

5-Fluorouracil induce the expression of TLR4 on HCT116 colorectal cancer cell line expressing different variants of TLR4

ABSTRACT

Two common single nucleotide polymorphisms (SNPs) of the human TLR4 gene, namely Asp299Gly (D299G) and Thr399Ile (T399I), have been shown to impair the ability of certain individuals to respond properly to TLR4 ligands. 5-Fluorouracil (5-FU) is widely used for the treatment of patients with advanced colon cancers. The present study examined the impact of two common polymorphisms of the TLR4 genes on the response of the HCT116 colorectal cancer cells to 5-FU. HCT116 was transfected with Flag-CMV1-TLR4 wild-type (WT) and D299G, T399I expression plasmids. The cytotoxic effect of 5-FU on transfected cells was assessed by MTT assay. FACS analysis was performed to show the effect of 5-FU and LPS on the expression of different variants of TLR4. The lowest IC₅₀-value was measured in cells expressing the WT TLR4 and non-transfected cells were more resistance to the drug compared to the other cells. 5-FU significantly induced the expression of TLR4 protein in the presence and absence of LPS. 5-FU also induced HMGB1 secretion, Cas3 and PARP activity and these effects were stronger in cells expressing WT TLR4 than the other cells. In conclusion, 5-FU-induced TLR4 expression and LPS had synergistic effect with 5-FU to induced apoptosis in colorectal cancer cells.

Keyword: TLR4; Polymorphisms; 5-FU; Colorectal cancer; Chemotherapy