Infinite Science Publishing

Role of glycolysis for intestinal inflammation and carcinogenesis

Jacob Hamm, Kenneth Klischies, Nina Sommer, Philip Rosenstiel, Felix Sommer*

Institut für Klinische Molekularbiologie, Christian-Albrechts-Universität zu Kiel, Germany

* *Corresponding author, email: f.sommer@ikmb.uni-kiel.de*

Keywords: glycolysis, hexokinase, inflammation, cancer, microbiota

Purpose/Objectives: Hexokinase (HK) catalyzes the first step of glycolysis and thereby determines the total glycolysis rate. HK and glycolysis are important for inflammation and carcinogenesis. Immune and cancer cells have elevated HK levels and an increased glycolysis rate to fuel their energetic demand. Inhibition of HK in cancer cells is protective. We showed previously that the microbiome modulates HK expression [1] and activity in intestinal epithelial cells (IECs). Now, we aim to test whether ablation of HK in the intestine protects from inflammation and colon cancer and whether modulation of HK through the microbiota could be a novel therapeutic option.

Materials/Methods: To that end, we generated HK-IEC mice lacking HK specifically in IECs and subjected them to experimental models of intestinal inflammation (dextran sulfate sodium, DSS) or colitis-associated carcinogenesis (azoxymethane-DSS, AOM-DSS). We also analysed the microbiome composition using 16S amplicon sequencing and transcriptional responses using RNA sequencing. We investigated the regulatory function of specific bacteria on HK using gnotobiotic mouse models and in vitro stimulation experiments. Finally, we investigated HK expression in patients with intestinal inflammation and colon cancer.

Results: HK-IEC mice showed reduced susceptibility to intestinal inflammation. Susceptibility to colitis-associated carcinogenesis is currently being evaluated. We identified specific bacteria and metabolites, which modulate HK expression. Finally, we found that HK is dysregulated during intestinal inflammation and in tumours of colon cancer patients.

Conclusion: Inhibition of epithelial glycolysis protects from acute intestinal inflammation and potentially colitis-associated carcinogenesis. Probiotic administration of HK-regulating bacteria or their modulation via prebiotics might serve as a novel non-invasive approach for inflammation and cancer therapy.

Reference

[1] Sommer, F., I. Nookaew, N. Sommer, P. Fogelstrand, and F. Backhed, Site-specific programming of the host epithelial transcriptome by the gut microbiota. Genome Biol, 2015. 16(1): p. 62.

Funded by Deutsche Forschungsgemeinschaft CRC1182 “Evolution and Function of Metaorganisms” and Excellence Cluster 306 “Inflammation at Interfaces”.