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TCA循环重编程：炎症性骨病中骨代谢紊乱的关键机制及治疗靶点

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摘　要

炎症性骨病是一种以持续的免疫激活和骨代谢失衡为特点的慢性炎症性疾病。越来越多的证据表明，免疫细胞和骨相关细胞的代谢状态是骨的吸收与形成改变的基础，决定着骨代谢趋势。代谢变化可以影响能量供应、细胞生物合成、信号传递和表观遗传调控，从而在一定程度上影响炎症性骨病的发生发展和结局。线粒体三羧酸循环(The tricarboxylic acid cycle)作为细胞代谢的引擎，一直被认为是一个经典的能量供应单元。最近对代谢重编程的研究极大地扩展了我们对TCA循环在信号转导、生物合成和细胞命运决定中的关键调控作用的理解。因此，针对TCA循环的关键酶及代谢物来治疗炎症性骨病是值得关注的。本综述旨在通过讨论TCA循环相关因素来阐明对其在炎症性骨病中的最新认识，从而强调TCA循环介导的代谢重编程所发挥的关键作用，并探索其作为治疗靶点的潜力。

关键词

三羧酸循环，骨代谢，线粒体，炎症，代谢重编程

TCA Cycle Reprogramming: A Key Mechanism and Therapeutic Target of Bone Metabolism Disorder in Inflammatory Bone Diseases

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Abstract

Inflammatory bone diseases are chronic inflammatory conditions characterized by sustained immune activation and imbalances in bone metabolism. A growing body of evidence indicates that the metabolic states of immune cells and bone-related cells underlie alterations in bone resorption and formation, shaping the overall trend of bone metabolism. Metabolic changes can influence energy supply, cellular biosynthesis, signal transduction, and epigenetic regulation, thereby playing a significant role in the pathogenesis, progression, and outcomes of inflammatory bone diseases. The mitochondrial tricarboxylic acid (TCA) cycle, often regarded as the engine of cellular metabolism, has long been recognized as a classic energy-producing unit. Recent studies on metabolic reprogramming have greatly expanded our understanding of the critical regulatory roles of the TCA cycle in signal transduction, biosynthesis, and cell fate determination. Therefore, targeting key enzymes and metabolites of the TCA cycle presents a promising therapeutic approach for inflammatory bone diseases. This review aims to elucidate the latest insights into the role of TCA cycle-related factors in inflammatory bone diseases, highlighting the pivotal function of TCA cycle-mediated metabolic reprogramming and exploring its potential as a therapeutic target.

Keywords

TCA Cycle, Bone Metabolism, Mitochondria, Inflammation, Metabolic Reprogramming

1. 引言

炎症性骨病属于骨骼系统的慢性炎症性疾病，这类疾病包括由外源性感染和自身免疫反应引发的骨平衡失调，常见类型包括骨质疏松症、骨关节炎和类风湿性关节炎等[1]。其共同病理学特征包括免疫系统激活以及骨相关细胞(如破骨细胞、成骨细胞和软骨细胞)的细胞命运改变。近年来，越来越多的证据表明，细胞代谢变化在炎症性骨病进展中所起的核心作用[2]。因此，作为免疫反应与细胞代谢的关键交汇点，线粒体三羧酸循环(The tricarboxylic acid cycle)在炎症性骨病中发挥的功能值得探讨。

TCA 循环(亦称柠檬酸循环或克雷布斯循环)作为需氧生物能量代谢的核心枢纽[3]，其功能涵盖细胞的多种生理及病理过程。该循环是碳水化合物、脂质及氨基酸完全氧化的主要途径，通过向线粒体电子传递链提供还原当量，满足细胞能量需求。此外，TCA 循环是驱动细胞内活性氧(ROS)产生的主要引擎，因此同细胞氧化还原状态息息相关[4]。值得注意的是，该循环过程中产生的中间代谢物可作为炎症及多种生物合成与代谢途径的信号分子，这使其与炎症性骨病建立深刻关联[5]。随着线粒体功能调控炎症性

骨病研究的深入，TCA 循环重编程已被证实对介质合成、炎症效应放大及氧化应激具有关键作用[6] [7]。

本文系统综述并阐明了 TCA 循环在炎症性骨病中日益凸显的作用，强调其作为代谢重编程枢纽在调节骨平衡和炎症反应中的功能。同时探讨了相关影响因素在炎症性骨病治疗中的潜在作用，旨在为治疗策略的设计提供依据。

