·综述·

基质细胞衍生因子1/CXC趋化因子受体4轴在骨免疫相关疾病中的研究进展

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【摘要】 骨免疫学是一个将骨生物学和免疫学领域结合起来的跨学科领域,近年来受到了学者的关注和深入探索。基质细胞衍生因子1(SDF-1)是一种趋化因子,影响各种生理途径。CXC趋化因子受体4(CXCR4)在各系统的细胞中广泛表达,参与机体生理及病理过程。在骨免疫疾病中,CXCR4与SDF-1结合并激活下游信号通路,在血管生成、免疫反应、骨吸收与骨生成中发挥着重要的作用。本文拟阐述目前SDF-1/CXCR4轴在骨免疫系统中的作用与机制,及其在骨免疫相关疾病中的研究进展,并探讨其在未来的发展前景。

【关键词】 基质细胞衍生因子1; 受体,CXCR4; 炎症反应; 骨疾病; 骨免疫

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Research progress of stromal cell derived factor-1/CXC-chemokine receptor 4 axis in bone-immune related diseases

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【**Abstract**】 Osteoimmunology is an interdisciplinarity which combines the fields of bone biology and immunology, and has been paid close attention to and deeply explored by scholars in recent years. Stromal cell derived factor-1 (SDF-1) is a chemokine that affects various physiological pathways. CXC-chemokine receptor 4 (CXCR4) is widely expressed in cells of various systems and participates in physiological and pathological processes. In bone-immune diseases, CXCR4 binds to SDF-1 and subsequently activates downstream signaling pathways, which plays an important role in angiogenesis, immune response, bone resorption and bone formation. In this review, the functions and mechanisms of SDF-1/CXCR4 axis in bone-immune system, its research progress in bone-immune related diseases as well as its prospect in the future were discussed.

【**Key words**】 Stromal cell derived factor-1 (SDF-1); Receptors, CXCR4; Inflammatory response; Bone diseases; Osteoimmunology

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近年来,骨免疫学(Osteoimmunology)领域的发现强调了骨骼系统与免疫系统之间通信和联系的重要性,具有广阔的应用前景。骨骼系统和免疫系统共享多种分子,包括细胞因子、趋化因子、受体、激素、转录因子和信号分子,骨细胞与免疫细胞在生理和病理条件下相互作用。CXC-趋化因子受体4(CXC-chemokine receptor 4,CXCR4)在机体中多个组织与器官广泛表达,在疾病状态下*CXCR4*表达上升介导炎症反应。基质细胞衍生因子1(stromal cell derived factor-1,SDF-1)是*CXCR4*的配体,参与机体发育并维持正常的生理活动。当异常刺激存在时,SDF-1与CXCR4结合可激活下游信号通路并形成复杂的网络结构,引发机体免疫反应。在骨免疫系统中,SDF-1/CXCR4轴通过不同的信号通路刺激免疫细胞分泌炎症因子,影响炎症的发展与转归,同时促进成骨细胞和破骨细胞的增殖与分化,进而影响骨再生与骨吸收的过程,SDF-1/CXCR4轴的信号异常也会导致骨免疫疾病的发生与恶化。本文拟阐述SDF-1/CXCR4轴与骨免疫学之间的关系,以及在干细胞动员与迁移、血管生成、炎症反应、骨生成与骨吸收中的作用,并着重介绍SDF-1/CXCR4轴在骨免疫相关疾病如骨关节炎(osteoarthritis,OA)、类风湿性关节炎(rheumatoid arthritis,RA)、骨质疏松症、牙周炎和恶性骨肿瘤的研究进展。

一、基质细胞衍生因子1/CXC趋化因子受体4轴的概述

趋化因子是介导淋巴组织发育和免疫细胞运输的小分

泌蛋白[1],相对分子质量为8 000～14 000,通过与趋化因子受体亚群相互作用从而调节白细胞运输。趋化因子是细胞因子最大亚家族,根据其N末端半胱氨酸残基的数量和位置细分为4类:CC-趋化因子、CXC-趋化因子、C3XC-趋化因子及C-趋化因子[2]。SDF-1,又名为CXCL12(CXC chemokine ligand 12),是一种持续产生的CXC-趋化因子,影响各种生理途径,如胚胎发育和器官稳态[3]。SDF-1可由免疫细胞、成骨细胞、基质细胞和肿瘤细胞等多种细胞分泌,并在许多器官中有组成型表达,如淋巴结、骨髓、肝脏和肺等[4],主要在肿瘤内或自身免疫性疾病期间的缺氧和促血管生成环境中高表达,其在基质干细胞从骨髓起源到受损组织或器官的运输和动员过程中起着至关重要的作用[5]。在缺氧条件或受损组织下,*SDF-1*受缺氧诱导因子-1α(hypoxia-inducible factor 1α,HIF-1α)和癌相关成纤维细胞(cancer-associated fibroblasts,CAF)的影响,其表达增加[6]。

CXCR4是一种G蛋白偶联受体,由1个细胞外N末端、3个细胞外环、3个细胞内环及1个细胞内C末端组成7次跨膜结构,作为一种保守蛋白,人类和小鼠共享89%的氨基酸序列[7]。*CXCR4*在多种类型的细胞中广泛表达,包括造血干细胞(hematopoietic stem cell,HSC)、T淋巴细胞、B淋巴细胞、单核细胞、巨噬细胞、上皮细胞、内皮细胞和神经细胞[8],并在多个器官中普遍分布,其在生殖细胞发育、神经发生、将祖细胞引导至骨髓等生理过程,以及肌肉再生和血管形成等病理过程中均发挥关键作用[9-12]。*CXCR4*在缺氧、压力和损伤条件下的组织中上调,介导炎症性疾病,赋予白细胞趋化性[6]。

SDF-1是唯一能与CXCR4结合并激活的趋化因子[13],成熟的SDF-1第12～17个残基为RFFESH基序,是CXCR4结合的最关键核心结构域,使受体构象发生变化启动信号传导,进而影响SDF-1蛋白序列N末端的氨基酸以激活SDF-1,从而启动了CXCR4与SDF-1的相互作用[5,14]。CXCR4激活Gi/o蛋白家族,进而导致磷脂酶C(phospholipase C,PLC)与磷脂酰肌醇3-激酶(phosphatidylinositide 3-kinases,PI3K)途径的活化,在基因转录、细胞迁移和细胞黏附的调节中发挥作用[4,15]。SDF-1/CXCR4轴参与淋巴细胞运输,以及骨髓中造血干细胞的保留和归巢,对机体发育、炎症、组织修复、神经发生、造血、血管生成、肿瘤转移和趋化均有重要的影响[16-19],同时也是骨髓来源的间充质干细胞与损伤宿主组织之间相互作用必需的信号分子[20]。

二、骨免疫学概述

1972年,Horton等[21]首次报道了牙周炎背景下免疫细胞与骨细胞之间的相互作用,细菌抗原刺激的免疫细胞产生破骨细胞激活因子。2000年,Arron和Choi创造了“骨免疫学”一词,强调了T细胞介导的自身免疫性关节炎背景下破骨形成的调节[22-23]。由此,骨免疫学作为一个将骨生物学和免疫学领域结合起来的跨学科领域,得到了学者的关注和深入探索。

