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# 骨质疏松中不同炎症因子的研究进展

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## 摘　要

**大量研究表明炎性细胞因子对各种炎性疾病发挥重要作用，但对其具体作用的报道并不总是一致的。它们可用作指示或监测疾病或其进展的生物标志物，也可用作治疗的临床适用参数。免疫系统的各种炎症因子可以上调核因子-κB受体活化因子配体(Receptor Activator for Nuclear Factor-κB Ligand, RANKL)的表达，RANKL与破骨细胞前体细胞的RANK结合促进破骨细胞的分化和活化，最终引起炎症性骨质疏松的发生发展。但迄今为止，炎症因子对骨质疏松的具体影响机制一直没有得到系统地归纳。因此，在这篇综述中，我们筛选总结了炎症因子白介素-1 (Interleukin-1, IL-1)、IL-33、IL-6、IL-8、IL-10和肿瘤坏死因子-$\alpha$ (tumor necrosis factor-$\alpha$, TNF-$\alpha$)的生物学信息在炎症和骨质疏松中的作用，为炎症性骨质疏松提供了一个系统的理论基础。**

## 关键词

**骨质疏松，炎症因子，炎症性疾病，破骨细胞，RANKL**

# Research Progress of Different Inflammatory Factors in Osteoporosis

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## Abstract

**A large number of studies have shown that inflammatory cytokines play an important role in var-**

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**ious inflammatory diseases, but the reports on their specific effects are not always consistent. They can be used as biomarkers to indicate or monitor the disease or its progress, and can also be used as clinical parameters for treatment. Various inflammatory factors in the immune system can up-regulate the expression of nuclear factor-kappa B receptor activating factor ligand (Receptor Activator for Nuclear Factor-κB Ligand, RANKL). The binding of RANKL to the RANK of osteoclast precursors promotes the differentiation and activation of osteoclasts, resulting in the occurrence and development of inflammatory osteoporosis. But so far, the specific mechanism of inflammatory factors on osteoporosis has not been systematically summarized. Therefore, in this review, we screened and summarized the biological information of inflammatory factors interleukin-1 (Interleukin-1, IL-1), IL-33, IL-6, IL-8, IL-10 and tumor necrosis factor-*α* (tumor necrosis factor-*α*, TNF-*α*) and their roles in inflammation and osteoporosis, which provided a systematic theoretical basis for inflammatory osteoporosis.**

## Keywords

**Osteoporosis, Inflammatory Factors, Inflammatory Diseases, Osteoclasts, RANKL**



## 1. 引言

骨质疏松症是一种全身性骨骼疾病，其特征是骨量减少，骨组织微结构恶化，骨脆性增强，骨折风险增加[1]。世界卫生组织使用骨密度(bone mineral density, BMD)和 T 评分来定义骨质疏松症。骨质疏松症的定义是 T 评分 $<-2.5$，介于正常与骨质疏松症中间的低骨密度被定义为 T 评分在−1.0 到−2.5 之间[2] [3]。据统计，中国至少有 9000 万人患有骨质疏松症[4]。髋部和脊柱骨折是骨质疏松症最具破坏性的后果，并与老年人的致残率和死亡率的增加有关[1] [5]。因此关于骨质疏松发病机制的研究成为当今老龄化社会的重要任务之一。

炎症在传统上被定义为身体对有害刺激的自然反应[6]，参与体内平衡和再生过程，例如伤口愈合。它还参与针对病原体的急性期反应和免疫反应。炎症是一个复杂的过程，涉及不同炎症因子的产生和释放，包括白介素-1*α* (IL-1*α*)、白介素-6 (IL-6)和白介素-1*β* (IL-1*β*)等[7] [8]，这些炎症因子本身也对炎症起到了重要作用[9]。它们可用作指示或监测疾病或其进展的生物标志物，也可用作治疗的临床适用参数。但炎症是一把双刃剑，其在体内发挥好或坏的作用取决于发生的环境、部位和时间。如果炎症持续存在，其恢复体内平衡的功能就会丧失，逐渐进展为慢性炎症[10]。慢性炎症是不受控制的炎症形式，在许多复杂疾病和机体紊乱的发展中起着至关重要的作用，例如慢性炎症性疾病，包括代谢综合征、神经退行性疾病和心血管疾病，以及自身免疫性疾病、癌症和骨质疏松症[11]-[17]。已经有研究证明，增加 IL-1 及 IL-6 家族的炎症因子水平可以上调 RANKL 的表达[18]。RANKL 和核因子-κB (nuclear factor kappa-B, NF-κB)受体激活因子(Receptor Activator for Nuclear Factor-κB, RANK)的结合引起肿瘤坏死因子受体相关因子 6 (tumor necrosis factor receptor-associated factor 6, TRAF6)的募集，触发下游信号通路(PI-3K/κ、NF-κB 和丝裂原活化蛋白激酶 MAPK (ERK、JNKK 和 p38))的激活，从而导致慢性炎症性骨质疏松症的发生[19] [20]。然而，尚未有报告系统地整理炎症因子对骨质疏松症的影响，不同的炎症性疾病涉及的炎症因子机制也有着明显的区别。因此，研究并总结相关炎症因子及其对骨质疏松症的影响对于炎症性疾

