读书报告

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Full paper

Celecoxib inhibits osteoblast maturation by suppressing the expression of Wnt target genes

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Celecoxib inhibits osteoblast maturation by suppressing the expression of Wnt target genes

Abstract.

- Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to impair bone healing. We previously reported that in colon cancer cells, celecoxib, a COX-2-selective NSAID, inhibited the canonical Wnt/b-catenin signaling pathway.
- Subsequently, we analyzed the effect of celecoxib on two osteoblast differentiation markers; runt-related transcription factor 2 (RUNX2) and alkaline phosphatase (ALP), both of which are the products of the canonical Wnt pathway target genes. Celecoxib inhibited the expression of both RUNX2 and ALP by suppressing their promoter activity. Consistent with these observations, celecoxib also strongly inhibited osteoblast-mediated mineralization.
- These results suggest that celecoxib inhibits osteoblast maturation by suppressing Wnt target genes, and this could be the mechanism that NSAIDs inhibit bone formation and fracture healing.

Introduction

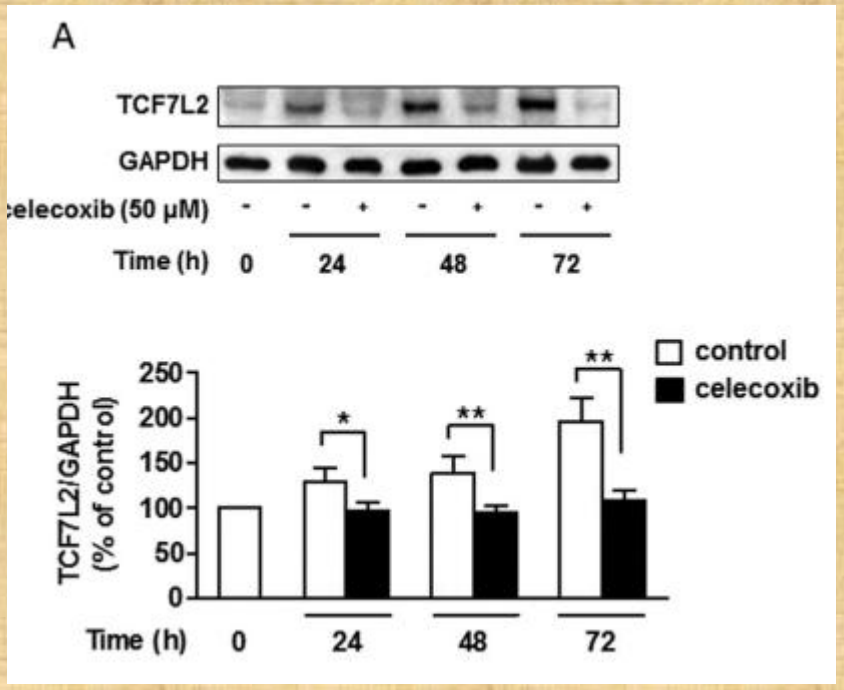
- We and others showed that celecoxib inhibits cancer cell growth by inhibiting the Wnt/b-catenin signaling (canonical Wnt) pathway .

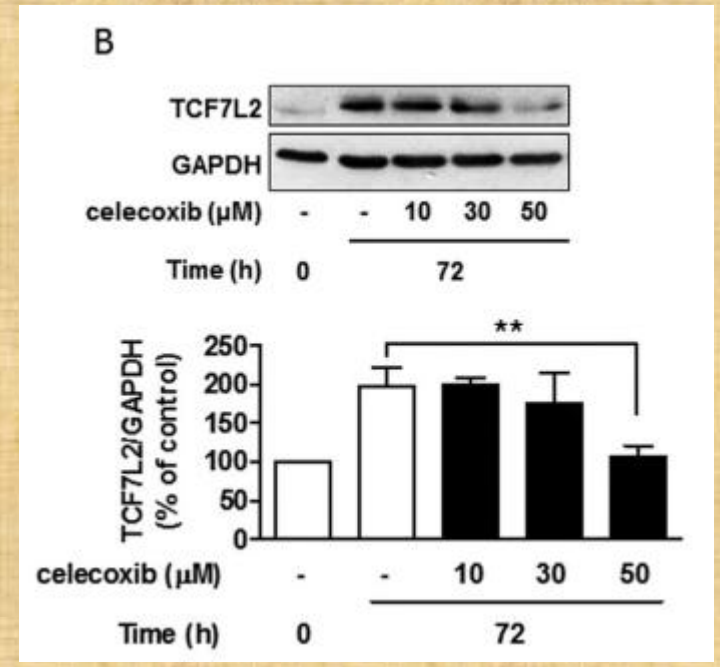
- Among them, the canonical Wnt pathway is a major osteogenic signaling cascade in osteoblast to induce differentiation and maturation, which up-regulates (RUNX2) runt-related transcription factor 2, an essential transcription factor for osteoblast differentiation .