2. 炎症性骨病相关细胞的三羧酸循环改变

在炎症性骨病病程中，免疫细胞、破骨细胞、成骨细胞、软骨细胞等细胞响应疾病的发生发展，其能量代谢状态发生显著改变。在对抗疾病的同时，这些变化也可能促进病程进展，导致更为广泛的组织损伤[8]。

2.1. 免疫细胞

炎症性骨病下多种免疫细胞被激活，其中巨噬细胞起到关键作用。在健康机体中，巨噬细胞负责清除衰老细胞、死亡细胞、代谢废物及病原体，同时参与抗原呈递和免疫调节。但在受到炎症性骨病的影响时，巨噬细胞被高度激活以应对炎症。其极化模式受代谢重编程影响，向促炎型(M1)转变，这种转变可能与细胞 TCA 循环改变密切相关[9]。表现为多个循环步骤的中断，以致特定代谢物水平的异常变化，这些代谢物可以作为信号分子或合成前体反过来影响炎症性骨病病程。首先，在骨髓巨噬细胞 TCA 循环的初始阶段，慢性炎症其代谢模式向糖酵解转变，这使大量丙酮酸被转化为乳酸，而非通过氧化脱羧作用形成乙酰辅酶 A 进入 TCA 循环，这降低了其 TCA 循环的整体通量和效率[10]。此外，骨髓巨噬细胞 α-酮戊二酸(α-KG)水平降低，抑制了其 M2 型极化[11]。另外，琥珀酸积累被认为是炎症性骨病中骨髓巨噬细胞最显著的特征之一。这是由于其琥珀酸脱氢酶(SDH)活性被抑制，琥珀酸消耗减少所致[12]。

T 细胞在炎症性骨病中的作用同样值得关注。此时，活化的 T 细胞(尤其是促炎性 T 细胞)，其琥珀酸与 α-KG 的比值发生改变，这种变化影响了双加氧酶活性，进而上调 Prdm1/Blimp-1 等促炎转录因子，促进 Th1 和 Th17 分化[13]。这种驱动效应与 TCA 循环重编程之间的关系远不止于此。在 γ-氨基丁酸(GABA)的调控下，循环中的碳会重新分配促进促炎性 Th17 细胞的分化，同时抑制抗炎性诱导调节性 T 细胞(iTregs)的分化[14]。此外，T 细胞中 TCA 循环的重编程可导致乌头酸外流，并促进 $CD4^+$ T 细胞的分化[15]。

中性粒细胞线粒体代谢随着细胞成熟而急剧减少，能量生产不再依赖于氧化磷酸化过程。但在炎症性骨病下，丙酮酸重新流入 TCA 循环，以响应病程[16]。

2.2. 破骨细胞

除了炎性损害外，最直接的损害是破骨细胞所介导的骨丢失。破骨细胞源自髓系造血祖细胞，在健康状态下，通过与成骨细胞的协调作用维持骨稳态。然而在炎症性骨病下，促炎细胞因子大量释放会导致破骨细胞过度活化并且数量显著增加[17]。此时破骨细胞的 TCA 循环也发生深刻改变。破骨细胞因其大量增殖和活化而面临更高的能量需求。鉴于炎症会损害细胞的线粒体功能，因而需要通过主动的代谢重编程来支持细胞需求。与巨噬细胞类似，破骨细胞也发生了 OXPHOS 向糖酵解的转变[18]。同时，破骨细胞内还原型辅酶 I (NADH)与辅酶 I (NAD^+)之比也发生变化，表现为 NAD^+快速耗竭和 NADH 水平相对升高[19] [20]。此外，炎症性骨病会显著增强破骨细胞关键调控因子核因子 κB 受体活化因子配体(RANKL)的活性，该因子通过上调琥珀酸脱羧酶(ACOD1)活性同时抑制柠檬酸合酶(citrate synthase)活性，最终导致破骨细胞中琥珀酸水平升高而异柠檬酸水平降低[21]。