病患者的骨质疏松症防治有着可观的临床意义。本综述将简要总结 IL-1、IL-6、IL-8、IL-10、IL-33 和 TNF-$\alpha$ 的特点并介绍其对骨质疏松症的影响。

## 2. IL-1

### 2.1. IL-1 的产生和分泌

IL-1 型细胞因子是先天性免疫反应的主要介质，IL-1 受体拮抗剂(interleu-kin-1 receptor antagonist, IL-1Ra)对 IL-1$\alpha$ 或 IL-1$\beta$ 的阻断已证明 IL-1 在许多人类自身炎症疾病中起着核心作用。虽然最初的 IL-1 家族仅包含 IL-1$\alpha$ 和 IL-1$\beta$，但目前 IL-1 家族已扩展至 11 名成员(IL-1$\alpha$、IL-1$\beta$、IL-18、IL-33、IL-36$\alpha$、IL-36$\beta$、IL-36$\gamma$、IL-1Ra、IL-36Ra、IL-37 和 IL-38) [21] [22] [23]。IL-1 主要由单核吞噬细胞谱系的细胞产生，但也可以由内皮细胞、角质形成细胞、滑膜细胞、成骨细胞、中性粒细胞、神经胶质细胞和许多其他细胞产生[22]。多种物质的刺激可以介导 IL-1 的产生，包括内毒素、其他细胞因子和微生物。IL-1$\alpha$ 和 IL-1$\beta$ 以及相关的蛋白质 IL-18 都是在没有分泌前导序列作为活性较低的前体的情况下合成的。IL-1 和 IL-18 分泌取决于被称为 IL-1 转化酶(Interleukin 1 converting enzyme, ICE)或半胱天冬酶 1 的特定转化酶的裂解，该转化酶将原细胞因子裂解为其活性分泌形式[24]。IL-33 的主要来源是非造血细胞，如内皮细胞和上皮细胞[25]。IL-33 是 TLR/IL1R 超家族孤儿受体 St2 的配体，通过 MyD88 激活典型的 NF-κB 通路[26]。

### 2.2. IL-1$\alpha$ 和 IL-1$\beta$ 的加工活化及分泌

IL-1$\alpha$ 在稳态条件下由多种造血细胞和非造血细胞表达，并且可以被诸如氧化应激或细胞因子暴露(例如其他 IL-1 家族细胞因子)等多种炎症的刺激上调 IL-1$\alpha$ mRNA 的表达[27]。与 IL-1$\beta$ 和 IL-33 相比，IL-1$\alpha$ 的前体(pro-IL-1$\alpha$)和重组人成熟 IL-1$\alpha$ 在诱导人外周血单个核细胞(Peripheral blood mononuclear cell, PBMC)和肺癌细胞中的 IL-6 和 TNF-$\alpha$ 方面具有相同的生物学活性[28]。与 pro-IL-1$\beta$ 一样，pro-IL-1$\alpha$ 也被包括促炎蛋白酶 caspase-1 在内的蛋白酶切割，产生具有生物活性的 17kDa 形式和 16 kDa N 末端切割产物[29]。虽然 caspase-1 对 pro-IL-1$\beta$ 的切割是产生生物活性 IL-1$\beta$ 所必需的，但根据诱导 IL-6 和 TNF 分泌的能力确定了 pro-IL-1$\alpha$ 和成熟 IL-1$\alpha$ 与 IL-1R 结合的动力学相近，且对上皮细胞和造血细胞具有相似的生物活性[28]。尽管 caspase-1 对 IL-1$\alpha$ 的处理对其生物活性是可有可无的，但炎症小体对 caspase-1 的激活能通过诱导细胞焦亡来促进 IL-1$\alpha$ (和其他炎症小体相关细胞因子)的分泌[29]，这体现了 IL-1$\alpha$ 作为警报素的特性。活性 caspase-1 还可以切割细胞死亡执行者 Gasdermin D (GSDMD)，使 GSDMD 的 N 端片段寡聚化并插入细胞膜，导致细胞肿胀和最终破裂，伴随包括 IL-1$\alpha$ 和 IL-1$\beta$ 的细胞内容物释放[30] [31] [32]。因此，炎症小体激活和随后的细胞焦亡是细胞释放 IL-1$\alpha$ 的一种机制，在炎症小体激活期间释放 IL-1$\alpha$ 和 IL-1$\beta$ 可能会补充 IL-1$\beta$ 对 IL-1R 的激活[33]。在某些细胞类型中，细胞溶质 IL-1R2 的结合使 pro-IL-1$\alpha$ 处于非活性状态，因为在细胞坏死死亡时释放的 pro-IL-1$\alpha$-IL1R2 复合物不能通过 IL-1R 发出信号。IL-1R2 对 IL-1$\alpha$ 活性的抑制可以通过活性 caspase-1 来缓解，因为它可以切割 IL-1R2，从而导致其与 pro-IL-1$\alpha$ 解离[33]。因此，炎症小体的激活可能通过减轻 IL-1R2 的抑制作用来间接促进 IL-1$\alpha$ 的生物利用度。由此可见，在炎症环境下，IL-1$\alpha$ 的释放和活性将会得到显著地放大。

