Abstract:
Manganese superoxide dismutase (MnSOD) has been shown to suppress the development of cancer. Tamoxifen (TAM), a nonsteroidal anti-estrogen that is widely used in chemotherapy, is known to be a modulator of antioxidant status. However, the mechanism by which TAM mediates antioxidant enzyme induction remains unclear. In this study we investigated TAM enhancement of MnSOD induction by TNF-alpha. The results show that co-treatment with TAM and TNF-alpha increases the MnSOD promoter/enhancer driven luciferase activity, MnSOD mRNA and protein levels. Interestingly, co-treatment with TAM and TNF-a drastically decreases the binding activity of the p50/p50 homodimer and increases that of the p50/p65 heterodimer compared to TNF-alpha alone. This change in DNA binding could not be attributed to a decrease in the level of p50, its precursor, p105, or its inhibitors. Furthermore, TAM did not enhance degradation of IkappaB-alpha. These results suggest that p50/p50 homodimer may act as an inhibitory complex of MnSOD expression. Modulation of the DNA binding activity in favor of the p50/p65 complex may enhance NF-kappaB mediated induction of MnSOD by TAM. These findings reveal a potential novel mechanism for the induction of the human MnSOD gene.

Keywords: NF-kappa B; tamoxifen; tumor control; MnSOD; tumor suppressor gene