Presentation Abstract

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Presentation Title: Using eicosapentaenoic acid to improve cetuximab sensitivity in KRAS mutants

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Abstract Body: It is known that epidermal growth factor receptor (EGFR) inhibitor, cetuximab, does not respond to cells with KRAS or BRAF mutations; therefore, a large proportion (more than 40%) of colorectal cancer patients are unable to receive this type of target therapy, and can only undergo surgical as a way of management. In this study, we aim to provide an alternative therapeutic strategy to KRAS or BRAF mutated neoplasms. Our previous studies have demonstrated that there may be better sensitivity to anti-EGFR antibody therapy in KRAS or BRAF mutants with increasing expression levels of miR-378. As known, miR-378 is embedded within PPARGC1b, which encodes PGC-1β, and could be stimulated by feeding lauric acid in cells. However, lauric acid is a type of saturated fatty acid, and therefore daily intake in humans is no recommended. Consequently, we tried to replace it with eicosapentaenoic acid (EPA or also eicosapentaenoic acid), an omega-3 unsaturated fatty acid that is FDA-approved. Following this, we modulated the expression level of miR-378 in KRAS or BRAF mutants by feeding EPA in vitro, and eventually revealed the mechanism of cancer cells remission that currently remains unknown. The western blotting and ELISA assay were performed to analyze the MAPK/ERK pathway and caspase pathway in three cell lines (SW480 and HCT116 with contain KRAS mutants, and HT29 with contain BRAF mutants), including cell lines before and after feeding with 40 μM concentration of EPA. All experiments were then compared to the wild type cells (caco2), the control cell line. The results showed higher expression of miR-378 in all types of mutated cells, except the wild type CRC cells. In addition, lower cancer cell survival rate was observed in cells that were given 0.2 μM of cetuximab treatment, especially in KRAS mutated cells as well as control wild type cells (p= 0.010–0.013). The total ERK1/2 protein in the KRAS mutant CRC cells
and wild type CRC cell showed lower expression levels after receiving 40 μM EPAee for 24 hours (p=0.022–0.035). A higher phosphorylated proteins status of ERK1/2 was also seen (p=0.006–0.047). However, the opposite result was noted in BRAF mutant cells. In cells further treated with anti-EGFR antibody for 48 hours, cell viability was significantly lowered in KRAS mutant and control wild type cells (p= 0.006–0.013), but there was no sensitivity of anti-EGFR antibody reaction to the EPA-fed BRAF mutant cell. The data demonstrated with EPA may indeed significantly induce the expression of miR-378, and further restored the sensitivity of anti-EGFR antibody in KRAS mutant cells. In conclusion, KRAS mutant cells may restore sensitivity to cetuximab after up-regulation of the miR-378 induced by EPA. This finding has offered a new alternative therapeutic solution for future patients suffering from KRAS mutated colorectal cancer.

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