骨骼系统和免疫系统共享多种分子,包括细胞因子、趋化因子、受体、激素、转录因子和信号分子,骨细胞在生理和病理条件下与免疫细胞相互作用[24]。在哺乳动物发育的过程中,HSC从主动脉-性腺-中肾区域出现并迁移至胎儿肝脏,最后迁移至骨髓,骨细胞和免疫细胞在骨髓中共享微生物环境,并参与造血的调节。因此,从进化的角度看,获得性免疫和骨骼系统的同步发展可能导致骨骼和免疫细胞之间出现共同的生物学机制与密切的相互作用[25]。一方面,由于免疫细胞来源于骨髓,成骨细胞、破骨细胞和骨细胞在免疫系统调节中均发挥着不同的功能。成骨细胞参与淋巴细胞的分化,在淋巴谱系的调节中起着关键作用[26]。研究表明,成骨细胞中*SDF-1*的耗竭减少了骨髓中B细胞祖细胞的数量[27];成骨细胞表达Notch配体δ样4(delta-like ligand 4,DLL4)有助于支持T细胞祖细胞[28]。破骨细胞对于骨髓腔的形成至关重要,其功能障碍会导致骨髓中没有足够的空间支持造血细胞分化从而发生髓外造血,异常的微环境损害免疫细胞的分化和功能[24]。此外,破骨细胞活性受到抑制后会使HSC、T细胞和B细胞的增殖能力受损[29-31]。骨细胞参与调节淋巴和骨髓分化,已有研究表明骨细胞消融小鼠骨髓、胸腺和脾脏均出现功能缺陷,导致淋巴细胞严重减少[32]。由此可见,骨骼系统的细胞维持着免疫细胞的正常增殖和分化,在免疫系统的功能实现中起着重要作用。另一方面,在生理和病理条件下,骨稳态都受到各种免疫反应的调节,免疫细胞在调节骨骼健康方面的作用已得到了充分的证实[33]。生理性骨更新是一个终生过程,包括骨生成和骨吸收,在此过程中,骨骼和免疫的成分之间有着复杂的交流,维持着机体的骨稳态。免疫系统的异常反应可造成骨形成和骨吸收过程之间的不平衡,导致各种炎症性骨病,如骨质疏松症、骨关节炎、类风湿性关节炎和牙周炎等[34],加剧骨丢失。在病理状态下,各种免疫细胞如中性粒细胞、淋巴细胞和单核巨噬细胞等激活并分泌各种细胞因子,发生一系列免疫反应,影响着骨骼系统疾病的发展与转归[35]。例如,Th17细胞通过释放白细胞介素(IL)-17、IL-22和IL-26等细胞因子,促进破骨细胞生成,增加骨吸收[36];M1型巨噬细胞产生促炎介质包括白细胞介素(如IL-1β、IL-6)及肿瘤坏死因子α(tumor necrosis factor-α,TNF-α),从而促进炎症和骨吸收的发展[37];调节性T细胞(regulatory cells,Tregs)参与刺激成骨细胞分化,促进骨再生[38];在机体恢复期,M2型巨噬细胞分泌IL-4、IL-10等抗炎因子,抑制破骨细胞生成并促进损伤愈合[39]。探索骨免疫学涉及的信号通路机制,设计针对免疫系统的治疗策略,有助于抑制骨持续性丢失,促进骨再生,为炎症性骨病的治疗提供新思路。

三、基质细胞衍生因子1/CXC趋化因子受体4轴与骨免疫系统的关系

骨免疫涉及骨骼和免疫系统,影响着干细胞/祖细胞归巢至骨髓、造血稳态、血管生成、免疫反应、骨稳态与骨重塑等过程。SDF-1与CXCR4结合激活及其与骨免疫相关的信号转导主要涉及丝裂原活化蛋白激酶(mitogen activated protein kinase pathway,MAPK)信号通路、核转录因子-κB

(nuclear factor-κB, NF-κB)信号通路、PI3K/丝(苏)氨酸激酶(Akt)信号通路、詹纳斯激酶(Janus kinase, JAK)/信号转导子和转录激活子(signal transducer and activator of transcription, STAT)信号通路[5-6,17],影响各种细胞的生物过程,包括细胞存活、增殖与分化、趋化、基因转录、凋亡和死亡。

1. SDF-1/CXCR4轴在干细胞动员和迁移中的作用:所有血细胞,包括淋巴细胞和骨髓细胞,都是在骨髓中由HSC的多能细胞谱系产生的。SDF-1/CXCR4信号传导在个体发育过程中HSC和祖细胞(hematopoietic stem and progenitor cell, HSPC)在骨髓中的定植起关键作用[40],SDF-1$^{-/-}$或CXCR4$^{-/-}$小鼠HSC在胚胎从肝脏到骨髓迁移障碍[16],淋巴组织、骨髓和血管等形成异常导致死亡[41]。表达CXCR4的CD34^{+} HSC细胞与SDF-1相互作用,使其在骨髓内保留和归巢。*CXCR4*的上调可能有助于增加细胞对较低SDF-1信号的敏感性,但阻断CXCR4将导致小鼠和人类干细胞和祖细胞动员显著减少;SDF-1抗体也有效减少了动员,证明了其在干细胞动员中的积极作用[42]。此外,SDF-1/CXCR4的激活可以诱导干细胞迁移以修复受损组织[43-44]。CXCR4诱导的迁移由多种信号通路调节,包括MAPK和PI3K/Akt途径[45-46],还可以通过诱导PLC/蛋白激酶C(protein kinase C, PKC)-Ca^{2+}信号来增强其介导的迁移[47]。CXCR4可使内源性或外源性干细胞迁移至受损部位[48-49],趋化性实验证实,过表达CXCR4的间充质干细胞(marrow stem/stromal cell, MSC)可以增强其向SDF-1高浓度的部位迁移[50]。

2. SDF-1/CXCR4轴在血管生成中的作用:SDF-1具有血管生成的特性[51],通过刺激人血管内皮细胞形成微血管从而介导血管生成[52]。SDF-1通过激活内皮细胞上的CXCR4受体进一步释放血管内皮生长因子(vascular endothelial growth factor, VEGF)来增加内皮细胞迁移和生长,从而提高血管生成的能力。VEGF和碱性成纤维细胞生长因子(basic fibroblast growth factor, bFGF)刺激内皮细胞中*CXCR4*和*SDF-1*的表达,形成正反馈[53],因此,SDF-1/CXCR4轴与VEGF存在着协同作用。此外,SDF-1/CXCR4轴可以增强其他血管生成信号的表达,如前列环素[54]。在细胞中,*SDF-1*和*CXCR4*的表达提示两者的相互作用可能在内皮细胞的保存过程中起关键作用,这可能意味着长时间的抗SDF-1或CXCR4可能会阻碍血管生成、血液供应和伤口愈合[55]。缺氧也是内皮细胞中SDF-1/CXCR4轴的重要调节因子,研究表明在缺氧条件下,*SDF-1*和*CXCR4*的表达增强,有助于血管生成,这可能是由于缺氧导致局部的pH值降低,机体处于病理状态从而激活了SDF-1/CXCR4轴,进而刺激血管内皮细胞的增殖及血管生成[56]。也有研究发现,阻断Toll样受体2(Toll like receptor 2, TLR2)可以使HUVEC的血管生成能力增加,原因可能是*TLR2*介导增强了CXCR4信号传导[57]。炎症介质γ干扰素(interferon-gamma, IFN-γ)和TNF-α降低血管内皮细胞中*CXCR4*和*SDF-1*的表达,从而降低其血管生成能力[58]。综上所述,SDF-1/CXCR4轴对血管生成具有增强作用,信号分子可以通过刺激SDF-1/CXCR4的表达从而促进机体血管生成,反之则抑制血管内皮细胞的成血管功能。

3. SDF-1/CXCR4轴在炎症反应中的作用:炎症的主要功能是消除病原体的入侵和清除组织坏死,维持组织的稳态。*SDF-1*在特定的淋巴或非淋巴组织中组成型表达,参与炎症反应[59]。*CXCR4*在炎症细胞中表达,并激发其向缺血组织的迁移能力,从而参与血运重建和组织修复。*CXCR4*在协调先天性和适应性免疫反应方面发挥着重要作用:它调节白细胞从外周组织运输和分布,参与淋巴结组织,最后通过促进免疫突触的形成和稳定来维持T细胞启动[60]。研究表明,*CXCR4*对B细胞的归巢、发育和功能至关重要,B细胞在整个发育过程中高度表达*CXCR4*,缺乏*CXCR4*或*SDF-1*的小鼠出现B淋巴细胞生成障碍[61]。在急性炎症反应期间,抵御入侵病原体的第一道防线是*CXCR4*表达的中性粒细胞亚群,迅速迁移到炎症部位[62-63],CXCR4与整合素CD11b一起通过淋巴管介导中性粒细胞重新定位,从炎症部位经淋巴管引流至淋巴结,以增强早期适应性免疫反应[64]。老化的中性粒细胞可以上调*CXCR4*在其表面的表达,从而使它们返回骨髓,最终被常驻巨噬细胞吞噬并消除,从而有助于缓解伤口炎症[65]。

