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Cbf-β在骨关节炎发病中的研究概况

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摘　要

骨关节炎(OA)是我国最常见的骨关节炎，是老年人活动能力受损的主要原因之一，占慢性中度至重度疼痛的三分之一以上。OA是一种累及关节及其周围组织的慢性疾病，主要导致关节软骨进行性损伤，进而导致软骨下骨和周围滑膜结构损伤。尽管受OA影响的人数逐年增多，但目前仍无法延缓OA的进展，主要治疗方案集中在缓解症状，关节置换术是最终结局。深入探讨分子靶点的作用在研究药物开发的过程中至关重要。特别是，Cbf-β作为一种与Runx2结合形成异质二聚体的共转录因子，不仅增强了Runx2与DNA的结合力，还通过阻止Runx2的泛素化来维持其稳定性，因此在软骨内骨化过程中的作用比膜内骨化更为显著。本文综述了与Cbf-β和骨关节炎发展相关的最新研究成果，并探讨了Cbf-β作为治疗目标的可能性。这些发现强调了深入理解分子机制对于开发新的治疗策略的重要性，并指出了Cbf-β在骨科疾病治疗领域内的潜在价值。

关键词

骨关节炎，疼痛，Runx2，Cbf-β

Overview of the Research of Cbf-β in the Onset of Osteoarthritis

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Abstract

Osteoarthritis (OA) is the most common osteoarthritis in China. It is one of the main causes of impaired mobility in the elderly, accounting for more than one-third of chronic moderate to severe

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pain. OA is a chronic disease involving joints and surrounding tissues, which mainly leads to progressive damage to joint cartilage, which in turn leads to structural damage to the lower cartilage and peripheral synovial membrane. Although the number of people affected by OA has increased year by year, it is still impossible to delay the progress of OA. The main treatment plan focuses on relieving symptoms, and joint replacement is the final result. It is very important to deeply explore the role of molecular targets in the process of drug development. In particular, Cbf-*β*, as a co-recording factor bound to Runx2 to form a heterogeneous dimer, not only enhances the binding force of Runx2 to DNA, but also maintains its stability by preventing the ubiquitinization of Runx2. Therefore, it plays a more significant role in the process of cartilage ossification than intramembrane ossification. This article reviews the latest research results related to the development of Cbf-*β* and osteoarthritis, and discusses the possibility of Cbf-*β* as a treatment target. These findings emphasize the importance of an in-depth understanding of molecular mechanisms for the development of new treatment strategies, and point out the potential value of Cbf-*β* in the field of orthopedic disease treatment.

Keywords

Osteoarthritis, Pain, Runx-2, Cbf-*β*

1. 背景

骨关节炎(Osteoarthritis, OA)已经成为全球最普遍的关节疾病，其患病率已达到流行病的程度[1]。到2040年，全球OA患病率预计将增加49%，并将主导40岁及以上人群的身体残疾和健康问题[2]。骨性关节炎被认为是一种涉及细胞和分子异常的全关节疾病，如关节软骨退化、滑膜增生、骨赘形成等[3]。

尽管目前还没有相关疗法或干预措施来减缓疾病进展，但近年来OA研究取得了重大进展。相关研究表明，多种生长因子，包括转化生长因子-*β* (TGF-*β*)、Wnt3a 和印度刺猬(Ihh)参与骨性关节炎的发展[4]-[10]。其他信号因子，如Smad3、*β*-catenin和缺氧诱导因子-2*α* (HIF-2*α*)，也可能在OA疾病进展中起关键作用[4]-[10]。在这里，本文总结了Cbf-*β*与Runx2的关系及Cbf-*β*在正常和病变关节组织中的作用。

