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Inhibitory Effect of P2Y1R Agonist 1-Indolinoalkyl 2-Phenolic Derivative on Prostate Cancer Cell Proliferation via the MAPK Signalling

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Abstract : Purinergic receptor 1 (P2Y1R) is the potential therapeutic target for inducing prostate cancer (PCa) cell death. Recently, 1-indolinoalkyl 2-phenolic derivative, HIC, was identified as a P2Y1R agonist that increases apoptosis and inhibits cell proliferation of PCa. However, the biological effects of HIC have not been extensively studied at the molecular level. In the present study, we have investigated the anticancer effects of HIC and the molecular mechanisms underlying in PCa cells. Half maximal inhibitory concentration (IC_{50}) of HIC was measured as 15.98 µM and 15.64 µM for DU145 and PC3 cells, respectively. In addition, we found that HIC inhibited cell growth and metastasis of PC3 and DU145 cells colonies, spheroid areas, and migrated cells. RNA seq analysis revealed significant changes of over 3000 genes (p value < 0.05) upon HIC treatment in PC3 and DU145 cells. Genes involved in DNA damage, apoptosis, cell cycle arrest at G1/S phase were modulated by HIC treatment. MAPK and NF-κB protein array revealed the increased expression of ERK1/2, JNK1/2, p53 phosphorylation, and p53 protein. ERK1/2 and JNK1/2 activations are known to increase the stabilization of p53, a tumor suppressor protein, which is required to arrest the cell cycle at G1/S phase and cause cell death of PCa cells. Overall, our results suggest that HIC can serve as a multi-dimensional chemotherapeutic agent possessing strong cytotoxic, anti-cancer, and anti-metastasis against PCa growth.

Keywords : prostate cancer, P2Y1 receptor, apoptosis, metastasis
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