SUMMARY

Metabolites such as lactate and free fatty acids (FFAs) abundantly occur in high concentrations in tumor and stromal cells of solid malignancies. Their known functions comprise the allocation of nutrients and intermediates for the generation of cell components, the evasion of immune destruction, the induction of vessel formation and the stimulation of cell migration in order to promote tumor growth, progression and metastasis. However, the role of metabolites as signaling molecules and the downstream mechanisms of metabolite receptor mediated signaling in tumor and stromal cells is poorly understood. Our study confirms the expression of Hydroxycarboxylic acid receptor 1 (HCA1) in solid human breast tumors and the expression of Free fatty acid receptor 4 (FFA4) in solid human colorectal tumors. In addition, the expression of HCA1 in human breast cancer cell lines as well as the expression of FFA4 in human colorectal cancer cell lines was proved. Moreover, our research reveals the expression HCA2, FFA2 and FFA4 in tumor associated macrophages (TAMs).

To test whether the loss of any of the metabolite receptors affects tumor growth and progression we utilized a syngeneic Lewis lung cancer (LLC1) tumor model, an azoxymethane (AOM) – dextran sulfate (DSS) colorectal cancer model and a Mouse mammary tumor virus Polyoma Virus middle T antigen (MMTV-PyMT) breast cancer model. The loss of HCA2 did not lead to a changed outcome compared to wild type littermates in any of the models. Likewise, the deletion of FFA4 had no influence on the LLC1 model and, surprisingly, tumor number and area in the AOM-DSS model also remained unaltered. The impact of HCA1 deficiency was investigated utilizing the MMTV-PyMT model and revealed a moderately improved tumor growth. The absence of FFA2 did not affect tumor growth in the LLC1 model but led to an increased number of colorectal tumors in the AOM-DSS model while the tumor area remained unchanged. The most compelling results were obtained upon the deletion of FFA2 in the MMTV-PyMT model. Here, we demonstrate that the loss of FFA2 significantly reduces tumor latency and also significantly improves tumor growth. Nevertheless, the formation of metastases in the LLC1 model and the MMTV-PyMT model did not show any changes upon the loss of any of the metabolite receptors.

Together, our results describe a tumor-protective effect of FFA2 with an unclear impact on metastatic processes. Considerations about putative mechanisms of short chain fatty acid (SCFA) mediated FFA2 signaling suggest potential targets for pharmacological interventions to treat mammary tumors.

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