β-Hydroxybutyrate promotes cancer metastasis through β-hydroxybutyrylation-dependent stabilization of Snail

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Background

β-Hydroxybutyrate (BHB) is a main metabolite of ketone bodies produced by liver and is used as an alternative energy source in other tissues under some circumstances. BHB was shown to have anti-tumor effect on a variety of cancer cells such as colon cancer and pancreatic cancer, while it was also shown to exert tumor-promoting effect on some other types of cancer cells such as breast cancer and liver cancer. β-Hydroxybutyrylation (Kbhb) modification regulates protein molecular fates, including cancer. However, the function and regulatory mechanism of Kbhb remain completely unknown in cancer metastasis.

Objective

The study aimed to investigate how BHB promotes pancreatic ductal adenocarcinoma (PDAC) metastasis through Kbhb modification of Snail and explore this pathway as a potential therapeutic target.

Results

The researchers first performed metabolomic screening and found elevated BHB levels in PDAC patients, correlating with advanced stage and poor survival. Next, cell migration and invasion assays and mouse metastasis models showed that BHB promoted PDAC metastasis. Western blot and IHC analysis revealed that BHB increased levels of Snail and Vimentin while decreasing E-cadherin, indicating EMT activation. Immunoprecipitation (IP) and mass spectrometry identified BHB-induced Kbhb of Snail at lysine 152, which stabilized Snail by preventing FBXL14-mediated ubiquitination. Moreover, co-immunoprecipitation (co-IP) and in vitro enzymatic assays confirmed CBP as the enzyme mediating Snail Kbhb. Finally, Snail K152 mutation or treatment with the CBP inhibitor (A-485) suppressed Snail stability, inhibited metastasis, and enhanced the efficacy of gemcitabine in orthotopical and intrasplenic xenograft models of PDAC.

Conclusion

In summary, Snail K152 is modified by BHB, which stabilizes and enhances Snail protein levels through CBP in a Kbhb-dependent manner, thereby promoting PDAC cell metastasis. These findings not only shed light on the modification of Snail by Kbhb but also pave the way for targeting cancer metastasis.