IL-1$\beta$ 的主要来源是造血细胞(如单核细胞)、巨噬细胞(如小胶质细胞)以及树突状细胞[34]。一般来说，血液单核细胞中活性 IL-1$\beta$ 的释放受到严格控制，只有不到 20%的 IL-1$\beta$ 前体被加工和释放。许多炎症性疾病的基础是活性 IL-1$\beta$ 的释放增加。活化的单核细胞/巨噬细胞释放的 ATP 在细胞外积累[35]，ATP 与 P2X7 受体结合后，细胞内钾离子迅速排出，胞内钾的下降会导致称为“炎性体”的一组高度特化的细胞内蛋白质的寡聚化，它将 procaspase-1 转化为活性酶[36]。活性 caspase-1 然后在专门的分泌性溶酶体或

胞质溶胶中切割 IL-1$\beta$ 前体，随后分泌具有生物活性的 IL-1$\beta$。

### 2.3. IL-1$\alpha$ 和 IL-1$\beta$ 促进炎症性骨质疏松发生发展

IL-1$\alpha$ 或 IL-1$\beta$ 首先与 I 型 IL-1 受体(IL-1RI)结合，随后募集 IL-1 受体辅助蛋白(Interleukin-1 Receptor Accessory Protein, IL-1RAcP)，形成由 IL-1RI、IL-1 和辅助受体组成的三聚体复合物。通过称为 Toll 和 IL-1R 样(Toll/Interleukin-1 receptor, TIR)结构域的保守胞质区域，该三聚体复合物快速组装两种细胞内信号蛋白，即骨髓分化初级反应基因 88 (myeloiddifferentiationfactor88, MyD88)和 IL-1 受体激活蛋白激酶(IL-1 receptor associated kinase, IRAK)。IL-1、IL-1RI、IL-RAcP、MyD88 和 IRAK 形成稳定的 IL-1 诱导的第一信号模块。随后 IRAK1 和 IRAK2 磷酸化，TRAF6 募集和寡聚化，NF-κB、c-Jun N-末端激酶(c-Jun N-terminal kinase, JNK)和 p38 MAPK 炎症信号通路被激活，最后使得炎症基因大量表达[23] [37]。

有研究表明，IL-1$\alpha$ 已成为皮肤炎症[38]、结肠炎症、癌症[39]、心血管疾病[40]和神经炎症[41]的顶端驱动因素。IL-1$\beta$ 也被视为多种炎症疾病的主要治疗靶点[42] [43]。尽管一些炎症性疾病是由于 caspase-1 活性的功能获得性突变引起的，但痛风、2 型糖尿病、心力衰竭、复发性心包炎、类风湿性关节炎等常见疾病也对 IL-1$\beta$ 中和有反应[23]。