另一项研究发现,在组织损伤后的野生型小鼠模型中,*SDF-1*在伤口表皮中上调,并将表达CXCR4的白细胞募集到损伤部位[66],白细胞破坏入侵的微生物并清除碎片。此外,SDF-1/CXCR4轴可促进炎症,导致纤维化和瘢痕形成。使用*CXCR4*抑制剂AMD3100可以显著减少募集表达CXCR4的白细胞,并实现小鼠皮肤伤口和附件再生的无瘢痕修复[66-67]。

4. SDF-1/CXCR4轴在骨生成与骨吸收中的作用:骨髓间充质干细胞(bone marrow mesenchymal stem cell, BMSC)是一类拥有多向分化潜能的成体干细胞,具有自我更新和成骨向分化的特性,是体内骨生成的主要细胞类型[68-69]。研究表明,BMSC可促进局部及全身的骨修复再生,对骨折、骨质疏松和OA等疾病具有重要的治疗潜能[70]。BMSC的归巢是BMSC治疗的关键,研究证明静脉输入BMSC后可在脾脏、骨骼、肾脏和皮肤等多个器官中检测到BMSC,而不是专门归巢于骨髓[71]。然而,BMSC的体内治疗效果有限,部分原因是BMSC对受损部位的归巢效率低。SDF-1/CXCR4在BMSC迁移到受损部位中起重要作用,*SDF-1*在损伤组织或器官中上调,从而通过*CXCR4*招募MSC[72]。调节BMSC的归巢能力有助于开发其治疗潜力。研究表明,虽然BMSC膜上*CXCR4*组成型表达量较少,但过表达*CXCR4*的BMSC可促进向目标部位的归巢,增强损伤器官的修复效果及衰竭骨髓的造血重建[71,73]。SDF-1信号传导对骨形成发生蛋白2(bone morphogenetic protein type 2, BMP2)引发的成骨分化具有调节作用,阻断SDF1/CXCR4信号通路阻碍了BMP2刺激后的BMSC分化为成骨细胞[74-76]。此外,SDF-1/CXCR4与破骨细胞存在着相互作用,破骨细胞骨吸收是骨髓腔形成所必需的。在骨髓微环境中,破骨细胞衍生的蛋白水解酶降解SDF-1,导致HSC动员。学者研究发现,破骨细胞分化因子RANKL可以增强破骨细胞的活性,*SDF-1*表达量下降,促进HSC动员[25,77]。另

外,CXCR4可以抑制破骨细胞分化,促进成骨细胞增殖,减少骨吸收而有助于骨再生[78]。

四、基质细胞衍生因子1/CXC趋化因子受体4轴在骨免疫相关疾病中的作用

SDF-1/CXCR4与骨免疫系统关系密切,在生理状态下维持着机体正常生理活动,而在病理状态下,SDF-1/CXCR4结合并激活下游信号通路,影响骨免疫相关疾病如OA、RA、骨质疏松症、牙周炎和骨肿瘤等的发生发展。目前,许多研究明确了SDF-1/CXCR4轴在骨免疫相关疾病中的作用极其复杂机制,验证了通过影响SDF-1/CXCR4表达及其信号转导,有助于干预机体的免疫细胞与骨细胞,为探索骨免疫疗法提供了新的治疗策略。

1. SDF-1/CXCR4轴与骨关节炎:OA是一种退行性关节疾病,涉及骨骼、软骨、滑膜、韧带和关节囊。OA导致长期慢性疼痛,是导致残疾的最常见原因[79]。OA的重要特征是进行性软骨退化,软骨下骨硬化,骨赘形成和滑膜炎症[80]。正常情况下,软骨细胞能分泌大量物质到细胞外基质(extracellular matrix,ECM),构成细胞外纤维网络成分,为细胞提供支持和保护、润滑和营养[81]。当软骨受损时,软骨组织释放的基质金属蛋白酶(matrix metalloproteinases,MMP)量增加,导致ECM的减少和降解,软骨组织的细胞外纤维网络破坏,软骨组织损伤进一步加重,导致OA的发生[82]。SDF-1/CXCR4在OA病理性软骨变性过程中起关键作用,调节许多稳态和病理过程。SDF-1具有诱导软骨细胞肥大的能力,在OA患者滑液中SDF-1浓度显著高于健康人,且浓度水平与疾病的严重程度成正比[83]。SDF-1的病理浓度可直接导致软骨细胞死亡,这意味着软骨基质的合成受到抑制。ECM分解代谢增加,合成代谢减少,促进软骨组织的功能障碍。滑液中的SDF-1与软骨细胞上的CXCR4结合,激活了PI3K/Akt信号通路以诱导Akt磷酸化,使转化生长因子β(transforming growth factor-β,TGF-β)/Smad3途径中的磷酸化过程受到影响,金属蛋白酶组织抑制剂-3(tissue inhibitor of metalloproteinase-3,TIMP-3)表达下调,导致聚集蛋白聚糖损失,促使OA的加重[84]。SDF-1/CXCR4还可以通过激活NF-κB、MAPK、Wnt/β-catenin通路,活化软骨细胞中的聚集蛋白聚糖酶,使软骨破坏与降解,OA严重程度增加[85]。

许多学者探讨了抑制SDF-1/CXCR4轴对OA模型的影响。使用TN14003、T140和AMD3100等3种拮抗剂可以靶向阻断SDF-1/CXCR4信号通路,减少软骨组织中*MMP-3*、*MMP-9*、*MMP-13*的表达和分泌,减少Ⅱ型胶原和聚集蛋白聚糖的降解,从而延缓关节软骨的退化[82]。拮抗剂还可以减少软骨下成骨分化和异常的H型血管形成,减少软骨破坏和骨吸收,抑制关节软骨变性[86]。另有研究表明,对滑膜关节施加横向负荷,可以增加OA小鼠模型中*SDF-1*的表达,SDF-1作为化学引诱剂将表达CXCR4的脂肪间充质干细胞(adipose-derived mesenchymal stem cell,ASC)募集到受损部位,增强了ASC的迁移,从而提高了ASC对OA的保护作用[87]。此外,使用过表达*CXCR4*的BMSC膜结构组装的纳米颗粒可以对*SDF-1*高表达的损伤软骨细胞和软骨具有主动靶向能力。利用SDF-1/CXCR4轴设计药物输送载体,可以在炎症微环境下增加靶细胞和组织的摄取,以保护受伤的软骨[88]。

2. SDF-1/CXCR4轴与类风湿性关节炎:RA是一种炎症性全身性自身免疫性疾病,其典型特征是炎症细胞浸润,导致持续性滑膜组织发炎及邻近骨和软骨关节的进行性破坏[89]。其发病机制与OA不同,因此SDF-1/CXCR4在RA的作用与OA也有很大的区别。*SDF-1*在滑膜中表达增加形成浓度梯度,将外周表达CXCR4的促炎细胞募集到滑膜中,包括T细胞、B细胞、巨噬细胞和其他免疫细胞[90],形成炎症环境。Th17细胞分泌的IL-17,参与炎症的维持。IL-17可诱导成纤维细胞样滑膜细胞分泌更多的SDF-1,再将Th17细胞募集到患病滑膜,形成正反馈[91]。SDF-1促进成纤维细胞样滑膜细胞增殖并形成滑膜增生,还通过促进破骨形成和保护破骨细胞凋亡来参与骨吸收,还促进MMP-9的释放并上调*RANKL*在T细胞和成纤维细胞样滑膜细胞中的表达,促进骨吸收[83]。此外,SDF-1激活PI3K/Akt途径以上调激活蛋白1(activator protein-1,AP-1)和IL-6的表达,可以增强MMP的活性,诱导基质降解[92]。在RA患者血清和关节滑液中,SDF-1和CXCR4蛋白含量均有明显上升[93],SDF-1/CXCR4轴可以促进关节软骨中血管内皮生长因子的表达,CXCR4阻滞剂可缓解滑膜血管生成,因此SDF-1/CXCR4轴参与该过程的调节[94]。

