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**Revealing and harnessing CD39 for the treatment of colorectal cancer and liver metastases by engineered T-cells - Potenza A, Balestrieri C, Spiga M, et al.**

Potenza A, Balestrieri C, Spiga M, et al. [*Revealing and harnessing CD39 for the treatment of colorectal cancer and liver metastases by engineered T-cells*](https://gut.bmj.com/content/72/10/1887). Gut 2023; 72: 1887-1903. doi: 10.1136/gutjnl-2022-328042

The tumour microenvironment (TME) in colorectal cancer (CRC) exhibits a phenomenon termed immune exhaustion, in which despite persistent antigen stimulation, inhibitory receptor expression in tumour infiltrative lymphocytes (TILs) lead to suppression of a pro-inflammatory response. Understanding its mechanisms may help discover novel therapeutic targets.

In this study, Potenza et al., sampled healthy, peritumoral and tumoral areas of seventeen primary colorectal cancers (pCRC) were sampled RNA-sequencing, flow cytometry and immunostaining. Spatial transcriptional differences in inflammatory signalling, T-cell regulation, amongst other pathways, along with differential infiltration of T-cell subtypes in the TME of pCRC were evident. With cluster analysis, they showed that specific clusters of CD4+ (cluster of differentiation 4) and CD8+(cluster of differentiation 8) cells are enriched in peritumoral and tumoral areas expressing varying levels of inhibitory receptors. Using a similar experimental method, they compared their findings to TME of metastatic CRC (mCRC) to liver (n=48), sampling from peritumoral and tumoral areas. Transcriptional signatures from tumour infiltrative (TI) cells broadly mirrored pCRC results, highlighting T-cells as key players. Specifically, CD39 (Ectonucleoside triphosphate diphosphohydrolase 1) expression was increased in TILs (tumour-infiltrating lymphocytes) in pCRC and mCRC. To test the role of CD39 in CRC TILs, peripheral blood mononuclear cells derived T-cells re-engineered against HER2 (human epidermal growth factor receptor 2) receptor of patient-derived CRC organoids were generated, with and without functional CD39, using CRISPR-Cas9 (Clustered regularly interspaced palindromic repeats-CRISPR associated protein 9) gene editing. In both, an in vitro and in vivo mouse model, CD39 gene-disrupted T-cells exhibit greater anti-tumour activity.

In summary, Potenza et al., show that CD39 may have a role in T-cell based therapy in CRC and have managed to dissect the pathways within the TME of CRC.