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IGF-1-INDUCIBLE GST EXPRESSION IN IGF-I RECEPTOR-OVEREXPRESSED HEPATOMA CELLS

Keon Wook Kang, Jeong Yong Lee
College of Pharmacy, Chosun University

Insulin-like Growth Factor type I receptor (IGF-IR) is frequently overexpressed in human hepatocellular carcinoma cells (HCC) and this overexpression has been correlated with increased tumor growth. The protective response of HCC to reactive oxygen species produced by chemotherapeutic agents is mediated with the induction of phase II detoxifying genes including glutathione S-transferase (GST). To understand the roles of IGF-IR overexpression in HCC in terms of its detoxifying effect on radicals and conferred resistance to chemotherapy, we analyzed whether overexpressions of IGF-IR affect IGF-1-inducible GST expression. GST was induced by exposure to IGF-1 in IGF-IR cells but not in cells expressing normal levels of IGF-IR. Furthermore, IR-HCCs are more resistant to doxorubicin than control HCC cells, which was associated with the increased GST induction by IGF-1. Molecular analyses using GSTA2 promoter supported the involvement of XRE in GST induction. IGF-1 caused the nuclear translocation of C/EBPβ, which might be responsible for the activation of XRE. In addition, IGF-1 increased the activities of PI3-kinase and ERK in IR-HCCs, as determined by the phosphorylations of these kinases. Moreover, the inhibition of PI3-kinase completely abolished the nuclear translocation of C/EBPβ and the upregulation of GST protein in IGF-IR-overexpressed HCC (IR-HCC) treated with IGF-1. However, specific inhibitors against ERK, JNK or p38 kinase did not alter IGF-1-inducible GST expression.

Key Words: IGF, GST, C/EBP-beta, Doxorubicin