炎症相关的骨质疏松症是由破骨细胞的激活驱动的，破骨细胞具有高度运动性，可在骨表面移动并吸收大面积的骨组织[44]。IL-1$\beta$ 与其 T 淋巴细胞、B 淋巴细胞和巨噬细胞上的受体结合可促进 RANKL [45]的产生，RANKL 与破骨细胞前体细胞的 RANK 结合，有助于破骨细胞的分化和活化。RANKL 活性被骨保护素(osteoclastogenesis inhibitory factor, OPG)抑制，OPG 是 RANKL 的可溶性诱饵受体并阻断 RANKL 介导的破骨细胞分化和促骨吸收活性，IL-1$\alpha$ 和 TNF-$\alpha$ 可以直接通过 RANK/RANKL/OPG 途径作用于破骨细胞[46] [47]，促进破骨细胞的分化增强骨吸收。此外，IL-1$\beta$ 可以通过增加巨噬细胞集落刺激因子(macrophage colony stimulating factor, M-CSF)的产生来激活破骨细胞，还可以抑制破骨细胞凋亡[48]。IL-1 也被认为是 TNF 介导的成骨的关键介质[49] [50]。TNF 和 IL-1 最初参与不同的信号通路，它们与 NF-κB 的激活和 MAPK 系统的刺激相融合。因此，两种细胞因子的串扰效应为破骨细胞生成提供有效信号，抑制成骨细胞功能，调节骨骼细胞的寿命[51]。另一方面，IL-1 对成骨细胞也有影响。IL-1$\alpha$ 可以通过 JNK 和 p38 MAPK 途径诱导减少的 MC3T3-E1 细胞的活力并抑制成骨细胞分化[52]。树突状细胞(dendritic cell, DC)被认为是能够有效激活幼稚 T 淋巴细胞的专业抗原呈递细胞，能够在早期发育阶段在体外分化成破骨细胞。当 M-CSF 和 RANKL 存在时，小鼠 IL-1$\beta$ 和 TNF-$\alpha$ 可以增加骨吸收。与 TNF-$\alpha$ 相比，IL-1$\beta$ 在促进骨吸收方面具有更高的效率[53]。

### 2.4. IL-33 具有潜在的骨保护作用

IL-33 是 IL-1 家族的最新成员，位于细胞核中，但也发现在细胞外作为警报素[54]。IL-33 的主要来源是非造血细胞，例如内皮细胞和上皮细胞[25]。与 IL-1 家族的其他成员(如 IL-1$\beta$)不同，IL-33 的 N 末端不需要激活处理[55]。IL-33 是一种 Th2 细胞因子，主要由炎症刺激后的基质细胞表达。它往往作为传统的细胞因子、警报素和能够控制基因转录的核因子发挥作用[56]。作为警报素，IL-33 在细胞损伤和细胞死亡后释放，参与应激反应并导致其他细胞因子的诱导[57]。IL-33 作为 IL-1 受体家族成员 ST2 的配体在细胞外发挥作用，IL-33 与 ST2 的结合可以进一步激活下游通路，导致 Th2 细胞因子的转录增加[58]。ST2 主要由先天免疫细胞、肥大细胞和 Th2 淋巴细胞表达，其连接的不同变体导致产生不同的受体形式，包括可溶性形式(sST2)，它通过结合细胞外 IL-33 充当诱饵受体，从而阻止其与膜受体的相互作用。IL-33 下游信号传导需要辅助受体 IL-1R3 才能发挥作用，ST2/IL-1R3 转导信号导致 NF-κB、JNK 和 MAPK 通路[59] [60]的激活。IL-33 激活幼稚 T 细胞并促进其向 Th2 表型成熟，从而导致 Th2 型细胞因子和趋化因

子的释放，IL-33 还影响各种适应性和先天免疫细胞，包括嗜酸性粒细胞、肥大细胞、2 型先天淋巴细胞和 Th2 淋巴细胞[59] [61] [62]。此外，通过 NF-kB 和 MAPK 信号通路，IL-33 可以诱导产生 IL-5、IL-13 和 CCL5、CCL17、CCL24 等趋化因子[63] [64]。

IL-33/ST2 信号通路与生理和病理条件下的骨转换有关。IL-33 通过调节抗破骨细胞基因(如干扰素调节因子 8 (Recombinant Interferon Regulatory Factor 8, IRF-8))抑制 RANKL 诱导的破骨细胞形成，该基因可以被抗 ST2 单克隆抗体阻断[62]。IL-33 可以作用于所有不同类型的骨细胞[65]。尽管 IL-33/ST2 通路与各种急性和慢性免疫性疾病和炎症性疾病有关，并伴有明显的骨吸收，如髋关节骨坏死和类风湿性关节炎，但 IL-33/ST2 通路已被认为是骨骼的重要保护信号，可通过减少破骨细胞生成和刺激成骨细胞功能，减少骨吸收量。[64]。此外，IL-33 还间接作用于骨骼，诱导能够干扰 M-CSF 和 RANKL 产生的抗破骨细胞因子的合成[55]。总之，IL-33 在细胞、分子和转录水平上发挥作用，介导骨重塑中的多能功能，并具有减轻骨质疏松症的潜在治疗价值。

