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CA102N Suppresses the Growth of Mouse Colon Cancer by Inhibiting PI3K Pathway and Immune Modulation

Abstract

Introduction

COX-2 inhibitors have the immense possibility in treating colorectal cancer (1). Nevertheless, the cardiovascular toxicity of COX-2 inhibitors hampered further development of these inhibitors in cancer management (2). CA102N is a covalently bound conjugate of the biological polymer sodium hyaluronate (NaHA) and nimesulide (Nim) aiming to deliver Nim directly to the tumor tissues to limit the systemic toxicity. Our laboratory has utilized allergo CT-26 syngeneic Balb/c mouse colon cancer model (3) to understand whether CA102N suppresses the development of colorectal cancer. We tested the inhibitory effect of CA102N on the tumor growth of colorectal cancer and its relevant molecular mechanism via targeting COX-2 pathway, immune modulation, and PI3Kinase pathway (4, 5). We also comprehended whether urinary COX-2 metabolites could serve as a surrogate biomarker for CA102N using mouse syngeneic colon cancer CT26 model.

Methods

• All animal experiments were approved by The University of Texas MD Anderson Cancer Center Animal Care and Use Committee. Mouse CT26 allograft colon cancer model was utilized to investigate the effect of CA102N on mouse tumor progression. Briefly, Six-week-old Balb/c mice were inoculated with CT-26 cells (5 x 10^5). When the tumor volumes were between 25-50 mm³, mice bearing the CT26 tumor were randomized to vehicle control, CA102N (50-200 mg/kg), Nimesulide (1.5 and 5.3 mg/kg), TAS/CA102N (100 mg/kg), and TAS/CA102N (100 mg/kg) and terminal tumor volume of CT26 tumor (B). *p < 0.05, **p < 0.01 treated versus control

Figure 1. Growth curve of the CT26 tumor treated with CA102N (50-200 mg/kg), Nimesulide (1.5 and 5.3 mg/kg), TAS/CA102N (100 mg/kg), and TAS/CA102N (100 mg/kg). Tumoral and urinary eicosanoid levels in mice bearing CT26 tumor (B). * p < 0.05, ** p < 0.01 treated versus control

Figure 2. The intratumor and urinary eicosanoids (E) were determined by LC/MSMS method (6). Serum cytokine levels were measured by Meso Scale Discovery. Cytotoxic T-cells population. C). Cytotoxic T-cells population. B). Data presented as Mean ± SD (n= 3-4).

Figure 3. Serum cytokine analysis suggested that levels of MCP-1 (108.9 ± 24.3 pg/ml) and IL-1β (38.0 ± 5.3 pg/ml) in CA102N (50 mg/kg) treated mice were significantly lower than that of control group (175.4 ± 21.0 pg/ml) and (123.3 ± 55.8 pg/ml), respectively (A). Levels of IL-13 was also reduced in CA102N treated mice (B). Data presented as Mean ± SD (n= 3-4).

Figure 4. Profiling of tumor infiltrating lymphocytes. A). Treg cell population. B). Cytotoxic T-cells population. C). Cytotoxic T-cells population. D). Data presented as Mean ± SD. * p < 0.05, ** p < 0.01 treated versus control

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References


Conclusion

We report that CA102N treatment implies a promising new approach to colon cancer treatment. Our data suggests that lower dose of CA102N (50 mg/kg) exerts antitumor activity in mouse tumor xenografts affecting tumor microenvironment whereas higher dose of CA102N (200 mg/kg) suppressed tumor growth through directly targeting tumor cells PI3Kinase pathway.