Nuclear factor–kappaB (NF-κB) transcription factors regulate a large number of genes that are activated to stress conditions such as inflammation, infection or injury. Blocking the canonical NF-κB pathway has been indicated as a possible strategy to treat osteoarthritis and rheumatoid arthritis in recent years. However, the roles of NF-κB in normal skeletal physiology are largely unknown owing to the lack of suitable animal models. In mice, we conditionally deleted Nemo (NF-κB essential modulator or IKK gamma), which is the key regulator of the NF-κB. With chondrocyte-specific Col2a1-Cre transgene we are able to clarify the physiological function of canonical NF-κB pathway in the cartilaginous skeleton. Nemo<sup>−/−</sup>;Col2a1-Cre and control mice were analyzed by skeletal staining, body weight and length measurements, histology, BrdU incorporation and TUNEL assays. Atomic force microscope demonstrated the structural and mechanical properties of the growth plate. Safranin orange histochemistry and immunohistochemistry for the aggrecan degradation product TEGE were utilized in hip explant culture to assess the impact of NEMO-deficiency in cytokine-induced cartilage degradation. To identify genes regulated via canonical NF-κB pathway in response to injury, an ex vivo hip avulsion model was applied to perform RT-PCR. With an established scoring system, we evaluated pathological changes of articular cartilage in spontaneous osteoarthritis (OA). Mutant mice exhibit moderate dwarfism characterized by shortened growth plate, mild disorganization of columnar chondrocytes at 2 weeks of age, decreased chondrocyte proliferation and increased apoptosis/necrosis. Primary chondrocytes displayed reduced migration and proliferation. In spontaneous OA model, mutant mice displayed milder OA symptoms compared to control. Exposure of TEGE and release of GAGs were less pronounced in mutant hip explants stimulated by cytokines. In spontaneous OA, aged mutant mice exhibited less degradation of the articular cartilage compared with control. The phenotype of Nemo-deficient mice indicated an important role of canonical NF-κB signaling in skeletal growth by modulating chondrocyte proliferation and survival. The catabolic effects of pro-inflammatory cytokines in cartilage could be partially eased by blocking the canonical NF-κB pathway. RT-PCR results revealed that IKK dependent pathway may not be the key of inducing inflammatory genes upon injury. Gradually, we demonstrated the potential of blocking canonical NF-κB pathway against OA.