Checkpoint Blockade Therapy

418 6-GINGEROL SUPPRESSES ANGIOGENESIS AND PROMOTES T-CELL CYTOTOXICITY IN MICE MODEL OF COLORECTAL CANCER

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Background Colorectal cancer (CRC) is the second most common adult cancer in women and the third most common in men, and it is the fourth leading cause of cancer death worldwide. Angiogenesis is a critical step in CRC progression and metastasis. Immune checkpoint proteins (ICP) such as programmed cell death 1 (PD1), PD1 ligand 1 (PD-L1) and cytotoxic T lymphocyte antigen 4 (CTLA4) act as inhibitory immunoreceptors that prevent cytotoxic T-cells from killing tumor cells. Studies have reported the contribution of angiogenesis and ICP to anti-tumor immunity. Indeed, targeting angiogenesis and use of ICP blockage have revolutionized colorectal cancer treatment and improved patients' survival. However, the use of immune checkpoint inhibitors has been shown to induce immune-related adverse reactions such as colitis. 6-gingerol (6G), the most pharmacologically active compound discovered in Zingiber officinale (ginger), We have reported the anti-tumor effects of 6-gingerol. However, there is a lack of information on the effect of 6G on angiogenic drivers and T-cell cytotoxicity in a mouse model of CRC. Herein, we investigated the effects of 6G angiogenesis and cytotoxic T-cell signaling in mice model of CRC.

Methods Male BALB/c mice were divided into three groups of 20 mice each. Group 1 mice served as controls Group 2 (CRC model) mice received a single dose of azoxymethane (AOM) 10mg/kg and, after one week, they received three cycles of dextran sulfate sodium (DSS) 4% in drinking water. Group 3 mice received 6G 10mg/kg/day by oral gavage in combination with AOM and three cycles of 4% DSS (W/V) in drinking water. The colons of the mice were observed daily for tumor development, and the experiment was terminated after confirmation of colorectal adenocarcinoma.

Results Tumor burden was observed to be decreased in CRC mice treated with 6G. Also, 6G decreases the expression of collagen (type I and I), vascular endothelial growth factor (VEGF), VEGF receptor, epidermal growth factor (EGF), and EGF receptor in mice with CRC when compared with control. Furthermore, mice administered 6G+AOM/DSS had increased expression of CD4 and CD8+ T-cells and decreased expression of tumor necrosis factor (TNF-α), cyclooxygenase-2 (COX-2), PD1, PD-L1, and CTLA4 when compared to mice with CRC. Using computational oncology, we observed a high binding affinity of 6G with VEGF, VEGFR, EGF, EGFR, PD1, PD-L1, and CTLA4.

Conclusions The result obtained from this study showed that 6-gingerol suppresses angiogenic drivers and promotes T-cell cytotoxicity in colorectal cancer.

Ethics Approval The work was approved by Ajayi Crowther Faculty of Natural Science Research Ethic Committee

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