SDF-1/CXCR4在RA的发病机制中的作用表明它是一种潜在的理想治疗靶点。花青素可以阻断响应IL-17A的p38MAPK信号传导的激活,下调*CXCR4*的表达,介导单核细胞迁移,抑制破骨形成,作为一种治疗RA的小分子药物具有巨大的潜力[95]。另有研究表明,改变微环境氧化还原状态可以影响SDF-1/CXCR4轴及其下游信号通路的激活,从而改变RA患者体内炎症细胞的迁移,控制RA炎症情况[96]。目前,临床上治疗RA的一线药物是甲氨蝶呤和糖皮质激素治疗。然而,长期使用糖皮质激素对骨量和结构的影响不容忽视。将SDF-1/CXCR4轴拮抗剂的安全性与传统治疗RA药物的安全性进行比较,前者具有明显的优势。然而,未来仍需要更多的实验探索。

3. SDF-1/CXCR4轴与骨质疏松症:骨质疏松症是一种常见的代谢性骨病,骨骼的强度和质量下降,骨骼脆性增加,从而增加骨折的易感性。骨质疏松性骨折严重影响患者的生活质量,提高了患者的死亡率[97]。衰老是骨骼系统退化的不可避免的危险因素,骨量在生命早期达到峰值,随着年龄的增长,骨质量逐渐下降[98]。实验证据表明,在骨质疏松症患者中,成骨细胞活性降低,而破骨细胞活性增加,骨吸收超过骨生成[99]。年龄的增长导致间充质祖细胞过早衰老,从而阻碍分化过程。SDF-1/CXCR4对骨质疏松症的影响较为复杂。一方面,如前所述,SDF-1/CXCR4对MSC的迁移和发育至关重要,该过程涉及软骨内和骨间骨形成,因此MSC的丢失可能诱发骨质疏松症[100]。研究表明,衰老的BMSC中SDF-1分泌减少,*CXCR4*基因的mRNA和蛋白表达降低,成骨分化

能力下降。CXCR4$^{-/-}$老年小鼠的BMSC成骨分化受损,表现为碱性磷酸酶、骨钙素合成和钙沉积下降,是通过抑制细胞内R-Smads和细胞外调节蛋白激酶(Erk1/2)或Erk1/2和p38蛋白的磷酸化来介导的。在老年小鼠的BMSC中过表达CXCR4可以恢复其体外成骨分化潜能[101]。另一方面,研究显示SDF-1随着年龄增长在血浆中的水平升高,从而募集破骨细胞,导致增加骨吸收并降低了骨矿物质密度,增加骨质疏松症的风险[102]。这些发现为BMSC成骨中与年龄相关的变化机制提供了新的见解,提示将CXCR4作为治疗靶点制定策略,有可能改善骨质疏松症状态下的骨修复与骨再生。有学者在钛植入物表面添加BMSC靶向肽和成骨生长肽后将其植入骨质疏松条件下的长骨中,发现在植入物表面原位募集的BMSC表达CXCR4受体与骨组织中的SDF-1结合并激活,促进了成骨分化[103]。此外已有研究表明,CXCR4可以基于CXCR4/SDF-1轴将纳米颗粒靶向骨质疏松下的骨微环境[78],促进成骨并抑制BMSC的脂肪生成,从而逆转骨小梁流失和降低皮质骨孔隙度[104]。

4. SDF-1/CXCR4轴与牙周炎:牙周炎是一种典型的骨免疫性疾病,是与菌群失衡有关的慢性感染性疾病,由菌斑生物膜引发的支持牙周组织的慢性破坏引起,其特征是微生物相关和宿主介导的炎症,导致牙周附着丧失[105]。牙周炎的临床表现主要包括牙齿支持组织的不可逆破坏和牙周袋的形成[106],主要病理特征是从牙龈到深部牙周组织、牙槽骨的牙周韧带的炎症,甚至牙骨质受累[107]。SDF-1/CXCR4轴对牙周炎的影响学者们持有不同的观点。一方面,有学者认为,*CXCR4*基因在牙周炎组织中上调,是牙周炎的危险因素,影响白细胞跨内皮迁移和破骨细胞分化,改变牙周炎的免疫微环境[108],在调节牙周炎的氧化应激损伤中起关键作用[109]。牙周炎与口腔鳞状细胞癌增加风险有关,牙龈卟啉单胞菌菌株侵入口腔鳞状细胞癌,通过*CXCR4*诱导炎症、血管生成、致癌蛋白刺激鳞癌增殖。抑制*CXCR4*可以减少牙龈卟啉单胞菌菌株诱导的鳞癌增殖并降低致癌蛋白的表达[110]。另一方面,也有学者研究发现,在口腔刺激炎症状态下,高迁移率族蛋白1(high mobility group protein 1,HMGB1)通过SDF-1/CXCR4轴增强趋化性,通过破骨细胞和成骨细胞活化调节血管生成和骨重塑,并促进口腔组织修复中的骨愈合[111]。此外,已有研究表明牙周炎组织中巨噬细胞聚集,且巨噬细胞高表达SDF-1,构建表面过表达CXCR4的工程化外泌体可靶向递送药物至巨噬细胞内,从而缓解牙周炎[112]。目前,SDF-1/CXCR4轴对牙周炎症发生发展的信号通路机制及基于SDF-1/CXCR4轴对牙周炎的治疗方法仍需要更深入地探索。

5. SDF-1/CXCR4轴与恶性骨肿瘤:骨肿瘤是发生于骨骼或其附属组织的肿瘤,恶性骨肿瘤发展迅速,预后不佳,死亡率高,目前很多骨肿瘤仍然缺乏有效的治疗方法。在癌细胞中,*SDF-1*与*CXCR4*高表达,缺氧环境及癌相关成纤维细胞诱导*SDF-1*表达上升,以及p53失去功能活性导致*CXCR4*抑制丧失,可能是*SDF-1*与*CXCR4*上调的其中一种机制[113-114]。研究表明,SDF-1与CXCR4结合激活G蛋白偶联受体激酶可促进下游Ras、PI3K、ERK1/2、PLC/MAPK、SAPK/JNK信号通路,在血管形成、肿瘤细胞生长、播散、转移发展、趋化性和肿瘤细胞增殖等几个过程中起着关键作用[6]。SDF-1/CXCR4反激活人类表皮生长因子受体2(human epidermal growth factor receptor 2,HER2),并显著增加骨内肿瘤的生长[115]。*CXCR4*在癌症中的激活导致*MMP*的上调,从而导致胶原蛋白破坏和增强肿瘤细胞侵袭。*SDF-1*的表达水平控制着癌细胞在肿瘤中的迁移,也诱导骨肉瘤细胞迁移和αvβ3整合素表达升高,进一步影响着癌症的播散[116]。Lu等[117]研究发现,SDF-1/CXCR4轴通过激活Akt和Wnt/β-catenin信号通路促进骨肉瘤细胞的迁移,使用AMD3100和LY294002抑制剂处理骨肉瘤细胞后,可抑制信号通路发挥作用。Xi等[118]指出,肿瘤抑制因子PTEN可以使*CXCR4*的表达下降,从而抑制骨骼中骨肉瘤的生长。此外,通过非编码基因调控改变*CXCR4*的表达也是治疗恶性骨肿瘤的一种思路,长链非编码RNA(long non-coding RNA,lncRNA)*FEZF1*反义RNA1(FEZF1-AS1)通过miR-144/CXCR4轴促进骨肉瘤细胞增殖、Warburg效应和抑制细胞凋亡[119],为骨肉瘤的进一步研究提供依据。

五、总结与展望

随着研究的不断深入,SDF-1/CXCR4轴对骨免疫系统生理和病理的调控作用正在逐步被揭示。SDF-1/CXCR4轴参与淋巴细胞运输,以及骨髓中造血干细胞的保留和归巢,在机体发育、炎症、骨生成与骨吸收、造血、血管生成、肿瘤转移和趋化中发挥作用。由于SDF-1/CXCR4轴是一个复杂的网络,在骨免疫系统中涉及甚广,在不同的生物微环境下,根据不同的细胞类型会激活不同的信号通路,产生不同的效果,这使得SDF-1/CXCR4对骨免疫系统的影响具有多种可能性,有助于发掘更多针对此生物轴的治疗策略。SDF-1/CXCR4轴是一个理想的治疗靶点,但目前对该生物轴的研究结果有限,多数研究仍局限在使用*CXCR4*的拮抗剂以阻断该生物轴,从而抑制疾病的进展。针对SDF-1/CXCR4轴上游及下游如此庞大的网络信息库,未来还需要学者们进行更深入的挖掘与突破。此外,非编码基因如microRNA、lncRNA和siRNA等在生物体的正常发育和异常调控中都发挥着重要作用,目前对于非编码基因对SDF-1/CXCR4轴在骨免疫系统中的影响了解甚少。因此,在未来研究中,更需要学者们了解非编码基因与SDF-1/CXCR4的联系,探索其在骨免疫疾病中的机制及治疗方法。目前,基于SDF-1/CXCR4生物轴的治疗方法距离临床应用还有一定的距离,相信在不久的将来,有关SDF-1/CXCR4的研究会有更深入的进展,有望成为临床治疗骨免疫疾病的新型靶点。

利益冲突 所有作者均声明不存在利益冲突

参 考 文 献

[1] Khan P, Fatima M, Khan MA, et al. Emerging role of chemokines in small cell lung cancer: Road signs for metastasis, heterogeneity, and immune response[J]. Semin Cancer Biol,

2022,87:117-126. DOI:10.1016/j.semcancer.2022.11.005.

