi: 10.1016/j.intimp.2021.107879.

[62] Zeng C, Duan F, Hu J, et al. NLRP3 inflammasome-mediated pyroptosis contributes to the pathogenesis of non-ischemic dilated cardiomyopathy[J]. Redox Biol, 2020, 34: 101523. doi: 10.1016/j.redox.2020.101523.

[63] Xu XN, Jiang Y, Yan LY, et al. Aesculin suppresses the NLRP3 inflammasome-mediated pyroptosis *via* the Akt/GSK3β/NF-κB pathway to mitigate myocardial ischemia/reperfusion injury[J]. Phytomedicine, 2021, 92: 153687. doi: 10.1016/j.phymed.2021.153687.

[64] Trimova G, Yamagata K, Iwata S, et al. Tumour necrosis factor alpha promotes secretion of 14-3-3eta by inducing necroptosis in macrophages[J]. Arthritis Res Ther, 2020, 22(1): 24. doi: 10.1186/s13075-020-2110-9.

[65] Santos WS, Solon IG, Branco LGS. Impact of periodontal lipopolysaccharides on systemic health: mechanisms, clinical implica-

tions, and future directions[J]. Mol Oral Microbiol, 2024. doi: 10.1111/omi.12490.

[66] Zhang R, Wu Z, Li M, et al. Canonical and noncanonical pyroptosis are both activated in periodontal inflammation and bone resorption[J]. J Periodontal Res, 2022, 57(6): 1183-1197. doi: 10.1111/jre.13055.

[67] Zhang X, Zhang Z, Zhao Y, et al. Sodium chloride promotes macrophage pyroptosis and aggravates rheumatoid arthritis by activating SGK1 through GABA receptors Slc6a12[J]. Int J Biol Sci, 2024, 20(8): 2922-2942. doi: 10.7150/ijbs.93242.

[68] Hajishengallis G, Chavakis T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities[J]. Nat Rev Immunol, 2021, 21(7): 426-440. doi: 10.1038/s41577-020-00488-6.

[69] Oliveira JA, de Oliveira Alves R, Nascimento IM, et al. Pro- and anti-inflammatory cytokines and osteoclastogenesis-related factors in peri-implant diseases: systematic review and meta-analysis[J]. BMC Oral Health, 2023, 23(1): 420. doi: 10.1186/s12903-023-03072-1.

[70] Komatsu N, Win S, Yan M, et al. Plasma cells promote osteoclastogenesis and periarticular bone loss in autoimmune arthritis[J]. J Clin Invest, 2021, 131(10): e150274. doi: 10.1172/JCI143060.

[71] Fane M, Weeraratna AT. How the ageing microenvironment influences tumour progression[J]. Nat Rev Cancer, 2020, 20(2): 89-106. doi: 10.1038/s41568-019-0222-9.

[72] Kesavardhana S, Malireddi RKS, Kanneganti TD. Caspases in cell death, inflammation, and pyroptosis[J]. Annu Rev Immunol, 2020, 38: 567-595. doi: 10.1146/annurev-immunol-073119-095439.

[73] Chapple ILC, Hirschfeld J, Cockwell P, et al. Interplay between periodontitis and chronic kidney disease[J]. Nat Rev Nephrol, 2024. doi: 10.1038/s41581-024-00910-5.

[74] Suárez LJ, Garzón H, Arboleda S, et al. Oral dysbiosis and autoimmunity: from local periodontal responses to an imbalanced systemic immunity. A review[J]. Front Immunol, 2020, 11: 591255. doi: 10.3389/fimmu.2020.591255.

[75] Gautam A, Chakraborty N, Dimitrov G, et al. Microgravity's effects on miRNA-mRNA regulatory networks in a mouse model of segmental bone defects[J]. PLoS One, 2024, 19(12): e0313768. doi: 10.1371/journal.pone.0313768.

[76] Wu P, Feng J, Wang W. Expression of miR-155 and miR-146a in the saliva of patients with periodontitis and its clinical value[J]. Am J Transl Res, 2021, 13(6): 6670-6677.

[77] Tavasolian F, Hosseini AZ, Soudi S, et al. MiRNA-146a improves immunomodulatory effects of MSC-derived exosomes in rheumatoid arthritis[J]. Curr Gene Ther, 2020, 20(4): 297-312. doi: 10.2174/1566523220666200916120708.

[78] Bagheri-Hosseinabadi Z, Mirzaei MR, Hajizadeh MR, et al. Plasma microRNAs (miR-146a, miR-103a, and miR-155) as potential biomarkers for rheumatoid arthritis (RA) and Disease Activity in Iranian patients[J]. Mediterr J Rheumatol, 2021, 32(4): 324-330. doi: 10.31138/mjr.32.4.324.

[79] Ruiz-Villaverde R, Cebolla-Verdugo M, Prados-Carmona A, et al. Mechanism, diagnostic and therapeutic novelties in dermatology: where are we going? [J]. Life(Basel), 2024, 14(10): 1236. doi: 10.3390/life14101236.

[80] Papatriantafyllou M. A lung-joint axis in smokers with RA?[J]. Nat Rev Rheumatol, 2025, 21(1): 2. doi: 10.1038/s41584-024-01200-x.

[81] Sim KY, Jang YS, Jang YS, et al. Association between smoking and periodontal disease in South Korean adults[J]. Int J Environ Res Public Health, 2023, 20(5): 4423. doi: 10.3390/ijerph20054423.

[82] Thiam HR, Wong SL, Wagner DD, et al. Cellular mechanisms of NETosis[J]. Annu Rev Cell Dev Biol, 2020, 36: 191-218. doi: 10.1146/annurev-cellbio-020520-111016.

[83] Maldonado A, Pirracchio L, Imber JC, et al. Citrullination in periodontium is associated with *Porphyromonas gingivalis*[J]. Arch Oral Biol, 2020, 114: 104695. doi: 10.1016/j.archoralbio.2020.104695.

[84] Shahbaz M, Al-Maleki AR, Cheah CW, et al. Connecting the dots: NETosis and the periodontitis-rheumatoid arthritis nexus[J]. Int J Rheum Dis, 2024, 27(11): e15415. doi: 10.1111/1756-185X.15415.

[85] Chen L, Min J, Wang F. Copper homeostasis and cuproptosis in health and disease[J]. Signal Transduct Target Ther, 2022, 7(1): 378. doi: 10.1038/s41392-022-01229-y.

[86] Zhang L, Tsai IC, Ni Z, et al. Copper chelation therapy attenuates periodontitis inflammation through the cuproptosis/autophagy/lysosome axis[J]. Int J Mol Sci, 2024, 25(11): 5890. doi: 10.3390/ijms25115890.

[87] Zhao J, Guo S, Schrodi SJ, et al. Cuproptosis and cuproptosis-related genes in rheumatoid arthritis: implication, prospects, and perspectives[J]. Front Immunol, 2022, 13: 930278. doi: 10.3389/fimmu.2022.930278.

[88] Li Q, Liu F, Dang R, et al. Epigenetic modifier trichostatin A enhanced osteogenic differentiation of mesenchymal stem cells by inhibiting NF-κB (p65) DNA binding and promoted periodontal repair in rats[J]. J Cell Physiol, 2020, 235(12): 9691-9701. doi: 10.1002/jcp.29780.

[89] Tang G, Sun C, Lv H, et al. Identification of novel meQTLs strongly associated with rheumatoid arthritis by large-scale epigenome-wide analysis[J]. FEBS Open Bio, 2022, 12(12): 2227-2235. doi: 10.1002/2211-5463.13517.

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