Novel quinazoline-based sulfonamide derivative (3D) induces apoptosis in colorectal cancer by inhibiting JAK2-STAT3 pathway

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Abstract

Introduction: Colorectal cancer (CRC) is a major worldwide health problem owing to its high prevalence and mortality rate. Developments in screening, prevention, biomarker, personalized therapies and chemotherapy have improved detection and treatment. However, despite these advances, many patients with advanced metastatic tumors still succumb to the disease. New anticancer agents are needed for treating advanced stage CRC as most of the deaths occur due to cancer metastasis. A recently developed novel sulfonamide derivative 4-((2-(4-(dimethylamino) phenyl)quinazolin-4-yl)amino)benzenesulfonamide (3D) has shown potent antitumor effect; however, the mechanism underlying the antitumor effect remains unknown.

Materials and methods: 3D-mediated inhibition on cell viability was evaluated by MTT and real-time cell proliferation was measured by xCelligence RTDP instrument. Western blotting was used to measure pro-apoptotic, anti-apoptotic proteins and JAK2-STAT3 phosphorylation. Flow cytometry was used to measure ROS production and apoptosis.

Results: Our study revealed that 3D treatment significantly reduced the viability of human CRC cells HT-29 and SW620. Furthermore, 3D treatment induced the generation of reactive oxygen species (ROS) in human CRC cells. Confirming our observation, N-acetylcysteine significantly inhibited apoptosis. This is further evidenced by the induction of p53 and Bax; release of cytochrome c; activation of caspase-9, caspa.se-7 and caspase-3; and cleavage of PA RP in 3D-treated cells. This compound was found to have a significant effect on the inhibition of antiapoptotic proteins Bcl2 and BclxL. The results further demonstrate that 3D inhibits JAK2-STAT3 pathway by decreasing the constitutive and IL-6-induced phosphorylation of STAT3. 3D also decreases STAT3 target genes such as cyclin Dl and survivin. Furthermore, a combination study of 3D with doxorubicin (Dox) also showed more potent effects than single treatment of Dox in the inhibition of cell viability.

Conclusion: Taken together, these findings indicate that 3D induces ROS-mediated apoptosis and inhibits JAK2-STAT3 signaling in CRC.

Keywords

Author Keywords: sulfonamide; apoptosis; colorectal cancer; STAT3 pathway; Bcl2 proteins; reactive oxygen species
KeyWords Plus: INFLAMMATORY-BOWEL-DISEASE; CELL-CYCLE ARREST; MEDIATED APOPTOSIS; MOLECULAR TARGETS; COLON-CANCER; TUMORS; STAT3; ACTIVATION; MECHANISMS; GENERATION

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