[2] Nagarsheth N, Wicha MS, Zou W. Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy [J]. Nat Rev Immunol, 2017,17(9):559-572. DOI:10.1038/nri.2017.49.

[3] Ratajczak MZ, Zuba-Surma E, Kucia M, et al. The pleiotropic effects of the SDF-1-CXCR4 axis in organogenesis, regeneration and tumorigenesis[J]. Leukemia, 2006,20(11):1915-1924. DOI:10.1038/sj.leu.2404357.

[4] Broussas M, Boute N, Akla B, et al. A new anti-CXCR4 antibody that blocks the CXCR4/SDF-1 axis and mobilizes effector cells [J]. Mol Cancer Ther, 2016,15(8):1890-1899. DOI:10.1158/1535-7163.MCT-16-0041.

[5] Sadri F, Rezaei Z, Fereidouni M. The significance of the SDF-1/CXCR4 signaling pathway in the normal development[J]. Mol Biol Rep, 2022,49(4):3307-3320. DOI:10.1007/s11033-021-07069-3.

[6] Mousavi A. CXCL12/CXCR4 signal transduction in diseases and its molecular approaches in targeted-therapy[J]. Immunol Lett, 2020,217:91-115. DOI:10.1016/j.imlet.2019.11.007.

[7] Altschul SF, Madden TL, Schäffer AA, et al. Gapped BLAST and PSI-BLAST: A new generation of protein database search programs[J]. Nucleic Acids Res, 1997,25(17):3389-3402. DOI:10.1093/nar/25.17.3389.

[8] Janssens R, Struyf S, Proost P. Pathological roles of the homeostatic chemokine CXCL12[J]. Cytokine Growth Factor Rev, 2018,44:51-68. DOI:10.1016/j.cytogfr.2018.10.004.

[9] Gros J, Manceau M, Thomé V, et al. A common somitic origin for embryonic muscle progenitors and satellite cells[J]. Nature, 2005,435(7044):954-958. DOI:10.1038/nature03572.

[10] Kim M, Kim DI, Kim EK, et al. CXCR4 overexpression in human adipose tissue-derived stem cells improves homing and engraftment in an animal limb ischemia model [J]. Cell Transplantation, 2017,26(2):191-204. DOI:10.3727/096368916X692708.

[11] Cui L, Qu H, Xiao T, et al. Stromal cell-derived factor-1 and its receptor CXCR4 in adult neurogenesis after cerebral ischemia [J]. Restor Neurol Neurosci, 2013,31(3):239-251. DOI:10.3233/RNN-120271.

[12] Petri RM, Hackel A, Hahnel K, et al. Activated tissue-resident mesenchymal stromal cells regulate natural killer cell immune and tissue-regenerative function[J]. Stem Cell Reports, 2017,9(3):985-998. DOI:10.1016/j.stemcr.2017.06.020.

[13] Ullah TR. The role of CXCR4 in multiple myeloma: Cells' journey from bone marrow to beyond[J]. J Bone Oncol, 2019,17:100253. DOI:10.1016/j.jbo.2019.100253.

[14] Li JH, Hamdan FF, Kim SK, et al. Ligand-specific changes in M3 muscarinic acetylcholine receptor structure detected by a disulfide scanning strategy[J]. Biochemistry, 2008,47(9):2776-2788. DOI:10.1021/bi7019113.

[15] Busillo JM, Benovic JL. Regulation of CXCR4 signaling [J]. Biochim Biophys Acta, 2007,1768(4):952-963. DOI:10.1016/j.bbamem.2006.11.002.

[16] Singh P, Mohammad KS, Pelus LM. CXCR4 expression in the bone marrow microenvironment is required for hematopoietic stem and progenitor cell maintenance and early hematopoietic regeneration after myeloablation[J]. Stem Cells, 2020,38(7):849-859. DOI:10.1002/stem.3174.

[17] García-Cuesta EM, Santiago CA, Vallejo-Díaz J, et al. The role of the CXCL12/CXCR4/ACKR3 axis in autoimmune diseases[J]. Front Endocrinol(Lausanne),2019,10:585. DOI:10.3389/fendo.2019.00585.

[18] Merino JJ, Bellver-Landete V, Oset-Gasque MJ, et al. CXCR4/CXCR7 molecular involvement in neuronal and neural progenitor migration: Focus in CNS repair[J]. J Cell Physiol, 2015,230(1):27-42. DOI:10.1002/jcp.24695.

[19] Décaillot FM, Kazmi MA, Lin Y, et al. CXCR7/CXCR4 heterodimer constitutively recruits beta-arrestin to enhance cell migration[J]. J Biol Chem, 2011,286(37):32188-32197. DOI:10.1074/jbc.M111.277038.

[20] Yamaguchi J, Kusano KF, Masuo O, et al. Stromal cell-derived factor-1 effects on ex vivo expanded endothelial progenitor cell recruitment for ischemic neovascularization [J]. Circulation, 2003,107(9):1322-1328. DOI:10.1161/01.cir.0000055313.77510.22.

[21] Horton JE, Raisz LG, Simmons HA, et al. Bone resorbing activity in supernatant fluid from cultured human peripheral blood leukocytes[J]. Science, 1972,177(4051):793-795. DOI:10.1126/science.177.4051.793.

[22] Arron JR, Choi Y. Bone versus immune system[J]. Nature, 2000,408(6812):535-536. DOI:10.1038/35046196.

[23] Takayanagi H, Ogasawara K, Hida S, et al. T-cell-mediated regulation of osteoclastogenesis by signalling cross-talk between RANKL and IFN-gamma[J]. Nature, 2000,408(6812):600-605. DOI:10.1038/35046102.

[24] Okamoto K, Nakashima T, Shinohara M, et al. Osteoimmunology: The conceptual framework unifying the immune and skeletal systems[J]. Physiol Rev, 2017,97(4):1295-1349. DOI:10.1152/physrev.00036.2016.

[25] Tsukasaki M, Takayanagi H. Osteoimmunology: Evolving concepts in bone-immune interactions in health and disease[J]. Nat Rev Immunol,2019,19(10):626-642. DOI:10.1038/s41577-019-0178-8.

[26] Takayanagi H. Osteoimmunology as an intrinsic part of immunology[J]. Int Immunol, 2021,33(12):673-678. DOI:10.1093/intimm/dxab057.

[27] Greenbaum A, Hsu YMS, Day RB, et al. CXCL12 in early mesenchymal progenitors is required for haematopoietic stem-cell maintenance[J]. Nature, 2013,495(7440):227-230. DOI:10.1038/nature11926.

[28] Yu VWC, Saez B, Cook C, et al. Specific bone cells produce DLL4 to generate thymus-seeding progenitors from bone marrow

[J]. J Exp Med, 2015, 212(5): 759-774. DOI: 10.1084/jem.20141843.

[29] Mansour A, Abou-Ezzi G, Sitnicka E, et al. Osteoclasts promote the formation of hematopoietic stem cell niches in the bone marrow[J]. J Exp Med, 2012, 209(3): 537-549. DOI: 10.1084/jem.20110994.

[30] Teufel S, Grötsch B, Luther J, et al. Inhibition of bone remodeling in young mice by bisphosphonate displaces the plasma cell niche into the spleen[J]. J Immunol, 2014, 193(1): 223-233. DOI: 10.4049/jimmunol.1302713.

