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EFFECT ON COLORECTAL CANCER BIOENERGETICS BY CHRONIC EXPOSURE TO RED MEAT METABOLITES

Effect on colorectal cancer bioenergetics by chronic exposure to red meat metabolites

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Reprogrammed cell metabolism is one of the cancer hallmarks [1] and encompasses the Warburg effect, glutamine addiction, increased dependency on one-carbon metabolism and fatty acid oxidation, and metabolic symbioses between different cell types [2-6]. Factors influencing the nutrients and metabolites present in the tumor microenvironment include diet, microbial fermentation, and metabolic processes throughout the body. Red and processed meat consumption is correlated with an increased risk for colorectal cancer (CRC). We hypothesized that such a chronic dietary pattern may alter CRC cells' metabolic flexibility, i.e. the ability to switch between substrates, and/or plasticity, i.e. the ability to process substrates in a different way [7].

A chronic, subtoxic-dose experimental set-up using HCT116 spheroids was developed to provide insights in (i) the chronic effects of luminal exposure to red meat-derived metabolites, and (ii) the impact of the nutrient richness of the medium. Using extracellular flux analysis complemented by bulk mRNA sequencing, we demonstrated that the access to glucose, glutamine, pyruvate and/or butyrate dictates the metabolic profile of CRC spheroids. Moreover, the exposure to meat metabolites altered the responses to a shift in nutrient richness of the medium and to inhibition of specific substrate oxidation pathways, for example through changes in expression of substrate transporters and alternative metabolic pathways, and in intracellular substrate storage.

These results show that chronic exposure to dietary compounds affected the metabolic flexibility and/or plasticity of CRC spheroids, and stress the importance of the medium composition, choice of cell line, and time of exposure in nutritional or metabolic research.

References

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