Impact of CD39 and purinergic signalling on the growth and metastasis of colorectal cancer

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Despite improvements in prevention and management of colorectal cancer (CRC), uncontrolled tumor growth with metastatic spread to distant organs remains an important clinical concern. Genetic deletion of CD39, the dominant vascular and immune cell ectonucleotidase, has been shown to delay tumor growth and blunt angiogenesis in mouse models of melanoma, lung and colonic malignancy. Here, we tested the influence of CD39 on CRC tumor progression and metastasis by investigating orthotopic transplanted and metastatic cancer models in wild-type BALB/c, human CD39 transgenic and CD39 deficient mice. We also investigated CD39 and P2 receptor expression patterns in human CRC biopsies. Murine CD39 was expressed by endothelium, stromal and mononuclear cells infiltrating the experimental MC-26 tumors. In the primary CRC model, volumes of tumors in the subserosa of the colon and/or rectum did not differ amongst the treatment groups at dayă10, albeit these tumors rarely metastasized to the liver. In the dissemination model, MC-26 cell line-derived hepatic metastases grew significantly faster in CD39 over-expressing transgenics, when compared to CD39 deficient mice. Murine P2Y2 was significantly elevated at both mRNA and protein levels, within the larger liver metastases obtained from CD39 transgenic mice where changes in P2X7 levels were also noted. In clinical samples, lower levels of CD39 mRNA in malignant CRC tissues appeared associated with longer duration of survival and could be linked to less invasive tumors. The modulatory effects of CD39 on tumor dissemination and differential levels of CD39, P2Y2 and P2X7 expression in tumors suggest involvement of purinergic signalling in these processes. Our studies also suggest potential roles for purinergic-based therapies in clinical CRC.
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