[31] Charles JF, Hsu LY, Niemi EC, et al. Inflammatory arthritis increases mouse osteoclast precursors with myeloid suppressor function[J]. J Clin Invest, 2012, 122(12): 4592-4605. DOI: 10.1172/JCI60920.

[32] Sato M, Asada N, Kawano Y, et al. Osteocytes regulate primary lymphoid organs and fat metabolism[J]. Cell Metab, 2013, 18(5): 749-758. DOI: 10.1016/j.cmet.2013.09.014.

[33] Dar HY, Azam Z, Anupam R, et al. Osteoimmunology: The Nexus between bone and immune system[J]. Front Biosci (Landmark Ed), 2018, 23(3): 464-492. DOI: 10.2741/4600.

[34] Weitzmann MN, Ofotokun I. Physiological and pathophysiological bone turnover - role of the immune system[J]. Nat Rev Endocrinol, 2016, 12(9): 518-532. DOI: 10.1038/nrendo.2016.91.

[35] Guder C, Gravius S, Burger C, et al. Osteoimmunology: A current update of the interplay between bone and the immune system[J]. Front Immunol, 2020, 11: 58. DOI: 10.3389/fimmu.2020.00058.

[36] Gravallese EM, Schett G. Effects of the IL-23-IL-17 pathway on bone in spondyloarthritis[J]. Nat Rev Rheumatol, 2018, 14(11): 631-640. DOI: 10.1038/s41584-018-0091-8.

[37] Huang Y, Tian C, Li Q, et al. TET1 knockdown inhibits *Porphyromonas gingivalis* LPS/IFN-γ-Induced M1 macrophage polarization through the NF-κB pathway in THP-1 cells[J]. Int J Mol Sci, 2019, 20(8): E2023. DOI: 10.3390/ijms20082023.

[38] Yu M, D′Amelio P, Tyagi AM, et al. Regulatory T cells are expanded by Teriparatide treatment in humans and mediate intermittent PTH-induced bone anabolism in mice[J]. EMBO Rep, 2018, 19(1): 156-171. DOI: 10.15252/embr.201744421.

[39] Viniegra A, Goldberg H, Çil Ç, et al. Resolving macrophages counter osteolysis by anabolic actions on bone cells[J]. J Dent Res, 2018, 97(10): 1160-1169. DOI: 10.1177/0022034518777973.

[40] Ara T, Tokoyoda K, Sugiyama T, et al. Long-term hematopoietic stem cells require stromal cell-derived factor-1 for colonizing bone marrow during ontogeny[J]. Immunity, 2003, 19(2): 257-267. DOI: 10.1016/s1074-7613(03)00201-2.

[41] Cencioni C, Capogrossi MC, Napolitano M. The SDF-1/CXCR4 axis in stem cell preconditioning[J]. Cardiovasc Res, 2012, 94(3): 400-407. DOI: 10.1093/cvr/cvs132.

[42] Petit I, Szyper-Kravitz M, Nagler A, et al. G-CSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4[J]. Nat Immunol, 2002, 3(7): 687-694. DOI: 10.1038/ni813.

[43] Leeper NJ, Hunter AL, Cooke JP. Stem cell therapy for vascular regeneration: Adult, embryonic, and induced pluripotent stem cells[J]. Circulation, 2010, 122(5): 517-526. DOI: 10.1161/CIRCULATIONAHA.109.881441.

[44] Ko IK, Lee SJ, Atala A, et al. In situ tissue regeneration through host stem cell recruitment[J]. Exp Mol Med, 2013, 45: e57. DOI: 10.1038/emm.2013.118.

[45] Ganju RK, Brubaker SA, Meyer J, et al. The alpha-chemokine, stromal cell-derived factor-1alpha, binds to the transmembrane G-protein-coupled CXCR-4 receptor and activates multiple signal transduction pathways[J]. J Biol Chem, 1998, 273(36): 23169-23175. DOI: 10.1074/jbc.273.36.23169.

[46] Teicher BA, Fricker SP. CXCL12(SDF-1)/CXCR4 pathway in cancer[J]. Clin Cancer Res, 2010, 16(11): 2927-2931. DOI: 10.1158/1078-0432.CCR-09-2329.

[47] Trautmann F, Cojoc M, Kurth I, et al. CXCR4 as biomarker for radioresistant cancer stem cells[J]. Int J Radiat Biol, 2014, 90(8): 687-699. DOI: 10.3109/09553002.2014.906766.

[48] Penn MS. Importance of the SDF-1: CXCR4 axis in myocardial repair[J]. Circ Res, 2009, 104(10): 1133-1135. DOI: 10.1161/CIRCRESAHA.109.198929.

[49] Fadini GP, Ferraro F, Quaini F, et al. Concise review: Diabetes, the bone marrow niche, and impaired vascular regeneration[J]. Stem Cells Transl Med, 2014, 3(8): 949-957. DOI: 10.5966/sctm.2014-0052.

[50] Wei JN, Cai F, Wang F, et al. Transplantation of CXCR4 overexpressed mesenchymal stem cells augments regeneration in degenerated intervertebral discs[J]. DNA Cell Biol, 2016, 35(5): 241-248. DOI: 10.1089/dna.2015.3118.

[51] Liekens S, Schols D, Hatse S. CXCL12-CXCR4 axis in angiogenesis, metastasis and stem cell mobilization[J]. Curr Pharm Des, 2010, 16(35): 3903-3920. DOI: 10.2174/138161210794455003.

[52] Mirshahi F, Pourtau J, Li H, et al. SDF-1 activity on microvascular endothelial cells: Consequences on angiogenesis in *in vitro* and *in vivo* models[J]. Thromb Res, 2000, 99(6): 587-594. DOI: 10.1016/S0049-3848(00)00292-9.

[53] Kijowski J, Baj-Krzyworzeka M, Majka M, et al. The SDF-1-CXCR4 axis stimulates VEGF secretion and activates integrins but does not affect proliferation and survival in lymphohematopoietic cells[J]. Stem Cells, 2001, 19(5): 453-466. DOI: 10.1634/stemcells.19-5-453.

[54] Molino M, Woolkalis MJ, Prevost N, et al. CXCR4 on human endothelial cells can serve as both a mediator of biological responses and as a receptor for HIV-2[J]. Biochim Biophys Acta, 2000, 1500(2): 227-240. DOI: 10.1016/s0925-4439(99)00110-6.

[55] Döring Y, Pawig L, Weber C, et al. The CXCL12/CXCR4

chemokine ligand/receptor axis in cardiovascular disease [J]. Front Physiol, 2014,5:212. DOI:10.3389/fphys.2014.00212.

[56] Jin F, Brockmeier U, Otterbach F, et al. New insight into the SDF-1/CXCR4 axis in a breast carcinoma model: Hypoxia-induced endothelial SDF-1 and tumor cell CXCR4 are required for tumor cell intravasation[J]. Mol Cancer Res, 2012,10(8):1021-1031. DOI:10.1158/1541-7786.MCR-11-0498.

[57] Wagner NM, Bierhansl L, Nöldge-Schomburg G, et al. Toll-like receptor 2-blocking antibodies promote angiogenesis and induce ERK1/2 and AKT signaling via CXCR4 in endothelial cells[J]. Arterioscler Thromb Vasc Biol, 2013,33(8):1943-1951. DOI:10.1161/ATVBAHA.113.301783.

[58] Salvucci O, Basik M, Yao L, et al. Evidence for the involvement of SDF-1 and CXCR4 in the disruption of endothelial cell-branching morphogenesis and angiogenesis by TNF-alpha and IFN-gamma[J]. J Leukoc Biol, 2004,76(1):217-226. DOI:10.1189/jlb.1203609.

[59] Moser B, Loetscher P. Lymphocyte traffic control by chemokines [J]. Nat Immunol, 2001,2(2):123-128. DOI:10.1038/84219.

[60] Pozzobon T, Goldoni G, Viola A, et al. CXCR4 signaling in health and disease[J]. Immunol Lett, 2016,177:6-15. DOI:10.1016/j.imlet.2016.06.006.

