3-Y-G3-4 YIA**Ca²⁺ release-activated Ca²⁺ channels are involved in osteoarthritic marker induction by interleukin-1 β in mouse chondrocytes**Risa Kurose, Yoshiaki Suzuki, Yuji Imaizumi, Hisao Yamamura*Dept. Mol. Cell. Pharmacol., Grad. Sch. Pharmaceut. Sci., Nagoya City Univ.*

In chondrocytes, changes in intracellular Ca²⁺ concentration ([Ca²⁺]_i) modulate chondrogenesis, cell proliferation, and death. Enhanced Ca²⁺ signaling facilitates the production of osteoarthritis (OA) markers including pro-inflammatory mediator (TNF- α) and matrix degrading enzymes (ADAMTS5 and MMP-13). However, the molecular mechanism responsible for the abnormal Ca²⁺ signaling is unknown. Here, we examined the functional roles of Ca²⁺ release-activated Ca²⁺ (CRAC) channels on Ca²⁺ signaling and OA marker production evoked by interleukin (IL)-1 β , a major cytokine associated with OA, in mouse primary-cultured chondrocytes. IL-1 β (5~10 ng/ml, for 2~6 h) upregulated the expression of OA markers and increased the number of [Ca²⁺]_i oscillation-positive chondrocytes. Furthermore, IL-1 β facilitated NFAT translocation into nucleus. A selective CRAC channel inhibitor, 10 mM YM58483, significantly attenuated IL-1 β -induced [Ca²⁺]_i oscillation, NFAT translocation, and OA marker production. A calcineurin inhibitor, 1 mM cyclosporin A, blocked both NFAT translocation and OA marker expression. These results suggest that IL-1 β enhances Ca²⁺ influx through CRAC channels and activates calcineurin-NFAT signaling, and thus, upregulated the expression of OA markers. CRAC channels may be a therapeutic target for the treatment of OA.