LOSS OF LOCAL HEPCIDIN DECREASES TUMORIGENESIS IN COLORECTAL CANCER

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The metabolism of macronutrients such as lipids, amino acids, and glucose are altered in cancers for efficient growth. These metabolic alterations in cancers are currently being exploited for novel therapies. However, very little is known about micronutrient metabolism in cancer. In many cancers, iron transport genes are dysregulated when compared to normal epithelium, particularly in colorectal cancer (CRC). Iron becomes sequestered in colorectal tumor tissue, leading to massive intratumoral iron stores. We have shown that colon tumors are addicted to high iron levels for growth. The master regulator of systemic iron metabolism is hepcidin, a small peptide hormone that is predominately synthesized and released by the liver. To control iron efflux and systemic iron load, hepcidin binds to the only known mammalian iron exporter, ferroportin, resulting in rapid internalization and degradation of ferroportin. Human epidemiological studies have shown a direct correlation between dietary iron intake and/or systemic iron levels and CRC risk. Despite this knowledge, the precise molecular role of iron metabolism in the pathogenesis of CRC remains largely unknown. The goal of this project is to investigate cellular iron metabolism in CRC in order to better understand how changes to iron metabolism drive the progression of CRC. An RT-qPCR analysis for iron metabolic genes in 10-paired human colorectal adenocarcinoma and normal epithelium samples revealed that the hepcidin transcript is one of the most robustly activated iron-related genes in human colorectal tumors. Kaplan-Meier survival analysis generated from 530 human CRC biopsies showed that high levels of intratumoral hepcidin expression portend a significant decrease in overall patient survival. An intestinal epithelial enrichment strategy demonstrated that tumor epithelial cells are a source for intratumoral hepcidin, data that aligns with a previous report. However, we have data to suggest that there are other intratumoral sources of hepcidin as well. The hepcidin target, ferroportin, was significantly decreased in tumor compared to adjacent normal tissues as assessed by IHC. To address the functional significance of hepcidin produced by tumor epithelium in CRC, mice deficient for the hepcidin gene specifically in colon epithelium were challenged in a sporadic model of CRC, which resulted in a significant decrease in tumor number, burden, and size compared to mice wild-type littermates. Hypoxia is a hallmark of the tumor microenvironment and a luciferase-based reporter construct of the hepcidin promoter demonstrated that hypoxia and its downstream transcription factor hypoxia inducible factors (HIFs) are sufficient to increase hepcidin promoter activity in colon-derived cell lines. HIFs regulate gene transcription by binding to HIF response elements (HRE) in the promoter of genes. Truncation of the hepcidin reporter construct to remove the HREs significantly dampened the responsiveness of the hepcidin promoter to hypoxia. Furthermore, a mouse model of sporadic CRC revealed that colonic HIF2α is essential for intratumoral hepcidin expression in vivo. These data suggest that the hypoxia-mediated induction of hepcidin in tumor epithelium may be one of the iron-dependent processes that are selected for by CRC cells, whereby intratumoral hepcidin might establish a paracrine and/or autocrine axis to degrade colonic ferroportin and thus sequester iron in colorectal tumors.