RelB-mediated EMT activation promotes bone metastasis of prostate cancer

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The NF-κB signaling pathway is well-known to be critical for cancer development; our previous studies demonstrated that the RelB-based NF-κB alternative pathway is essential for tumorigenesis of prostate cancer. Here, we show that RelB contributes to bone metastasis of prostate cancer through an EMT-activating process. High constitutive nuclear levels of RelB were observed in human prostate cancer tissues with high Gleason scores. Up-regulation of RelB in prostate cancer cells led to cell invasion and migration, which was mediated by activation of Snail I and Twist I. ChIP revealed that RelB binds to NF-κB enhancer elements located at the 5′-flanking regions of both Snail I and Twist I genes, which interact with Sp1-based promoters for transcriptional activation of the genes. In addition, the high levels of RelB also increased cell mineralization that was correlated to up-regulation of the bone formation relating protein, S100A4. The RelB-mediated aggressiveness of prostate cancer cells through Snail I- and Twist I-activated PI3K-AKT pathway, which was induced by TNFα, but suppressed by an anticancer agent, parthenolide. These results suggest that the activation of NF-κB alternative pathway enhances metastasis of prostate cancer cells by activation of the EMT process.

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