- Here, we show that celecoxib prevents osteoblast maturation by reduction of TCF7L2 and its downstream gene products, RUNX2 and alkaline phosphatase (ALP)

RESULTS

1、Celecoxib inhibited the canonical Wnt pathway in MC3T3-E1





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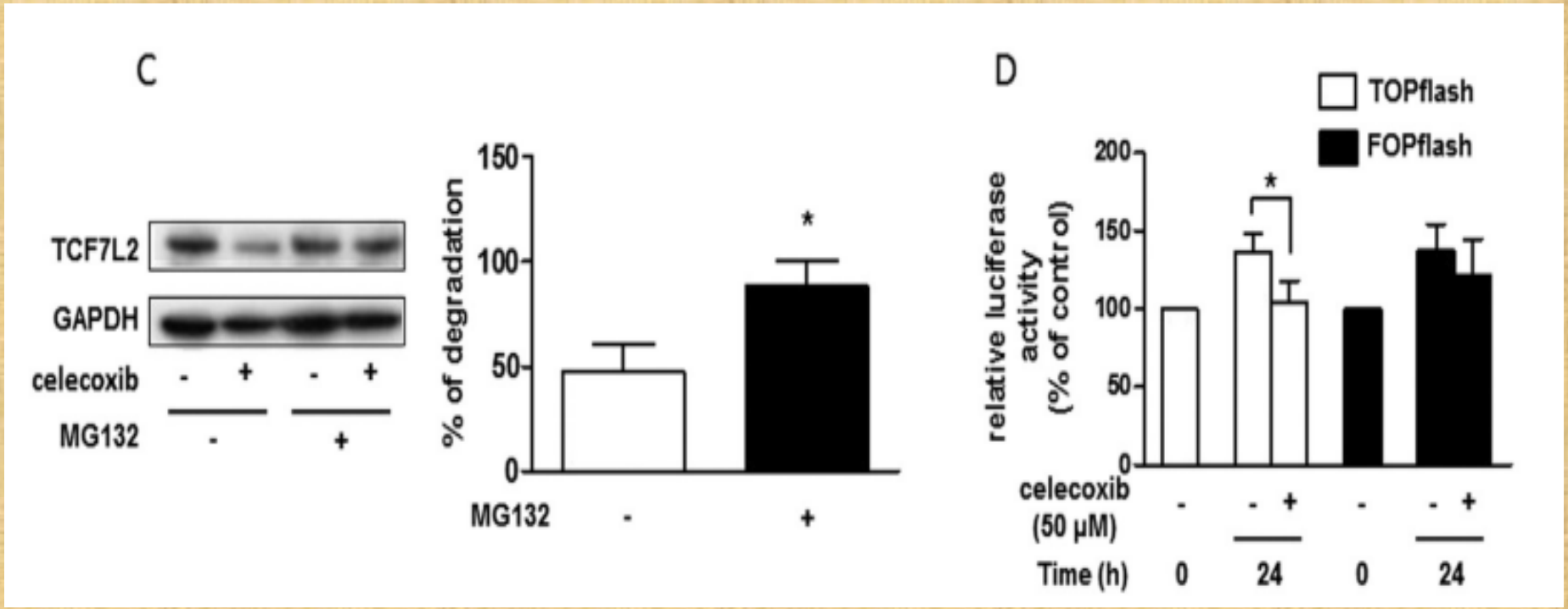
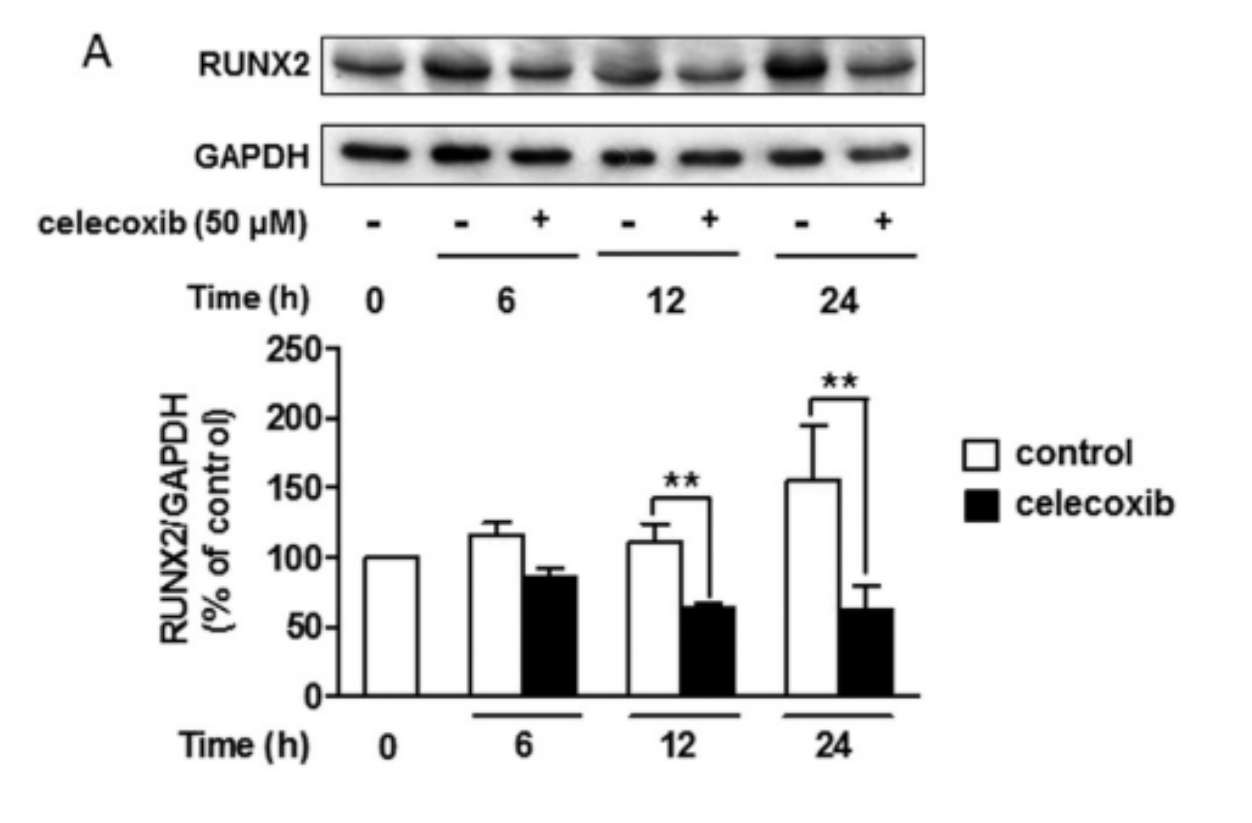


