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Heregulin-β1 Induces Manganese Superoxide Dismutase in Human Breast Cancer Cells through Activation of the Nrf2-ARE Signaling Pathway

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Ligands of ErbB family receptors are known to control the proliferation of breast cancer cells. Multiple lines of evidence suggest that heregulin-β1, a ligand of ErbB receptors, potentiates oncogenicity and metastatic potential of breast cancer cells. Recently, the role of antioxidative and detoxifying enzymes in the proliferation and invasiveness of tumor cells has been reported. It has been proposed that manganese superoxide dismutase (MnSOD), one of the typical antioxidant enzymes, may contribute to sustained proliferation and elevated metastatic potential of cancer cells by changing the intracellular reactive oxygen species level. In the present work, treatment of human breast (MCF-7) cancer cells with heregulin-β1 caused increased expression and activity of MnSOD. In addition, we found that heregulin-β1-induced MnSOD expression was mediated via the Nrf2-ARE signaling pathway. Heregulin-β1 appears to activate Nrf2 transcription factor through phosphory- lation of upstream kinases, such as extracellular signal-regulated protein kinase (ERK) and Akt/protein kinase B. In support of this supposition, heregulin-β1-induced Nrf2-ARE signal pathway and subsequent MnSOD expression were abrogated by the MEK inhibitor U0126 and the PI3K inhibitor LY294002. In conclusion, heregulin-β1 induces expression of MnSOD through activation of Nrf2 in MCF-7 cells, which may contribute to metastatic potental and invasiveness of breast cancer cells.

Keyword : MCF-7, Heregulin-β1, Nrf2, ARE, MnSOD