2.3. 成骨细胞

成骨细胞起源于骨髓间充质干细胞(BMSCs)，主要负责构建新骨。在炎症性骨病下，成骨细胞的分化

和活性均受到抑制。并且，干细胞会因表观遗传而导致其代谢异常“烙印”在后续分化出的后代细胞中。

在炎症状态下，BMSCs 和成骨细胞的线粒体功能受损，表现为膜电位紊乱和电子传递链活性抑制[22] [23]。与此同时，炎症细胞因子会诱导干细胞发生糖酵解重编程，这导致丙酮酸被转化为乳酸，而非通过氧化脱羧作用生成乙酰辅酶 A 进入 TCA 循环[24]。这些变化导致成骨细胞中乙酰辅酶 A 水平降低。由于乙酰辅酶 A 是三羧酸循环的“燃料”，其缺乏会显著降低整个 TCA 循环的通量和效率。

作为 BMSCs 的主要分化方向之一，骨细胞构成了整个骨骼系统的基石，长期以来被视为柠檬酸盐储存库。在炎症性骨病诱导的骨质流失过程中，骨细胞和成骨细胞中的柠檬酸盐水平均呈现下降趋势[25]。此外，在氧化应激损伤下，BMSCs 中基质金属蛋白酶-9 (MMP-9)的表达增加，从而促进柠檬酸合酶的降解。这最终导致骨髓间充质干细胞(BMSCs)中柠檬酸合成减少及柠檬酸水平进一步下降[26]。此外，由于慢性炎症的持续刺激，成骨细胞 TCA 循环在琥珀酸脱氢酶处出现中断点，这导致细胞内琥珀酸积累。这也是炎症性骨病的典型特征，并在后续病程进展中起重要作用[12]。

2.4. 软骨细胞

软骨细胞也起源于间充质干细胞，主要负责合成和维持软骨的细胞外基质。它们是软骨组织中的主要细胞。因此，在关节病变中，软骨细胞会因受到疾病直接损伤，导致细胞功能障碍，反过来会加重炎症性骨病损伤。在此过程中，其 TCA 循环会发生显著变化。

在上述病程中，丙酮酸脱氢酶激酶 1 (PDK1)表达的显著增加会导致丙酮酸脱氢酶(PDH)失活，从而限制丙酮酸进入 TCA 循环，降低循环的通量和效率[27]。此外，软骨细胞中 α-KG 水平的降低是累及关节的炎症性骨病最显著的特征之一，这进一步削弱了软骨细胞对抗炎症和氧化应激的能力，抑制细胞增殖甚至诱导凋亡[28]。此外，炎症性骨病可导致软骨细胞铁过载。这样会使得 TCA 循环中对铁硫簇敏感的酶乌头酸酶活性降低甚至失活，使得循环在此处中断，进而引起异柠檬酸水平下降[29] [30]。

3. TCA 循环代谢紊乱在炎症性骨病中的级联效应

炎症性骨病下，相关细胞 TCA 循环受到不同程度的干扰，甚至发生紊乱和重构。可表现为 TCA 循环中间代谢物水平的改变。这种改变干扰能量生产，还可作为信号分子影响其他基因的表达和细胞行为。这种现象折射了细胞对外部环境变化的适应性反应，基于代谢网络的解构与重编程，在疾病早期阶段发挥一定的保护作用。然而，当外部刺激持续存在时，这种防御机制效用减退，甚至因长期功能紊乱导致细胞受损或死亡。

3.1. TCA 循环代谢物水平失调加剧炎症效应

作为一种慢性炎症性非自限性疾病，炎症性骨病的炎性损害随病程持续存在，TCA 循环代谢物水平的紊乱在这一过程中起着关键作用。

由于瓦博格效应，巨噬细胞的乙酰辅酶 A 供应中断，其胞内水平急剧下降。这不仅降低了 TCA 循环的整体通量，还抑制 SIRT2 去乙酰化能力，在第 310 位赖氨酸(K310)抑制这种去乙酰化会促进巨噬细胞的促炎极化，增加 $CD8^+$T 细胞的数量和活性，推动炎症进程[31] [32]。此外，由于柠檬酸具有一定的抗炎特性，其水平在炎症性骨病中的下降会削弱骨骼系统对抗炎症的能力，进一步促进了炎症效应的扩大。炎症性骨病下细胞异柠檬酸水平升高，竞争性抑制脯氨酰羟化酶(PHD)，从而稳定缺氧诱导因子 1α (HIF-1α)，这会激活促炎基因，加剧炎症反应[33]。在琥珀酸下游，延胡索酸同样会在炎症性骨病中积累，这促使线粒体 DNA 泄漏，激活 cGAS-sting 通路，同样加剧了炎症反应[34]。另外，由于苹果酸是天冬氨酸等重要分子的前体，而其在炎症性骨病中会显著减少。这种由 TCA 循环重构导致的苹果酸水平降低，最