2. Cbf-*β* 对 Runx2 的调控

研究表明选择性敲除Cbf-*β*基因的小鼠，会影响胎肝造血功能而导致小鼠死亡，同时也缺失Runx蛋白，表明Cbf-*β*对Runx2表达具有调控作用，通过治疗因Cbf-*β*缺失而导致造血缺陷的小鼠，可以延长其生存，说明Cbf-*β*对骨骼发育、Runx2转录激活及其与DNA的结合至关重[11]。有研究发现，在特定转基因小鼠模型中，Cbf-*β*的条件性敲除揭示了其对软骨细胞增殖、成熟及成骨细胞分化的必需性[12]。此外，Runx蛋白的稳定与Cbf-*β*通过抑制泛素化介导的降解密切相关。相关研究表明，Cbf-*β*在不同Runx家族蛋白中被依赖水平也存在差异[13]，其依赖程度为Runx1 > Runx3 > Runx2，且颅骨软骨组织中的依赖水平低于四肢。相关研究表明，Cbf-*β*在支持膜内骨化作用方面不如在软骨内骨化中的作用大，前者需要更多Runx2的参与[14]。Cbf-*β*分为Cbf-*β*1和Cbf-*β*2两个功能异构体，研究表明，敲除小鼠Cbf-*β*1，其Cbf-*β*2上调，而敲除Cbf-*β*2，Cbf-*β*1不存在，显示出Cbf-*β*1在软骨和成骨细胞分化及Runx2 DNA结合中的高效作用，且Cbf-*β*1和Cbf-*β*2之间存在相互调节机制，共同维持Runx2在适宜水平，对骨骼发

育至关重要[15]。

3. Cbf-β 在不同的关节组织中起作用

软骨退化是骨关节炎进展的标志，表明该疾病的不可逆性。然而，骨关节炎影响整个关节，尤其是骨关节炎的患者，他们的关节表现出多种病理变化。这些变化包括软骨下骨的增厚和骨赘的形成，这些骨赘可能限制关节的活动范围并引起疼痛；此外，滑膜的炎症也是常见的病理现象，有研究证实疼痛与滑膜炎之间的关系，并指出疼痛评分变化随着滑膜炎的变化而变化，较高级别的滑膜炎使膝关节疼痛性OA的风险增加9倍[16] [17]，进而影响关节的正常功能；关节周围的韧带和关节囊也可能发生变性和肥大，这些变化不仅影响关节的稳定性，还可能加剧疼痛和功能受限[18] [19]。

关节周围肌肉、神经、脂肪垫和滑囊的变化也可促进OA的发展[18] [19]。所有这些病理改变都会影响关节和骨关节炎，导致整个关节衰竭[18] [19]。

3.1. 关节软骨细胞

研究指出，关节软骨细胞在骨关节炎(OA)的形成与进展中扮演关键角色。炎症因子和软骨分解酶在软骨细胞上发挥作用，它们之间的相互作用促进了特定类型的巨噬细胞在关节组织中渗透，这与炎症和骨关节炎的发展密切相关。这些巨噬细胞在关节中的活性增强不仅加剧了炎症反应，还影响了软骨的结构和功能，进一步导致关节病变和疼痛的加剧[20]。这种病理过程显示出炎症因子和软骨分解酶对关节健康的关键影响，强调了在治疗策略中需要针对这些因素的重要性。

研究发现，在骨关节炎(OA)的背景下，Cbf-β 的上调与肥大细胞分化及其相关的代谢性改变密切相关。特别是，Cbf-β 的增加与Col10a1、Ihh、Mmp13、Alp等增殖标志物的提升有关联[21] [22]。在OA的发展中，Cbf-β 的表达上升是由多种信号途径的综合作用导致的，包括 β-catenin、Wnt、Ihh、IKK-α、TGF-β 和 Hif-2α 等关键通路[23]-[28]。

