E51

Study Of IL4Rα And IL13Rα1 Expression In Gallbladder Cancer

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Background : Gallbladder cancer is commonly associated with inflammation. Therefore, inflammation-related cytokines and cytokine receptors might be related to the progression of gallbladder cancers. Recently, it has been reported that IL4Rα and IL13Rα1, constituents of type II IL4 receptors, are involved in the progression of human cancers through activation of the JAK2 pathway. However, studies on IL4Rα and IL13Rα1 in gallbladder cancers have been limited. Therefore, this work investigated the expression of IL4Rα and IL13Rα1 in 122 gallbladder carcinomas and the effect of inhibition of JAK2 in SNU308 gallbladder cancer cells.

Methods : To evaluate the clinicopathological significance of the expression of IL4Rα and IL13Rα1 in human gallbladder cancers, 122 cases of gallbladder carcinomas treated between January 2000 and December 2009 were evaluated. In human gallbladder carcinomas, the expression of IL4Rα and IL13Rα1 were evaluated with immunohistochemical staining in tissue microarray sections. In knock-down IL4Rα or IL13Rα1 of SNU308 gallbladder cancer cells, we checked expression level of phosphorylated JAK2 and also, evaluated proliferation and apoptosis level after the treatment of AZD1480, a JAK2 inhibitor.

Results : Immunohistochemical expression of IL4Rα was significantly associated with the expression of IL13Rα1 in human carcinoma tissue. Additionally, in univariate analysis, nuclear expression of IL4Rα, cytoplasmic expression of IL4Rα, nuclear expression of IL13Rα1, and cytoplasmic expression of IL13Rα1 were significantly associated with overall shorter survival and shorter relapse-free survival. Multivariate analysis revealed nuclear expression of IL4Rα as an independent poor prognostic indicator of overall survival ($P < 0.001$) and relapse-free survival ($P < 0.001$). In SNU308 gallbladder cancer cells, knock-down of IL4Rα or IL13Rα1 decreased expression of phosphorylated JAK2. The treatment of AZD1480, a JAK2 inhibitor, inhibited proliferation and increased apoptosis of SNU308 cells. In the western blot, treatment of AZD1480 increased expression of cleaved PARP1, cleaved caspase-3, Bax, Bim, p21, p27, and FOXO3, but decreased expression of Bcl2 and pJAK2 in SNU308 cells.

Conclusions : In conclusion, this study showed that the expression of IL4Rα and IL13Rα1, especially nuclear expression of IL4Rα, was a potential prognostic indicator of gallbladder carcinomas. Furthermore, suppression of the IL4R pathway with the treatment of JAK2 inhibitor might be an effective therapeutic approach to gallbladder carcinomas.

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