[61] Payne D,Drinkwater S,Baretto R,et al. Expression of chemokine receptors CXCR4, CXCR5 and CCR7 on B and T lymphocytes from patients with primary antibody deficiency [J]. Clin Exp Immunol, 2009,156(2):254-262. DOI:10.1111/j.1365-2249.2009.03889.x.

[62] Nauseef WM, Borregaard N. Neutrophils at work [J]. Nat Immunol, 2014,15(7):602-611. DOI:10.1038/ni.2921.

[63] Uhl B, Vadlau Y, Zuchtriegel G, et al. Aged neutrophils contribute to the first line of defense in the acute inflammatory response[J]. Blood, 2016,128(19):2327-2337. DOI:10.1182/blood-2016-05-718999.

[64] Hampton HR, Bailey J, Tomura M, et al. Microbe-dependent lymphatic migration of neutrophils modulates lymphocyte proliferation in lymph nodes[J]. Nat Commun, 2015,6:7139. DOI:10.1038/ncomms8139.

[65] Martin C, Burdon PCE, Bridger G, et al. Chemokines acting via CXCR2 and CXCR4 control the release of neutrophils from the bone marrow and their return following senescence [J]. Immunity, 2003,19(4):583-593. DOI:10.1016/s1074-7613(03)00263-2.

[66] Leung TH, Snyder ER, Liu Y, et al. A cellular, molecular, and pharmacological basis for appendage regeneration in mice[J]. Genes Dev, 2015,29(20):2097-2107. DOI:10.1101/gad.267724.115.

[67] Chen H, Li G, Liu Y, et al. Pleiotropic roles of CXCR4 in wound repair and regeneration[J]. Front Immunol, 2021,12:668758. DOI:10.3389/fimmu.2021.668758.

[68] Gómez-Barrena E, Rosset P, Gebhard F, et al. Feasibility and safety of treating non-unions in tibia, femur and humerus with autologous, expanded, bone marrow-derived mesenchymal stromal cells associated with biphasic calcium phosphate biomaterials in a multicentric, non-comparative trial [J]. Biomaterials, 2019,196:100-108. DOI:10.1016/j.biomaterials.2018.03.033.

[69] García-García A, de Castillejo CLF, Méndez-Ferrer S. BMSCs and hematopoiesis[J]. Immunol Lett, 2015,168(2):129-135. DOI:10.1016/j.imlet.2015.06.020.

[70] Hutchings G, Moncrieff L, Dompe C, et al. Bone regeneration, reconstruction and use of osteogenic cells; from basic knowledge, animal models to clinical trials[J]. J Clin Med, 2020,9(1):E139. DOI:10.3390/jcm9010139.

[71] Chen L, Li Y, Chen W, et al. Enhanced recruitment and hematopoietic reconstitution of bone marrow-derived mesenchymal stem cells in bone marrow failure by the SDF-1/CXCR4[J]. J Tissue Eng Regen Med, 2020,14(9):1250-1260. DOI:10.1002/term.3096.

[72] Zhao A, Chung M, Yang Y, et al. The SDF-1/CXCR4 signaling pathway directs the migration of systemically transplanted bone marrow mesenchymal stem cells towards the lesion site in a rat model of spinal cord injury[J]. Curr Stem Cell Res Ther, 2023,18(2):216-230. DOI:10.2174/1574888X17666220510163245.

[73] Liu N, Patzak A, Zhang J. CXCR4-overexpressing bone marrow-derived mesenchymal stem cells improve repair of acute kidney injury[J]. Am J Physiol Renal Physiol, 2013,305(7):F1064-F1073. DOI:10.1152/ajprenal.00178.2013.

[74] Guang LG, Boskey AL, Zhu W. Regulatory role of stromal cell-derived factor-1 in bone morphogenetic protein-2-induced chondrogenic differentiation *in vitro*[J]. Int J Biochem Cell Biol, 2012,44(11):1825-1833. DOI:10.1016/j.biocel.2012.06.033.

[75] Potter ML, Smith K, Vyavahare S, et al. Characterization of differentially expressed miRNAs by CXCL12/SDF-1 in human bone marrow stromal cells[J]. Biomol Concepts, 2021,12(1):132-143. DOI:10.1515/bmc-2021-0015.

[76] Zhu W, Boachie-Adjei O, Rawlins BA, et al. A novel regulatory role for stromal-derived factor-1 signaling in bone morphogenic protein-2 osteogenic differentiation of mesenchymal C2C12 cells [J]. J Biol Chem, 2007,282(26):18676-18685. DOI:10.1074/jbc.M610232200.

[77] Kollet O, Dar A, Shivtiel S, et al. Osteoclasts degrade endosteal components and promote mobilization of hematopoietic progenitor cells [J]. Nat Med, 2006,12(6):657-664. DOI:10.1038/nm1417.

[78] Zhang C, Zhang W, Zhu D, et al. Nanoparticles functionalized with stem cell secretome and CXCR4-overexpressing endothelial membrane for targeted osteoporosis therapy [J]. J Nanobiotechnology, 2022,20(1):35. DOI:10.1186/s12951-021-01231-6.

[79] Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: Estimates from the global burden of disease 2010 study[J]. Ann Rheum Dis, 2014,73(7):1323-1330. DOI:

10.1136/annrheumdis-2013-204763.

[80] Mathiessen A, Conaghan PG. Synovitis in osteoarthritis: Current understanding with therapeutic implications[J]. Arthritis Res Ther, 2017, 19(1): 18. DOI: 10.1186/s13075-017-1229-9.

[81] Bagi CM, Berryman ER, Teo S, et al. Oral administration of undenatured native chicken type Ⅱ collagen (UC-Ⅱ) diminished deterioration of articular cartilage in a rat model of osteoarthritis (OA)[J]. Osteoarthritis Cartilage, 2017, 25(12): 2080-2090. DOI: 10.1016/j.joca.2017.08.013.

[82] Wang G, Li Y, Meng X, et al. The study of targeted blocking SDF-1/CXCR4 signaling pathway with three antagonists on MMPs, type Ⅱ collagen, and aggrecan levels in articular cartilage of guinea pigs[J]. J Orthop Surg Res, 2020, 15(1): 195. DOI: 10.1186/s13018-020-01646-1.

[83] Li J, Chen H, Zhang D, et al. The role of stromal cell-derived factor 1 on cartilage development and disease[J]. Osteoarthritis Cartilage, 2021, 29(3): 313-322. DOI: 10.1016/j.joca.2020.10.010.

[84] Lu W, He Z, Shi J, et al. AMD3100 attenuates post-traumatic osteoarthritis by maintaining transforming growth factor-β1-induced expression of tissue inhibitor of metalloproteinase-3 via the phosphatidylinositol 3-kinase/akt pathway[J]. Front Pharmacol, 2019, 10: 1554. DOI: 10.3389/fphar.2019.01554.

[85] Lu W, Shi J, Zhang J, et al. CXCL12/CXCR4 axis regulates aggrecanase activation and cartilage degradation in a post-traumatic osteoarthritis rat model[J]. Int J Mol Sci, 2016, 17(10): E1522. DOI: 10.3390/ijms17101522.

[86] Qin H, Zhao X, Hu YJ, et al. Inhibition of SDF-1/CXCR4 axis to alleviate abnormal bone formation and angiogenesis could improve the subchondral bone microenvironment in osteoarthritis[J]. Biomed Res Int, 2021: 8852574. DOI: 10.1155/2021/8852574.

[87] Zhang Y, Li X, Li J, et al. Knee loading enhances the migration of adipose-derived stem cells to the osteoarthritic sites through the SDF-1/CXCR4 regulatory axis[J]. Calcif Tissue Int, 2022, 111(2): 171-184. DOI: 10.1007/s00223-022-00976-y.

[88] Zhang X, Sun Y, Chen W, et al. Nanoparticle functionalization with genetically-engineered mesenchymal stem cell membrane for targeted drug delivery and enhanced cartilage protection[J]. Biomater Adv, 2022, 136: 212802. DOI: 10.1016/j.bioadv.2022.212802.

[89] Zhou S, Lu H, Xiong M. Identifying immune cell infiltration and effective diagnostic biomarkers in rheumatoid arthritis by bioinformatics analysis[J]. Front Immunol, 2021, 12: 726747. DOI: 10.3389/fimmu.2021.726747.