终会引发细胞氧化应激和促炎状态[35]。

3.2. TCA 循环代谢物水平紊乱促进骨破坏

作为炎症性骨病最典型的临床表现，骨破坏与 TCA 循环代谢物水平紊乱密切相关。与其他细胞不同，破骨细胞可通过提升细胞内乙酰辅酶 A 水平来抵消乙酰辅酶 A 可用性的下降，从而增强破骨细胞蛋白酶组织蛋白酶 K (CTSK)的活性，诱发异常骨化[36]。不仅如此，乙酰辅酶 A 还可以在 ATP-柠檬酸裂解酶(ACLY)的调节下介导组蛋白 H3 上的 H3K9、H3K27、H3K14 和 H3K18 四个赖氨酸位点的乙酰化水平，增强破骨细胞分化和功能，促进骨破坏[37]。由于代谢物 NAD^+的水平会影响去乙酰化酶 Sirtuin 家族能力，故而炎症性骨病下细胞 NAD^+池的耗竭会促进活性氧(ROS)的积累，进而激活 RANKL 等信号通路，驱动破骨细胞分化和骨吸收[38] [39]。此外，TCA 循环关键代谢物 α-KG 作为抗氧化剂，其功能会因胞内水平降低而减弱，同样促进了 ROS 快速积累和破骨细胞分化[40]。α-KG 还可以通过影响细胞一氧化氮(NO)水平来调控破骨细胞分化，当其在炎症性骨病水平降低时，会降低 NO 水平而解除对破骨分化的抑制，达到促进骨破坏的效果[41]。在骨质疏松条件下，α-KG 的减少似乎会增强破骨细胞前体对 RANKL 的敏感性，从而提高破骨细胞分化的效率[42]。琥珀酸在炎症性骨病中会显著升高，这不仅催动巨噬细胞促炎型极化，还通过琥珀酸受体 1 (SUCNR1)作用于破骨细胞前体，促进破骨细胞分化和骨吸收[43] [44]。

3.3. TCA 循环代谢物水平紊乱抑制骨形成

在骨吸收之外，作为骨平衡的另一方向，骨生成被抑制也是造成炎症性骨病病程进展的重要原因之一。这种源自于 BMSCs，由成骨细胞担任的细胞活动与 TCA 循环代谢物水平之间同样存在着密切关联。

首先，在炎症状态下，一方面，BMSCs 中乙酰辅酶 A 水平降低会导致线粒体功能障碍，无法满足干细胞的能量需求。另一方面，乙酰辅酶 A 水平降低会抑制 N4-乙酰化(acC)，从而损害成骨作用[45]。此外，BMSCs 中的 NAD^+水平下降了 SIRT3 锌指结构域 C191、C194、C215、C218 的 S-硫水化修饰，从而损害了其对 BMSCs 的保护作用，使其对氧化应激损伤抵抗减弱[46]。这在炎症性骨病下是极为不利的，不仅使得 BMSC 核 DNA 更易受到氧化应激损伤，造成周期阻滞；还使得线粒体出现功能异常和能量障碍，最终导致骨生成障碍。不仅如此，NAD^+水平下降还会破坏 SIRT1 的抗衰老作用，这导致 BMSC 衰老加速，成骨分化受阻[47] [48]。再者，炎症性骨病患者的 BMSCs 胞内 α-KG 水平也会降低。由于 α-KG 作为组蛋白去甲基化酶和 DNA 去甲基化酶的必要辅因子，其水平下降会损害骨形态发生蛋白 2 (BMP2)的产生，从而抑制骨形成[41] [49]。

4. 基于 TCA 循环的炎症性骨病治疗前景

4.1. 靶向 TCA 循环关键酶的治疗策略

整个 TCA 循环由多种催化反应过程的酶驱动。其中，柠檬酸合酶、异柠檬酸脱氢酶和 α-酮戊二酸脱氢酶复合体(KGDHc)这三种酶被视为关键酶，它们被称为限速酶，控制着 TCA 循环的开关，靶向 TCA 循环关键酶进行治疗是值得考量的。