2、Celecoxib inhibited RUNX2 expression



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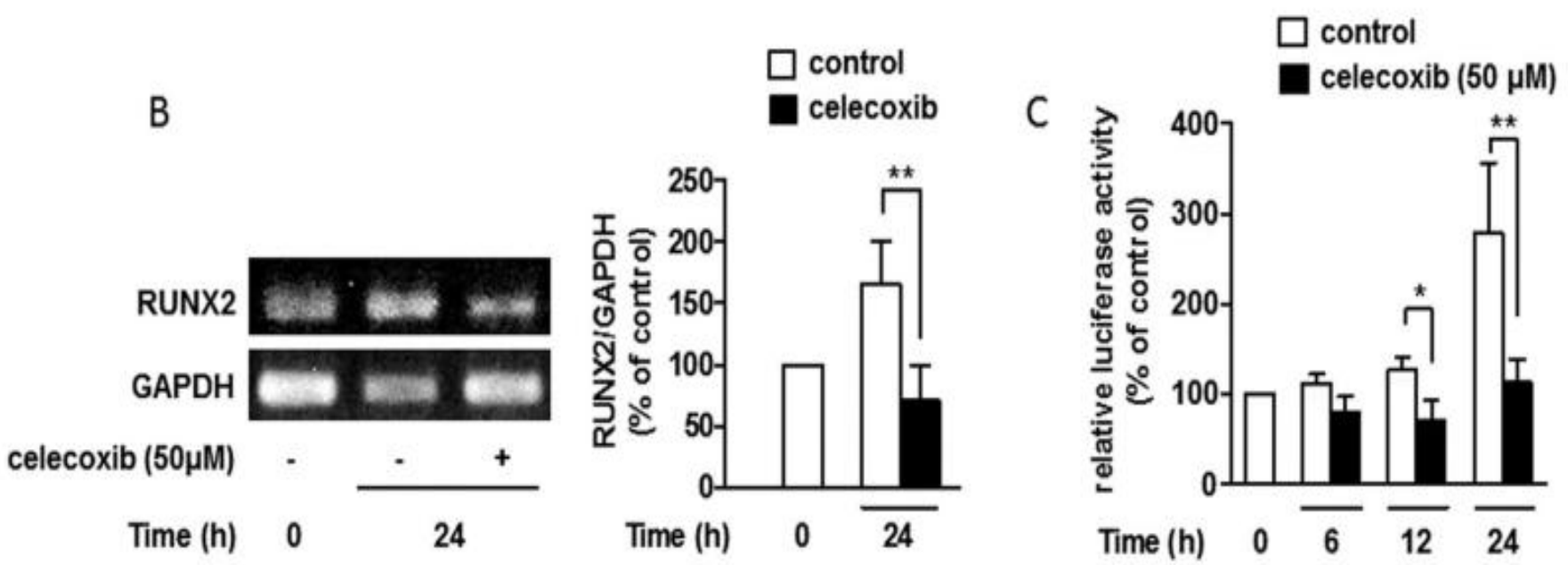
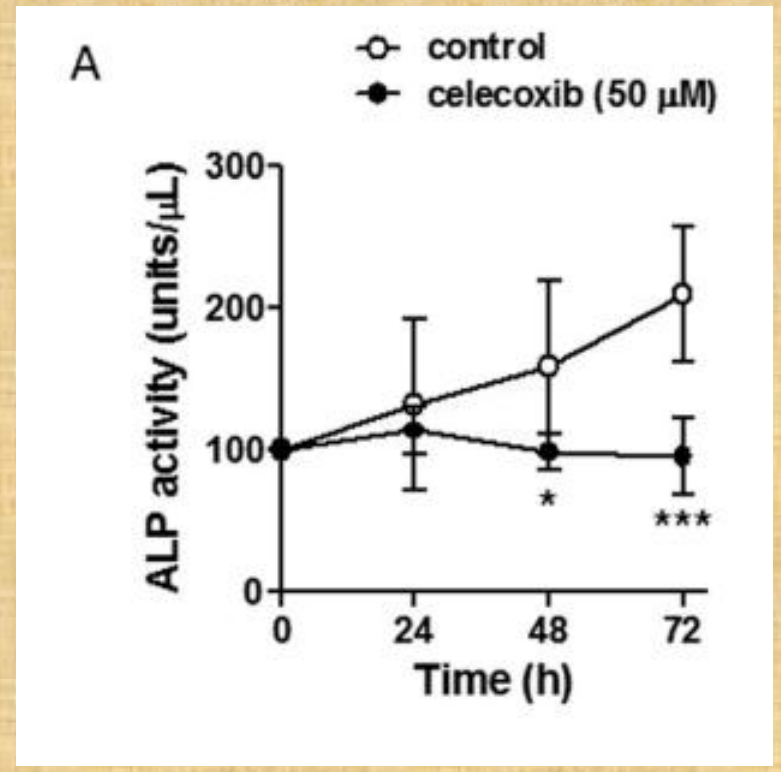
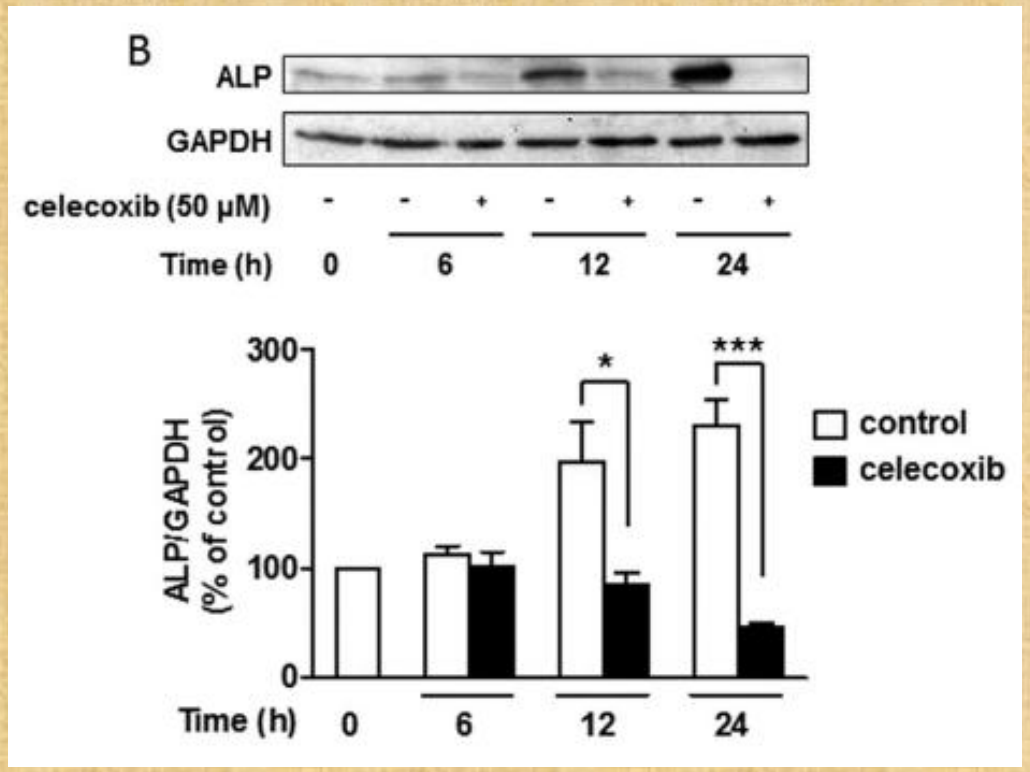


