Activation of S1PR2 upregulates tumoral DPD by promoting the interaction of TWIST1 with the JMJD3-RNA Pol II complex bound to the DPYD promoter

Zhi-Kun Guo¹, Ying-Zhi Zhang¹, Yu-Hang Zhang², Dong-Dong Luo³, Sheng-Biao Wan³, Xianjun Qu¹, and shuxiang cui¹

¹Capital Medical University

²Peking University First Hospital

³Ocean University of China School of Medicine and Pharmacy

February 1, 2022

Abstract

Background and Purpose: Dihydropyrimidine dehydrogenase (DPD) is a major determinant of 5-FU resistance in cancers. DPD catalyzes 5-FU into FBAL (α -fluoro- β -alanine) to lower intracellular 5-FU level. We aimed to investigate mechanism and clinical significance of FBAL-stimulated sphingosine 1-phosphate receptor 2 (S1PR2) in upregulation of DPD in colonic cancer. **Experimental Approach:** Cancer cells transfected or silenced S1PR2 were exposed to FBAL for analyzed S1PR2 and DPD levels. Luciferase reporter assay analyzed S1PR2-activated TWIST1 binding to DPYD promoter. Co-IP assay analyzed TWIST1 interaction with JMJD3-RNA Pol II complex binding to DPYD promoter. HT-29sh-S1PR2 or SW480TgS1PR2 cells xenografted nude mice were used to evaluate clinical significance of S1PR2-upregulated tumoral DPD. **Key Results:** Activation of S1PR2 upregulated DPD in colonic cancer cells and human fresh cancer specimens. FBAL was first time identified as an etiological stimulator of S1PR2 activation. The FBAL-stimulated S1PR2 increased TWIST1 binding to DPYD promoter and interacting with JMJD3-RNA Pol II complex, enhancing H3K27me3-enriched DPYD transcription elongation. Transfection of S1PR2 in SW480TgS1PR2 xenograft contributed 5-FU resistance by 45.14%, and silence of S1PR2 improved 5-FU sensitivity by 62.12% in HT-29sh-S1PR2 xenograft. S1PR2 inhibitor JTE013 prevented the FBAL-stimulated S1PR2's effects in upregulating DPD. Cancer cells with high S1PR2 are more resistant to 5-FU, strongly suggesting clinical significance that combination use of S1PR2 inhibitors may be the appropriate 5-FU-based regimens of colonic cancers. **Conclusions and Implications:** The FBAL-stimulated S1PR2 increased TWIST1 binding to DPYD promoter and interacting with JMJD3-RNA Pol II, enhancing the H3K27me3-enriched DPYD transcription elongation.

Hosted file

manuscript.doc available at <https://authorea.com/users/458424/articles/554988-activation-of-s1pr2-upregulates-tumoral-dpd-by-promoting-the-interaction-of-twist1-with-the-jmjd3-rna-pol-ii-complex-bound-to-the-dpyd-promoter>