首先对于柠檬酸合酶来说，使用线粒体醌提高其 mRNA 和蛋白水平可显著增强细胞抗氧化和抗炎能力[50]，继而有效提升 BMSCs 在炎症性骨病中的修复能力。此外，D-葡萄糖胺作为公认的膳食补充剂和关节炎症缓解辅助剂，增加外源性摄入可显著增强柠檬酸合酶的生物合成功能，这种对挽救炎症性骨病中受损的 TCA 循环通量有极大帮助[51]。另外，由于异柠檬酸脱氢酶(IDH)活性的下调会抑制 α-KG 的生成并导致琥珀酸积累，因此抑制核受体 Nur77 有望纠正这种代谢失衡[52]。不止如此，调节异柠檬酸脱氢酶活性还能改善细胞甲基化状态和抗氧化能力，显示出一定的缓解炎症性骨病损伤的潜力。最后，由于

α-酮戊二酸脱氢酶复合体(KGDHc)易受炎症性骨病的氧化应激损伤，补充其关键辅因子硫辛酸可能有助于恢复其活性。这种形式的疗法在帕金森病中得到验证，为炎症性骨病的治疗提供了参考依据[53]。

4.2. 靶向 TCA 循环代谢物的治疗策略

4.2.1. α-KG 的应用

α-KG 的抗炎和抗氧化能力为人熟知，并在多种炎症性疾病的治疗中有所报道。在骨关节炎中，α-KG 不仅表现出优异的抗炎作用，还能促进成纤维细胞和软骨细胞的生长，并加速软骨基质的合成[54]。此外，α-KG 还能激活 PERK-ATF4 信号通路，减轻炎症性骨病下软骨细胞的内质网应激，抑制软骨基质的降解[55]。α-KG 还能通过胶原蛋白间接增强成骨能力，并通过表观遗传机制调控骨相关细胞的成骨功能，促进炎症性骨病的骨质修复[56]。针对炎症性骨病所导致的 BMSCs 衰老，补充 α-KG 通过上调 BMP 信号通路挽救衰老 BMSCs 成骨潜能[57]。

α-KG 不仅调控细胞成骨，还通过表观遗传调控破骨行为从而平衡骨稳态。补充 α-KG 促进破骨细胞前体转化为 M2 型巨噬细胞。这不仅抑制促炎基因表达，还能限制异常破骨分化和骨吸收，有利于挽救炎症性骨病骨稳态失衡[11]。

4.2.2. 其他 TCA 循环代谢物的应用

作为 TCA 循环的燃料，乙酰辅酶 A 扮演关键角色。因此可以通过补充柠檬酸钠的方式提高乙酰辅酶 A 水平，从而通过 ATP-柠檬酸裂解酶途径影响 N-乙酰基转移酶 10 表达，恢复 N4-乙酰化水平，挽救炎症下细胞成骨能力[45]。此外，基于柠檬酸的特性，外源性柠檬酸补充能有效促进骨细胞外基质矿化，还能通过促进胶原矿化恢复骨质[58]。另外，外源性补充 NAD^+可部分恢复炎症性骨病下耗竭的 NAD^+池，这有助于重新激活 Sirtuin 酶家族，增强细胞对氧化应激的抵抗力，在一定程度上逆转细胞衰老[59]。此外，还能利用靶向抑制剂抑制 CD38 酶，减少 NAD^+消耗，增强对炎性损伤的抵抗力[10]。

5. 讨论

总的来说，炎症性骨病的治疗策略涉及多个维度。基于 TCA 循环与炎症反应及骨稳态密切相关，靶向 TCA 循环已成为治疗炎症性骨病的重要方向。然而，TCA 循环调控的靶点众多，且代谢重编程中的交互作用复杂，目前该领域研究仍存在较大局限。近期研究进一步明确了炎症性骨病与线粒体 TCA 循环的相关作用，但如何逆转这些负面影响以实现治疗效果仍不明确。目前的干预措施主要集中于缓解炎症与氧化应激损伤，以及对因 TCA 循环紊乱所导致的代谢物水平改变的挽救。虽然在细胞和动物模型层面已取得令人鼓舞的进展，但人体应用仍任重道远。综上所述，代谢重编程的概念为调控 TCA 循环功能障碍以减轻炎症性骨病引发的损伤提供了诸多新颖切入点，这无疑为破解炎症环境下骨修复难题提供了新视角与希望，值得研究者深入探索。

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