3、Celecoxib suppressed ALP expression by suppression of the promoter activity





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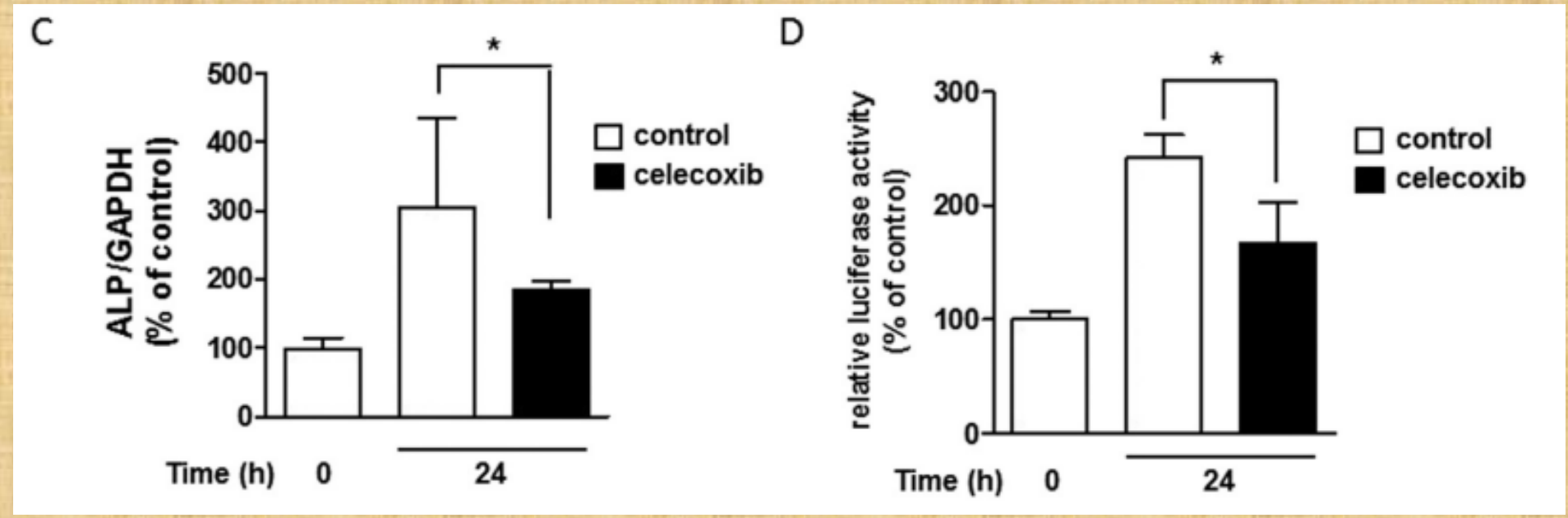
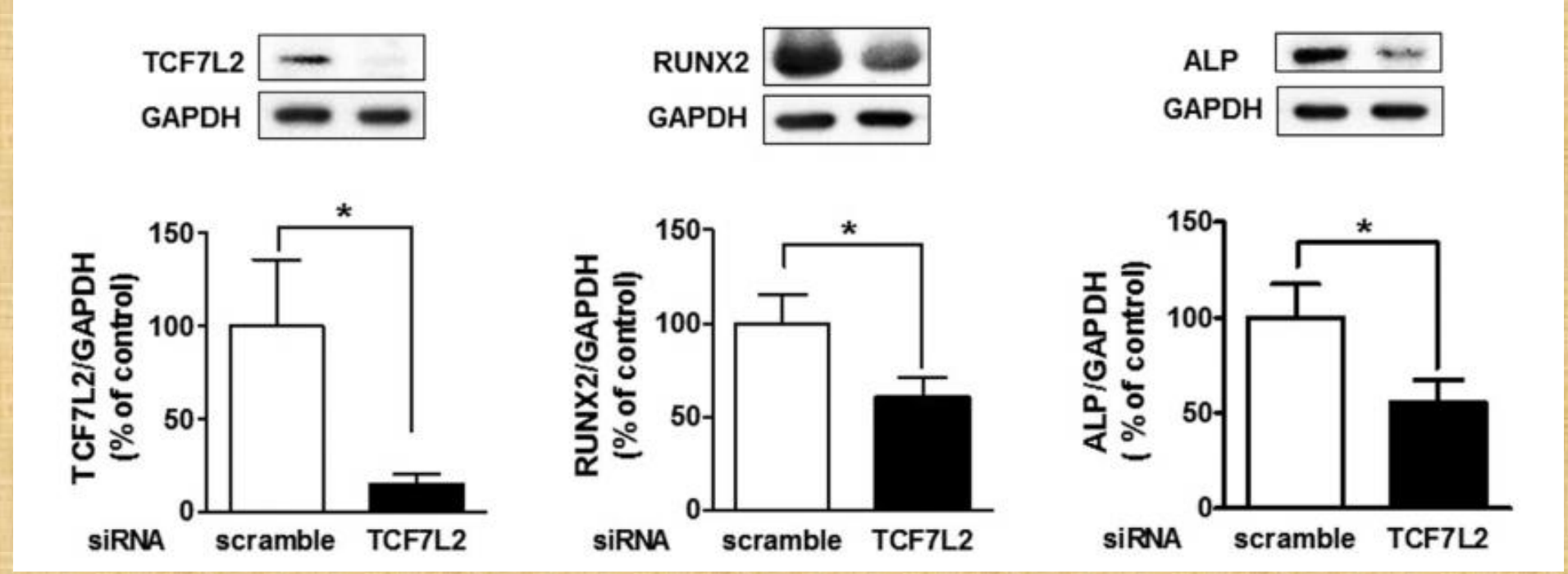
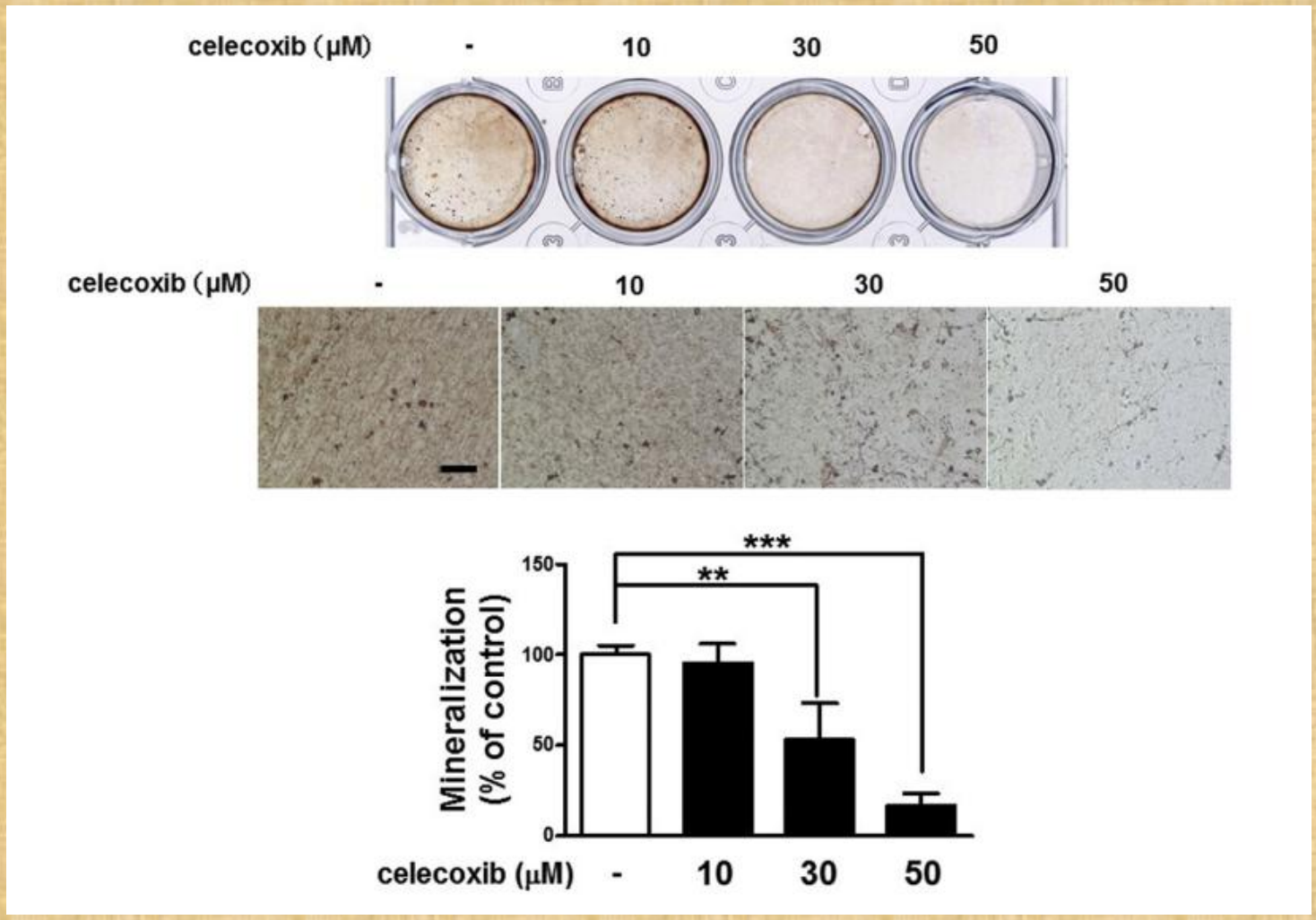