[90] Bragg R, Gilbert W, Elmansi A M, et al. Stromal cell-derived factor-1 as a potential therapeutic target for osteoarthritis and rheumatoid arthritis[J]. Ther Adv Chronic Dis, 2019, 10: 20406 22319882531. DOI: 10.1177/2040622319882531.

[91] Kim KW, Cho ML, Kim HR, et al. Up-regulation of stromal cell-derived factor 1 (CXCL12) production in rheumatoid synovial fibroblasts through interactions with T lymphocytes: Role of interleukin-17 and CD40L-CD40 interaction[J]. Arthritis and Rheumatism, 2007, 56(4): 1076-1086. DOI: 10.1002/art.22439.

[92] Chen HT, Tsou HK, Hsu CJ, et al. Stromal cell-derived factor-1/CXCR4 promotes IL-6 production in human synovial fibroblasts[J]. J Cell Biochem, 2011, 112(4): 1219-1227. DOI: 10.1002/jcb.23043.

[93] Peng L, Zhu N, Mao J, et al. Expression levels of CXCR4 and CXCL12 in patients with rheumatoid arthritis and its correlation with disease activity[J]. Exp Ther Med, 2020, 20(3): 1925-1934. DOI: 10.3892/etm.2020.8950.

[94] Wang S, Zhou C, Zheng H, et al. Chondrogenic progenitor cells promote vascular endothelial growth factor expression through stromal-derived factor-1[J]. Osteoarthritis Cartilage, 2017, 25(5): 742-749. DOI: 10.1016/j.joca.2016.10.017.

[95] Samarpita S, Rasool M. Cyanidin attenuates IL-17A cytokine signaling mediated monocyte migration and differentiation into mature osteoclasts in rheumatoid arthritis[J]. Cytokine, 2021, 142: 155502. DOI: 10.1016/j.cyto.2021.155502.

[96] Cecchinato V, D'Agostino G, Raeli L, et al. Redox-mediated mechanisms fuel monocyte responses to CXCL12/HMGB1 in active rheumatoid arthritis[J]. Front Immunol, 2018, 9: 2118. DOI: 10.3389/fimmu.2018.02118.

[97] He Y, Chen Y. The potential mechanism of the microbiota-gut-bone axis in osteoporosis: A review[J]. Osteoporos Int, 2022, 33(12): 2495-2506. DOI: 10.1007/s00198-022-06557-x.

[98] Sözen T, Özişik L, Başaran NÇ. An overview and management of osteoporosis[J]. Eur J Rheumatol, 2017, 4(1): 46-56. DOI: 10.5152/eurjrheum.2016.048.

[99] Liu Q, Zhang X, Jiao Y, et al. *In vitro* cell behaviors of bone mesenchymal stem cells derived from normal and postmenopausal osteoporotic rats[J]. Int J Mol Med, 2018, 41(2): 669-678. DOI: 10.3892/ijmm.2017.3280.

[100] Garg P, Mazur MM, Buck AC, et al. Prospective review of mesenchymal stem cells differentiation into osteoblasts[J]. Orthop Surg, 2017, 9(1): 13-19. DOI: 10.1111/os.12304.

[101] Guang LG, Boskey AL, Zhu W. Age-related CXC chemokine receptor-4-deficiency impairs osteogenic differentiation potency of mouse bone marrow mesenchymal stromal stem cells[J]. Int J Biochem Cell Biol, 2013, 45(8): 1813-1820. DOI: 10.1016/j.biocel.2013.05.034.

[102] Gilbert W, Bragg R, Elmansi AM, et al. Stromal cell-derived factor-1 (CXCL12) and its role in bone and muscle biology[J]. Cytokine, 2019, 123: 154783. DOI: 10.1016/j.cyto.2019.154783.

[103] Bai J, Ge G, Wang Q, et al. Engineering stem cell recruitment and osteoinduction via bioadhesive molecular mimics to improve osteoporotic bone-implant integration[J]. Research (Wash D C), 2022: 9823784. DOI: 10.34133/2022/9823784.

[104] Hu Y, Li X, Zhang Q, et al. Exosome-guided bone targeted delivery of Antagomir-188 as an anabolic therapy for bone loss[J]. Bioact Mater, 2021, 6(9): 2905-2913. DOI: 10.1016/j.

bioactmat.2021.02.014.

[105] Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition[J]. J Periodontol, 2018, 89(Suppl 1): S159-S172. DOI: 10.1002/JPER.18-0006.

[106] Sun X, Gao J, Meng X, et al. Polarized macrophages in periodontitis: Characteristics, function, and molecular signaling [J]. Front Immunol, 2021, 12: 763334. DOI: 10.3389/fimmu.2021.763334.

[107] Bosshardt DD. The periodontal pocket: Pathogenesis, histopathology and consequences [J]. Periodontology 2000, 2018, 76(1): 43-50. DOI: 10.1111/prd.12153.

[108] Zhang X, Jin Y, Wang Q, et al. Autophagy-mediated regulation patterns contribute to the alterations of the immune microenvironment in periodontitis [J]. Aging (Albany NY), 2020, 13(1): 555-577. DOI: 10.18632/aging.202165.

[109] Zhang Z, Zheng Y, Bian X, et al. Identification of key genes and pathways associated with oxidative stress in periodontitis[J]. Oxid Med Cell Longev, 2022: 9728172. DOI: 10.1155/2022/9728172.

[110] Arjunan P, Meghil MM, Pi W, et al. Oral pathobiont activates anti-apoptotic pathway, promoting both immune suppression and oncogenic cell proliferation[J]. Sci Rep, 2018, 8(1): 16607. DOI: 10.1038/s41598-018-35126-8.

[111] Yamashiro K, Ideguchi H, Aoyagi H, et al. High mobility Group Box 1 expression in oral inflammation and regeneration [J]. Front Immunol, 2020, 11: 1461. DOI: 10.3389/fimmu.2020.01461.

[112] Luo H, Chen D, Li R, et al. Genetically engineered CXCR4-modified exosomes for delivery of miR-126 mimics to macrophages alleviate periodontitis [J]. J Nanobiotechnology. 2023, 21(1): 116. DOI: 10.1186/s12951-023-01863-w.

[113] Mehta SA, Christopherson KW, Bhat-Nakshatri P, et al. Negative regulation of chemokine receptor CXCR4 by tumor suppressor p53 in breast cancer cells: Implications of p53 mutation or isoform expression on breast cancer cell invasion[J]. Oncogene, 2007, 26(23): 3329-3337. DOI: 10.1038/sj.onc.1210120.

[114] Orimo A, Gupta PB, Sgroi DC, et al. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion [J]. Cell, 2005, 121(3): 335-348. DOI: 10.1016/j.cell.2005.02.034.

[115] Chinni SR, Yamamoto H, Dong Z, et al. CXCL12/CXCR4 transactivates HER2 in lipid rafts of prostate cancer cells and promotes growth of metastatic deposits in bone[J]. Mol Cancer Res, 2008, 6(3): 446-457. DOI: 10.1158/1541-7786.MCR-07-0117.

[116] Lai TH, Fong YC, Fu WM, et al. Stromal cell-derived factor-1 increase alphavbeta3 integrin expression and invasion in human chondrosarcoma cells[J]. J Cell Physiol, 2009, 218(2): 334-342. DOI: 10.1002/jcp.21601.

[117] Lu Y, Hu B, Guan GF, et al. SDF-1/CXCR4 promotes F5M2 osteosarcoma cell migration by activating the Wnt/β-catenin signaling pathway[J]. Med Oncol, 2015, 32(7): 194. DOI: 10.1007/s12032-015-0576-0.

[118] Xi Y, Qi Z, Ma J, et al. PTEN loss activates a functional AKT/CXCR4 signaling axis to potentiate tumor growth and lung metastasis in human osteosarcoma cells[J]. Clin Exp Metastasis, 2020, 37(1): 173-185. DOI: 10.1007/s10585-019-09998-7.

[119] Liu J, Feng G, Li Z, et al. Long non-coding RNA FEZF1-AS1 modulates CXCR4 to promote cell proliferation, warburg effect and suppress cell apoptosis in osteosarcoma by sponging miR-144 [J]. Onco Targets Ther, 2020, 13: 2899-2910. DOI: 10.2147/OTT.S235970.

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