研究进一步揭示，在OA进展的过程中，X型胶原、碱性磷酸酶、Cbf-β 和MMP13在关节软骨细胞中表达增加，而蛋白聚糖的含量降低，导致关节软骨内的钙化软骨带扩大[29] [30]。有相关研究称，研究显示，与未患有骨关节炎(OA)的个体相比，OA患者的关节软骨中DNA甲基化模式及Cbf-β 的表达有明显不同[31]。这一发现揭示了Cbf-β 作为关键转录因子在OA患者关节软骨细胞的分化过程中扮演着的重要角色。Cbf-β 的变化可能影响软骨细胞的行为和功能，从而在骨关节炎的发展中起着核心作用。

3.2. 滑膜细胞

在炎症和疼痛的情况下，有学者研究了骨关节炎发生或进展中的滑膜病理变化[29] [30]。趋化因子和细胞因子可能会导致滑膜炎症的增加，其可能代表OA发展的标志[32] [33]。在滑膜中发现的与软骨细胞的代谢分解作用有关的细胞因子包括IL-1、IL-6、IL-8、CCL-5和TNF-α *[34]*。即便在缺少关节炎和巨噬细胞渗透的情况下，骨关节炎(OA)患者的滑液中，这些炎症因子的水平也表现为升高[34]。滑膜炎，无论是否伴有显著的关节炎症表现，已经被公认为在骨关节炎(OA)的发展过程中扮演着关键的促进角色。这一现象强调了对滑膜炎机制的深入研究的重要性。深入探索滑膜炎如何影响OA的进程不仅有助于理解疾病的复杂性，还可能揭示新的治疗靶点，从而为OA患者提供更有效的治疗选项。

研究显示，滑膜液中的成纤维细胞生长因子2 (FGF-2)与骨关节炎(OA)中软骨退化的程度存在显著相关性[34]。FGF-2在维持软骨结构的完整性方面起到了关键作用，主要是通过促进软骨细胞的分化来实现这一点[35] [36]。在OA患者的软骨组织中，Cbf-β 的表达受FGF-2通过MEK/ERK信号途径来调节，进而影响Mmp13的活性。因此，OA患者关节滑液中的FGF-2积聚，促进Cbf-β 的活化，并增加Mmp13

的表达[37]。

3.3. 软骨下骨细胞

相关实验证实 Cbf-β 对骨骼、软骨和髁突发育至关重要[38] [39] [40]。由于 Cbf-β 在骨关节炎发病的软骨细胞肥大中起核心作用，有研究发现 Cbf-β 缺失抑制了软骨细胞向祖细胞的转分化，其原因可能是 Cbf-β 缺失断了软骨细胞转位到软骨下骨区[41]。相比之下，组织学分析揭示，与对照组相比，小鼠的髁软骨和软骨下骨中出现了大量的软骨细胞生长，这说明 Cbf-β 在软骨下骨的改造过程中发挥关键作用[41]。研究表明，Cbf-β 在增生性和肥厚性软骨细胞中的表达水平较高，这暗示了 Cbf-β 在调控软骨下骨重塑过程中可能发挥重要作用。结合研究表明 Cbf-β 缺失会导致肥大软骨细胞的丢失[42]，在出生后阶段，Cbf-β 在协调增殖和肥大进展中至关重要。

3.4. 半月板

有研究表明，在 KOA 早期，半月板病变通常早于其他部位病变[43] [44] [45]。但行半月板切除术会不可避免地会导致骨关节炎的发展[43] [44] [45]，其原因与半月板和骨关节炎的相互依赖性密切相关。尽管外侧半月板可以通过手术修复恢复其正常功能[46]，但内侧半月板由于缺乏血管，无法自我修复或完全恢复功能[47] [48]。然而，最近的研究表明，内侧半月板对生长因子和纤维蛋白凝块有反应[49]。相从骨关节炎(OA)患者获取的内侧缺血部位的半月板样本中，研究人员培养出了一种迁移性多谱系的多能细胞[47] [48]，称为人类半月板祖细胞(MPCs)。这类细胞仅在受损组织中被发现，而在健康的对照样本中未观察到。研究表明，这些 MPCs 受 Cbf-β 的调控，这与早期研究结果相符。在研究中发现，受损半月板样本中 Cbf-β 的表达显著增高，而在健康的半月板样本中，Cbf-β 以及 Runx2 的表达非常低，Runx2 的 mRNA 水平也相应减少。将人半月板内组织的 MPCs 三维外植体培养物分化为软骨细胞谱系时，损伤的半月板细胞未检测出 Cbf-β 水平，而 Sox9 水平升高。先前研究表明，Sox9 和 Smad2 表达水平的上调与通过 MPCs 敲低 Cbf-β 有关，这表明 Cbf-β 的调控对于 OA 的发展至关重要，是半月板 OA 进展的关键调节因素之一，也是治疗受损半月板的潜在药物靶点。