4、TCF7L2 depletion suppressed RUNX2 and ALP expressions



5、Celecoxib suppressed osteoblast-mediated mineralization

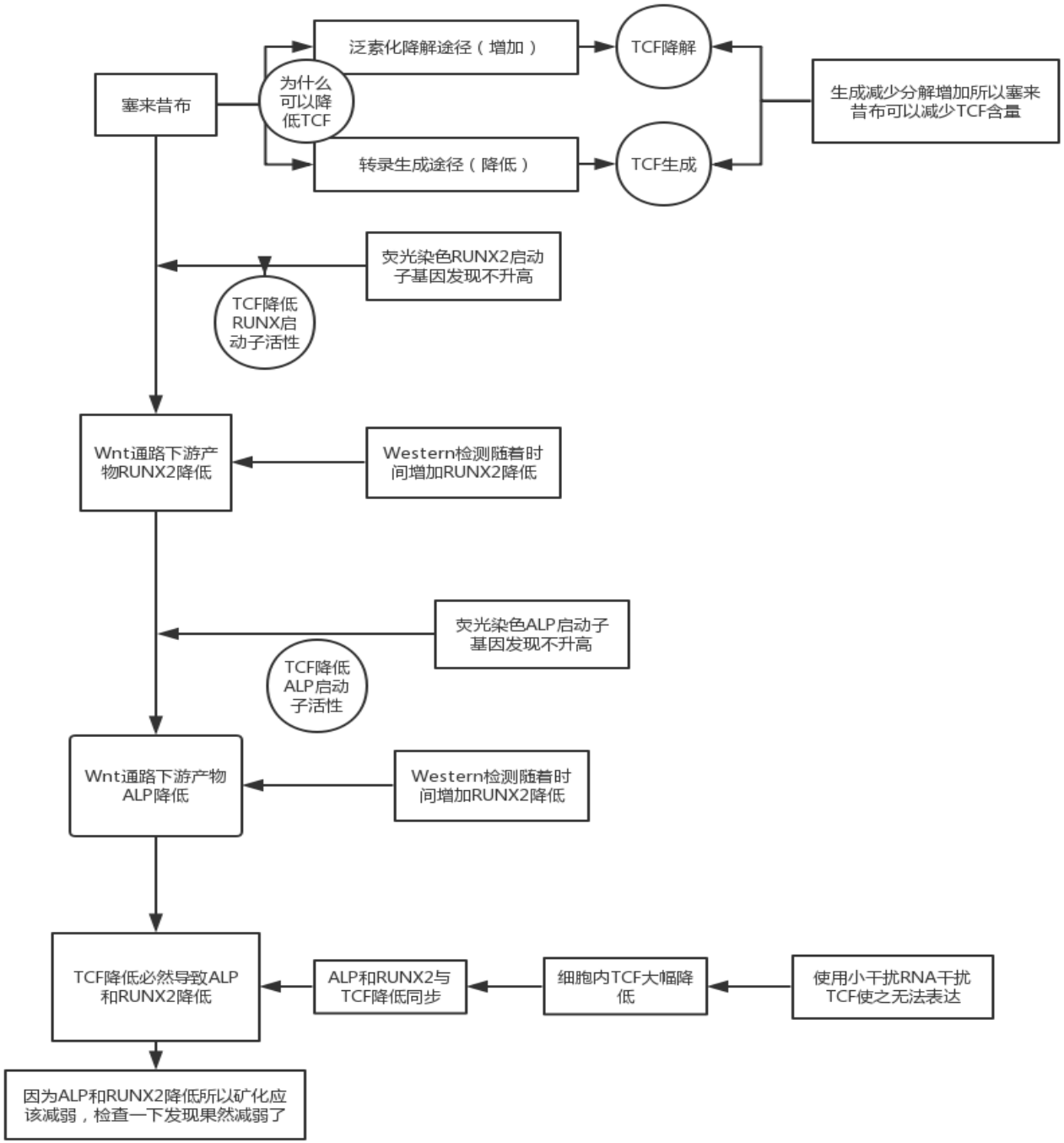


Discussion

1、In this study, we found that celecoxib inhibited the canonical Wnt pathway by suppressing TCF7L2 expression and thereby reduced amounts of RUNX2 and ALP, via inhibition of their promoters' activity. Further, we found that celecoxib strongly suppressed osteoblast-mediated mineralization. that this could be the one mechanism by which celecoxib inhibits bone formation and fracture healing.

2、 NSAIDs, including COX-2 specific inhibitor, are known to prevent bone formation and fracture healing in vivo.

3、 Therefore, celecoxib might suppress the Wnt/b-catenin signaling pathway via two different mechanisms, the degradation of TCF7L2 and the inhibition of PGE2 production, thereby inhibiting bone formation and fracture healing.


塞来昔布
为什么可以降低TCF
泛素化降解途径（增加）
转录生成途径（降低）
TCF降解
TCF生成
生成减少分解增加所以塞来昔布可以减少TCF含量
荧光染色RUNX2启动子基因发现不升高
TCF降低RUNX启动子活性
Wnt通路下游产物RUNX2降低
Western检测随着时间增加RUNX2降低
荧光染色ALP启动子基因发现不升高
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Wnt通路下游产物ALP降低
Western检测随着时间增加RUNX2降低
TCF降低必然导致ALP和RUNX2降低
ALP和RUNX2与TCF降低同步
细胞内TCF大幅降低
使用小干扰RNA干扰TCF使之无法表达
因为ALP和RUNX2降低所以矿化应该减弱，检查一下发现果然减弱了

谢谢

- 2019-05-15