## 3. IL-6

IL-6 是一种多效性细胞因子，不仅参与免疫反应，还参与炎症、造血、骨代谢、胚胎发育和其他基本过程[66] [67] [68]。IL-6 经过糖基化并由 T 细胞、单核细胞、内皮细胞和成纤维细胞分泌[69]，同时具有促炎和抗炎的特性。IL-6 下传指令是通过两种不同的机制实现的；其中之一是 IL-6 与其膜结合的 IL-6 受体(membrane-bound interleukin-6 receptor, mbIL6R) [70]结合。该复合物随后通过 Janus 激酶/信号转导和转录激活因子(STAT)激酶、磷酸肌醇 3-激酶(phosphoinositide 3-kinase, PI3K)和 MAPK 激酶(如 p38)募集了两个膜结合糖蛋白 130 分子(glycoprotein 130, gp130) [71] [72]。对 IL-6 的可持续反应的一个主要限制是 mbIL6R 的可用性，它仅在某些细胞类型上表达，而 gp130 几乎存在于每个细胞中[73]。这意味着 IL-6 通过经典信号传导的系统性影响是相当有限的[69]。IL-6 识别的第二种机制依赖于可溶性 IL-6 受体(Soluble interleukin 6 receptor, sIL6R)，它通过 mRNA 剪接或解聚素和金属蛋白酶的蛋白水解来表达[69]。有趣的是，ADAM 蛋白酶不仅能被其他细胞因子激活，例如 IL-1$\beta$ 或 TNF-$\alpha$ [74]，也可以被细菌毒素诱导[75]。在 sIL6R 表达的情况下，IL-6 与 sIL6R 结合并构建 IL6/sIL6R 复合物，进而激活 mbIL6R-less 细胞上的 gp130 [76]。这个过程被称为转信号，是 IL-6 诱导炎症发生发展的主要推动力[77]。目前，与 C 反应蛋白(C-reactive protein, CRP)类似，IL-6 用于“监测”癌症、感染或自身免疫性疾病患者的炎症水平[67] [78]。

IL-6 放大器(Interleukin 6 amplifier, IL-6 Amp)是通过信号传导及转录激活因子 3 (signal transducer and activator of transcription 3, STAT3)和 NF-κB 之间的协同相互作用产生更多的 IL-6 及多种其他细胞因子和趋化因子，它也在炎症性疾病中发挥关键作用，包括细胞因子风暴综合征、自身免疫性疾病和癌症[17] [79] [80] [81] [82]。在所谓的“细胞因子风暴”(一种由 T 细胞过度活化引起的可能致命的免疫反应)期间，观察到 IL-6 大幅度增加，明显高于其他炎性细胞因子。最近的一项研究表明，使用 T 细胞转染的癌症免疫疗法诱导的细胞因子风暴被抗 IL-6 受体抗体托珠单抗所抵消[83]。IL-6 在炎症初期在局部病变部位合成后，通过血流进入肝脏，随后迅速诱导大量急性期蛋白如 CRP、血清淀粉样蛋白 A (serum amyloid A protein, SAA)、纤维蛋白原、触珠蛋白和 $\alpha$1-抗胰凝乳蛋白酶的产生[84]。另一方面，IL-6 减少纤连蛋白、白蛋白和转铁蛋白的产生。当高浓度的 SAA 长期存在时，它会通过 SAA 淀粉样变性的产生导致几种慢性炎症性疾病的严重并发症[85]。这导致淀粉样蛋白原纤维沉积，从而导致各种器官进行性恶化。此外，IL-6 与转化生长因子(TGF)-$\beta$ 结合对于从幼稚 CD4 + T 细胞分化 Th17 是必不可少的[86]，但 IL-6 也抑制 TGF-$\beta$ 诱导的 Treg 分化[87]。Th17/Treg 平衡的上调被认为是造成免疫耐受性破坏的原因，因此在病理上 IL-6 与自身免疫和慢性炎症性疾病的发展有关[88]。

当 IL-6 在骨髓基质细胞中产生时，它会刺激 RANKL 产生[89]，这对于破骨细胞的分化和活化是必不可少的[90]，并且这会导致骨吸收和骨质疏松症[91]。IL-6 不仅刺激成骨细胞前体细胞中 RANKL 的表达[92]，还通过病理细胞促进 RANKL 的表达，例如类风湿性关节炎的滑膜成纤维细胞[93]。IL-6 通过 IL-6R 对破骨细胞前体发挥调节作用：当 RANKL 水平较高时抑制破骨细胞的形成，而当 RANKL 水平较低时刺激破骨细胞的形成[94]。过量表达 IL-6 的转基因小鼠血清中 IL-6 的循环水平很高，破骨细胞数量增加，小鼠的骨小梁质量较低[95]。然而，IL-6 基因敲除小鼠在破骨细胞形成或松质骨量方面没有表现出缺陷[91]，表明 IL-6 在正常的松质骨生理中没有独特的作用。与此相对的是，IL-6 似乎在破骨细胞数量增加的病理过程中起着重要作用。例如，IL-6 基因缺失的小鼠在实验性炎性关节炎中表现出钝化的卵巢切除诱导的骨丢失[91]和破骨细胞形成减少[93]。总之，IL-6 在骨质疏松中扮演重要角色，并加快骨吸收的进程。

