# Transcriptional Induction of Cyclooxygenase-2 in Osteoclast Precursors is Involved in TRANCE-induced Osteoclastogenesis

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Osteoclast are specialized cells derived from the monocyte/macrophage haematopoietic lineage that develop and adhere to bone matrix, then secrete acid and lytic enzymes that degrade it in a specialized, extracellular compartment. Regulation of osteoclast differentiation is central to the understanding of the pathogenesis and treatment of bone diseases such as osteoporosis. Discovery of the TRANCE/ TRANCE-R signaling pathway in the osteoclast has provided insight into the mechanisms of osteoclastogenesis and activation of bone resorption, and how hormonal signals impact bone structure and mass.

During the course of our study to investigate TRANCE signaling in osteoclast precusors, we found that TRANCE induces Rac1 activation that leads to activation of NF-κB and p38 MAP kinase, both of which were known to be critical for osteoclast differentiation. To gain insight into the mechanism of the TRANCE-Rac1-specific induction of the osteoclast differentiation program, we took suppression-subtractive hybridization screening approach to identify genes specifically induced via TRANCE-Rac1 signaling pathway. Among identified targets, we found that TRANCE selectively induces cyclooxygenase (Cox)-2 expression via Rac1 that results in $PGE_2$ production in RAW 264.7 cells. By using transient transfection assays, we found that the –592/-564 region of the Cox-2 promoter gene was critical for TRANCE-induced promoter activity. This TRANCE-responsive region contained a NF-κB site that, when mutated, completely abolished Cox-2 promoter activity by TRANCE. Blockade of Cox-2 by a Cox-2 specific inhibitor, Celecoxib inhibits differentiation of macrophages to TRAP-positive osteoclastic cells. This inhibition can be rescued by exogenous $PGE_2$, suggesting that Cox-2-dependent $PGE_2$ production appears to be necessary, but not sufficient, for osteoclast differentiation. These findings implicate that Cox-2 in osteoclastogenesis is a novel target for the development of therapeutics against osteoporosis.

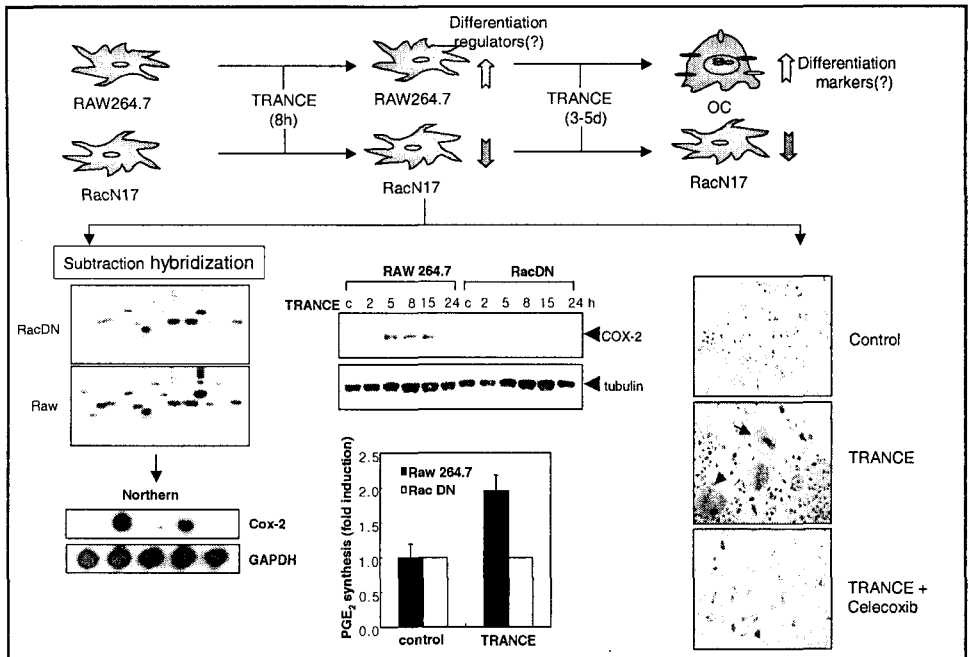


그림 1. TRANCE-Rac1 특이적 발현 유전자 탐색 체계도 및 Cox-2 유전자의 발현, 파골세포 분화시 Cox-2 억제제의 효과

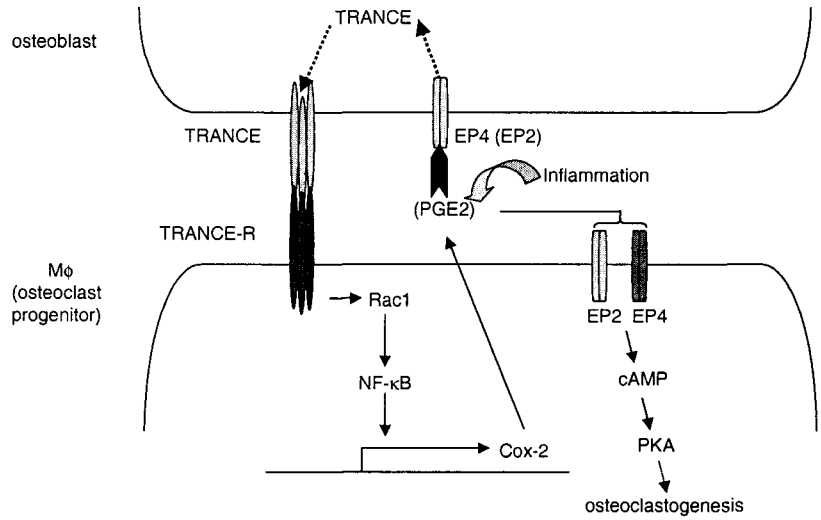


그림 2. TRANCE에 의해 생성된 Cox-2가 파골세포 분화에 미치는 작용 모델. Cox-2는 TRANCE-Rac1-NF-κB 의존적으로 합성되어 $PGE_2$를 합성한다. $PGE_2$는 그 수용체 (EP2 또는 EP4)를 통해 PKA를 거쳐 파골세포 분화에 관여한다.