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Pharmacological inhibition of the 3-mercaptopyruvate sulfurtransferase / hydrogen sulfide system in colon cancer

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Hydrogen sulfide (H_2S), historically considered merely as an environmental toxin, has emerged as an important mammalian endogenous modulator. Designated as the "third" gasotransmitter, H_2S is intracellularly produced by several biochemical reactions, mainly by three enzymes: cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (3-MST).
Over the recent years, a significant number of independent studies revealed multiple regulatory functions of H_2S in tumor biology, suggesting it as a key player in various cancer cells that upregulate their endogenous H_2S production. However, until recently, the attention was mainly given to CBS and CSE, and the role of 3-MST remained largely unexplored.
The pharmacological inhibition of 3-MST enzyme was used to investigate the potential role of 3-MST / H_2S system in colon cancer models. First, functional role of 3-MST catalytic activity in the murine colon cancer cell line CT26 was explored using the novel selective 3-MST inhibitor HMPSNE. Measurements of cell viability, proliferation, migration and bioenergetics demonstrated the attenuation of CT26 growth and metabolic activity in the presence of HMPSNE together with the suppression of H_2S production. In a second part, the HMPSNE structure was used as a basis to design analogs and test their potency and selectivity. The newly synthesized 3-MST inhibitors exerted inhibitory effects on murine MC38 and CT26 colon cancer cell proliferation, and the most potent analog also attenuated MC38 tumor growth in mice.
In conclusion, the anticancer effect of pharmacological 3-MST inhibition was demonstrated in vitro and in vivo colon cancer models, and valuable chemical and biological tools were highlighted to further examine and understand pathophysiological roles of 3-MST-H_2S pathway.

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