## 4. IL-8

白介素 8 (IL-8)，也称为 CXCL8，是一种有着促炎作用的 CXC 趋化因子。IL-8 的表达主要受激活蛋白和/或 NF-κB 介导的转录活性的调节，尽管在 IL-8 基因启动子上已经表征了额外的激素反应元件和 NF-IL-6 共有位点。因此，IL-8 的表达已显示受多种不同刺激的调节，包括炎症信号(例如，TNF-$\alpha$、IL-1$\beta$)、化学和环境压力(例如，暴露于化疗药物和缺氧)和类固醇激素(例如，雄激素、雌激素和地塞米松) [96] [97]。IL-8 的生物学效应是通过 IL-8 与两种细胞表面 G 蛋白偶联受体(称为 CXCR1 和 CXCR2)结合来介导的[98] [99]。这些受体具有相当大的结构相似性，表明这些基因是通过基因复制产生的。这些信号通过配体诱导的构象变化跨膜传递，暴露细胞内环和受体羧基末端尾部上的表位，促进与功能性异源三聚体 G 蛋白的偶联。CXCR1 和 CXCR2 也表现出明显不同的配体结合药理学。CXCR1 仅能被 IL-8 和粒细胞趋化蛋白 2 的结合而被激活。然而，CXCR2 可以被多种 CXC 趋化因子激活，包括生长相关癌基因(GRO$\alpha$、$\beta$ 和 $\gamma$)、中性粒细胞激活肽和粒细胞趋化蛋白 2 [96]。IL-8 信号还调节 MAPK 信号级联的活性，该级联构成许多丝氨酸/苏氨酸激酶，它们通过与紧邻细胞表面受体的支架蛋白相互作用而共定位。这些激酶的底物特异性导致不同信号级联的激活，其中最好的特征是 Raf-1/MAP/ERK 激酶 1/Erk 级联。IL-8 信号传导已被证明可诱导这种经典 MAPK 信号级联的激活，在中性粒细胞[100]和癌细胞[101] [102] [103]中检测到 Erk1/2 的下游磷酸化。在中性粒细胞中，磷脂酰肌醇-3 激酶活性已被确定为将 IL-8 受体与 MAPK 信号传导耦合的关键中间体[100]。MAPK 信号的激活与 IL-8 在嗜中性粒细胞[104]、内皮细胞[105]和癌细胞系[101] [102] [103]的细胞增殖和细胞存活促进作用一致。Erk-MAPK 信号的激活最终指明了将 IL-8 信号与 E2F 和激活蛋白转录因子的激活联系起来的推定途径，其功能主要是调节许多与细胞增殖有关的基因的转录。此外，IL-8 信号还激活 p38 MAPK 信号级联[106]。然而，这种 MAPK 对 IL-8 诱导的反应的功能重要性仍有待确定。

IL-8 能将中性粒细胞引导至炎症方向(趋化性)，ARDS 患者的肺中这种细胞因子的浓度增加很明显[107]。此外，IL-8 在体外不会直接激活 NAPDH 氧化酶，但它通过募集 N－甲酰－甲硫氨酰－亮氨酰－苯丙氨酸(formylmethionyl leucyl phenylalanine, fMLP)受体和 P-选择素配体来增强呼吸爆发活性进入脂质[108]。用 IL-8 cDNA 转染的结肠癌细胞的体外研究显示，这些细胞的细胞增殖、迁移和侵袭显着增加[109]。由此可见，IL-8 是细胞迁移和增殖的非常有效的触发因素，因此应始终在炎症模型中加以考虑。一项分析儿童烧伤后 60 天全身 IL-8 水平的研究(n = 468)提供了有趣的见解：IL-8 水平与烧伤的全身表面积百分比相关，可预测多器官衰竭和死亡率[110]。需要注意的是，全身性 IL-8 水平不仅通过读取绝对水平提供预后价值，而且还可以通过记录持续高 IL-8 水平的持续时间来用于诊断。

IL-8 与其他炎症因子有关，在骨重塑中发挥作用。患有骨质疏松症和骨质流失的绝经后妇女的 IL-8 显着增加[111]。阿托伐他汀以其对骨组织的多效性作用而闻名，它降低了遭受糖皮质激素诱导的骨质疏

松症的大鼠的 IL-8 水平和骨质流失[112]。COPD 患者的血浆 IL-8 水平升高，并且与中性粒细胞的 RANKL 表达相关。表达 RANKL 的中性粒细胞在患有慢性阻塞性肺病(chronic obstructive pulmonary disease, COPD)的男性患者中增加，且与骨矿物质密度和肺功能相关，这表明 IL-8 促进了 COPD 患者破骨细胞生成及骨流失[113]。