3.5. Cbf-β 在关节组织中的表达上调

目前骨关节炎的发生和进展仍然知之甚少，特别是在分子水平上。最近的证据表明，表观遗传和 microRNA (miRNA)的改变可能在 OA 疾病病理中起作用[50]。已经报道了几种 miRNA 和 DNA 甲基化模式调节 OA 软骨中 Cbf-β 的表达[51]。这些发现表明表观遗传修饰或 miRNA 调控可能是 OA 的重要介质。

4. 相关因子与 OA 的关系

关节软骨细胞肥大是一种促进骨关节炎(OA)发生和进展的现象，其通过 TGF-β/Smad 信号通路进行调控[52]。在这个过程中，TGF-β 与 TGF-β 受体 II (Tgfbr2)结合，形成异聚体 Smad2,3,4 复合物磷酸化，并进入细胞核与其他 DNA 结合蛋白相互作用，从而调节 TGF-β/Smad 信号传导并诱导软骨细胞中的 OA 病变。

刺猬(Hh)信号通路是调控胚胎发育、婴儿期骨骼发育和软骨细胞分化的主要机制[53] [54]。在软骨细胞中，印度刺猬(Ihh)是主要的 Hh 信号配体，它是由肥厚前软骨细胞产生和分泌的蛋白质。Ihh 的主要作用是在软骨中通过调节靶标基因，促进软骨细胞肥大和骨内形成[55]。相关研究表明，利用软骨特异性诱导功能丧失(LOF) Ihh 转基因小鼠。小鼠在 3 月龄时接受 DMM 手术以诱导创伤后 OA。DMM 手术后小鼠的组织学分析表明，Ihh 失活可减轻 OA 软骨损伤[56]。这些发现表明，Ihh 的缺失下调了 Runx2 的表达，并提示 OA 早期患者的软骨保护作用[7]。

β-catenin 是经典 Wnt 信号通路中的中心分子，它控制骨骼和关节发育中的多个发育过程对 OA 的进展至关重要[57]。研究表明，Wnt/β-catenin 信号转导失调代表了 OA 的一种可能机制。经典的 Wnt 抑制剂可以通过阻断 Wnt3a 受体来调节特征性软骨细胞基因(Sox9、Col2 和 ACAN)的表达[58]。Wnt3a 可以通过 LRP6 磷酸化和稳定 β-连环蛋白来调节软骨基质制造基因(Sox9、Col2 和 ACAN) [59]。相关研究证实，Wnt3a 敲低可增加 Col2 表达并降低 β-连环蛋白的表达[60]，提示 Wnt3a 被证明是软骨稳态的重要因素，在 OA 的发展中发挥着重要作用。

5. 总结

综上所述，Cbf-β 已被作为骨关节炎(OA)的关键指标之一，在 OA 的小鼠模型和人类病例中表现出较高的表达水平。众多研究指出，Cbf-β 在 OA 相关各种关节组织中，包括半月板、滑膜和骨下软骨细胞中发挥作用。因而，Cbf-β 不仅是 OA 发展的潜在新靶点，也是缓解 OA 相关疼痛和炎症的潜在目标。

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