Pharmacologic inhibitors of IκB kinase suppress growth and migration of mammary carcinosarcoma cells in vitro and prevent osteolytic bone metastasis in vivo

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Résumé en anglais	The NF-κB signaling pathway is known to play an important role in the regulation of osteoclastic bone resorption and cancer cell growth. Previous studies have shown that genetic inactivation of IκB kinase (IKK), a key component of NF-κB signaling, inhibits osteoclastogenesis, but the effects of pharmacologic IKK inhibitors on osteolytic bone metastasis are unknown. Here, we studied the effects of the IKK inhibitors celastrol, BMS-345541, parthenolide, and wedelolactone on the proliferation and migration of W256 cells in vitro and osteolytic bone destruction in vivo. All compounds tested inhibited the growth and induced apoptosis of W256 cells as evidenced by caspase-3 activation and nuclear morphology. Celastrol, BMS-345541, and parthenolide abolished IL1β and tumor necrosis factor α–induced IκB phosphorylation and prevented nuclear translocation of NF-κB and DNA binding. Celastrol and parthenolide but not BMS-345541 prevented the activation of both IKKα and IKKβ, and celastrol inhibited IKKα/β activation by preventing the phosphorylation of TAK1, a key receptor–associated factor upstream of IKK. Celastrol and parthenolide markedly reduced the mRNA expression of matrix metalloproteinase 9 and urinary plasminogen activator, and inhibited W256 migration. Administration of celastrol or parthenolide at a dose of 1 mg/kg/day suppressed trabecular bone loss and reduced the number and size of osteolytic bone lesions following W256 injection in rats. Histomorphometric analysis showed that both compounds decreased osteoclast number and inhibited bone resorption. In conclusion, pharmacologic inhibitors of IKK are effective in preventing osteolytic bone metastasis in this model and might represent a promising class of agents to the prevention and treatment of metastatic bone disease associated with breast cancer.

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