## 5. IL-10

白介素-10 (IL-10)细胞因子家族由九个成员组成，即 IL-10；IL-20 亚家族成员 IL-19、IL-20、IL-22、IL-24 和 IL-26；以及远缘相关的细胞因子 IL-28A、IL-28B 和 IL-29，它们常被归类为 III 型干扰素(Interferon, IFN)并分别命名为 IFN-λ2、IFN-λ3 和 IFN-λ1 [114]。IL-10 是该细胞因子家族的创始成员，最初被认为是从活化的 CD4 + T 辅助(Th2)细胞中纯化的活性物质，称为细胞因子合成抑制因子(CSIF) [114]。在其克隆之后，还发现 IL-10 可刺激肥大细胞、胸腺细胞和 B 细胞，并对骨髓细胞具有主要的免疫抑制作用[115] [116] [117] [118]。

IL-10 由几乎所有的白细胞亚群产生，包括 DC、巨噬细胞、T 细胞、NK 细胞和 B 细胞。IL-10 是一种通用的抑制性细胞因子。它抑制先天性和适应性免疫的炎症反应，并防止由加剧的适应性免疫反应引起的组织损伤。因此，IL-10 是炎症消退阶段的中心细胞因子[119]。IL-10 通过抑制炎症因子和抗原呈递细胞(antigen-presenting cells, APC)和其他功能引发其对骨髓细胞的主要抑制作用。IL-10 信号通路受损与炎症性疾病如炎症性肠病(IBD)相关，并且在感染期间通常伴有免疫病理学；相反，IL-10 的高产量或失调可能导致慢性感染[114]。阻断小鼠中的 IL-10 通路会导致 IBD 自发发展，但进化中的病原体可以利用 IL-10 的功能来抑制感染期间的正常宿主炎症反应，从而建立慢性感染状态。增加的 IL-10 表达与许多慢性细菌和病毒感染有关。此外，一些病毒可以产生自己的 IL-10 (vIL-10)，直接抑制宿主的免疫反应[115]。某些病原体甚至通过 DCs 和巨噬细胞诱导出 IL-10 形成了一种强大的免疫逃避机制。在淋巴细胞性脉络丛脑膜炎病毒(lymphocytic choroid plexus meningitis virus, LCMV)感染模型中，IL-10 本身或随后诱导的 T 调节细胞会损害病原体控制和清除。巨噬细胞衍生的 IL-10 可以抑制邻近细胞分化为经典激活的巨噬细胞，从而使巨噬细胞能够自我调节[120]。总之，Th1 细胞分泌 IL-10 代表了一个有效的自动调节反馈回路，可在 Th1 细胞驱动的抗感染反应期间防止过度炎症和潜在的组织破坏。然而，病原体利用这种机制来阻止它们的消除，从而导致慢性感染。

在骨生物学方面，IL-10 具有对破骨细胞生成的有效抑制作用和对成骨细胞分化的促进作用。在 IL-10 敲除小鼠中，可以观察到骨质疏松症的特征，包括 RANKL 和 OPG 水平升高、骨吸收增加、骨形成较少和骨小梁结构改变[121]。研究表明，IL-10 基因多态性可能影响其 mRNA 和蛋白质的产生，并与骨质疏松症的发展有关。IL-10 的丢失还加剧了早期 1 型糖尿病引起的骨丢失[122]。由此可见，IL-10 具有良好的骨保护作用，减少骨质疏松发展的可能性。

## 6. TNF-$\alpha$

TNF 是一种炎症因子，可在受伤后数分钟内在血液中检测到，在感染性疾病中具有重要的保护作用[123]。其中 TNF-$\alpha$ 是一种多效性炎症因子，以其促炎活性而闻名。TNF-$\alpha$ 的主要来源是巨噬细胞和 T 细胞，但许多其他细胞，如 B 细胞、中性粒细胞和内皮细胞也被描述为产生 TNF-$\alpha$。TNF-$\alpha$ 的靶标包括两种 I 型跨膜受体，TNF 受体 I (TNFR-I 或 CD120a)和 TNF 受体 II (TNFR-II 或 CD120b)。TFNR-I 在除红细胞外的每个细胞上都有表达，而 TNFR-II 仅在内皮细胞和免疫细胞上发现[9]。TNF-$\alpha$ 的失调与多种病理状况有关，例如感染、自身免疫性疾病、癌症、动脉粥样硬化、阿尔茨海默病和炎症性肠病。TNF-$\alpha$ 在调节多种发育和免疫过程中也发挥着不同的作用，包括炎症、分化、脂质代谢和细胞凋亡[124]。据报

道，人类免疫系统的几乎所有成分都与 TNF-α 有功能关系。

TNF-α 的功能性相当广泛，一个突出的特征是 TNFR-I 通过 NF-κB 和 AP-1 介导细胞存活和促炎反应[125]。此外，TNF-α 通过 Fas 和半胱天冬酶激活引起细胞死亡的信号通路。TNF-α 可以通过免疫炎症方面的作用影响骨质疏松的发生发展。TNF-α 在某些分化阶段抑制成骨细胞活性，并刺激破骨细胞增殖和分化[126]。与 IL-6 类似，TNF-α 可以通过内分泌方式调节骨代谢[127]。在早期阶段，TNF-α 通过下调 Runx2 的表达来抑制成骨细胞的分化，而 Runx2 对成骨细胞的分化至关重要。TNF-α 通过上调降解 Runx2 蛋白的 S-1 和 S-2 来阻止成骨细胞骨形成。此外，TNF-α 通过抑制胰岛素样生长因子-1 的作用来抑制成骨细胞分化[126]。有研究表示，Notch 和非经典 NF-κB 信号通路在转 TNF-α 的小鼠骨髓间充质干细胞中明显上调，提示 TNF-α 可能通过 Notch 和非规范 NF-κB 信号之间的相互作用来抑制骨髓间充质干细胞的成骨分化[128]。此外，TNF-α 通过激活 SAPK/JNK 和 NF-κB 来抑制骨形态发生蛋白信号转导[129]。但是，其他研究也有报道 TNF-α 具有增强成骨分化的功能，这是因为较低浓度的 TNF-α 可增加骨髓间充质干细胞中 Runx2、Osx、Ocn 和碱性磷酸酶的水平，而较高浓度的 TNF-α 则可降低它们的水平[130]。TNF-α 被认为是破骨细胞分化的重要刺激因子。TNF-α 治疗可以通过激活 NF-κB 信号，在没有 RANKL 的野生型(wild type, WT)小鼠中局部和系统地增加抗酒石酸酸性磷酸酶(tartrate-resistant acid phosphatase, TRAP)阳性破骨细胞的数量。已经证明，用 TNF-α 处理处于破骨细胞前体细胞阶段的骨髓来源的巨噬细胞，可以促进破骨细胞的生成[131]。TNF-α 被认为是促进成熟造血干细胞分化为破骨细胞的关键因子，可提高巨噬细胞和干细胞中 RANK 和 RANKL 的水平，刺激 RANKL 与其受体 RANK 结合，激活受 RANKL 调控的多条信号通路，如 MAPK、TRAF-2、c-jun、JNK、NF-κB 和 AP-1，从而介导破骨细胞的增殖和分化[132]。此外，TNF-α 诱导的破骨细胞生成在 TRAF6-/-OC 前体中上调，这是通过刺激诱导 TRAF3 的自噬降解来实现的[133]。因此，RANKL 还可以通过 TRAF6 非依赖的信号通路促进 TNF-α 诱导的破骨细胞生成[133]。在体外，TNF-α 通过激活 NF-κB 和激活的 T 细胞核因子途径，在没有成骨细胞/基质细胞的情况下直接刺激破骨前体细胞形成成熟的破骨细胞。TNF-α 通过促进 c-fms 的表达促进骨髓中破骨细胞前体细胞的增殖和分化，从而增加循环中破骨细胞前体的数量。TNF-α 诱导的 c-fms 表达必须通过 M-CSF 和独立的机制发挥作用，还促进 T 淋巴细胞产生 M-CSF 和成骨细胞产生 RANKL，从而间接刺激破骨细胞的形成[134]。不难看出，较高浓度的 TNF-α 可以通过抑制成骨细胞分化和促进破骨细胞增殖达到促进骨质疏松发展的效果。

## 7. 结论与展望

骨质疏松症被认为是一种沉默的疾病，前期几乎无明显症状，等到发现时常常已经发生严重的并发症，如骨折[2] [135]。鉴于其危险性，骨质疏松症的研究一直没有停止。在过去的几年中，对炎症状态下骨重塑的病理生理学有了很多深入的了解。很明显，涉及慢性炎症(例如炎症性肠病)的几种炎症因子不仅在炎症的主要发生部位(例如肠道)中至关重要，而且在骨骼中也具有至关重要的作用，可调节骨代谢的进程。一些炎症因子如 TNF-α、IL-1、IL-6、IL-8 可以调节骨重塑、激活破骨细胞并最终促进骨质疏松症的发展。然而也有一些炎症因子如 IL-10 和 IL-33 却在炎症中起到了不错的骨保护作用。尽管骨质疏松症的发展涉及多个方面，但到目前为止，炎症作为一个关键因素只得到了部分解决。对于临床医生来说，有个重要任务是确定与炎症性疾病相关的骨质疏松症的危险因素，然后在这一类人群中进行骨质疏松相关指标的筛查，作出相应的预防性措施，并对这种情况进行适当的早期治疗。

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