Background

Intraepithelial lymphocytes (IELs), including $\gamma\delta$ and $\alpha\beta$ T cells (T-IELs) constantly survey and play a critical role in maintaining the gastrointestinal (GI) epithelium. Recent reports highlight a critical function for $\gamma\delta$ T-IELs in defense against colorectal carcinoma (CRC).1-3

Methods

Tumor biopsies from patients with stage III CRC were analysed by multiplex immunohistochemistry to investigate immune cell location and immune cell phenotypes were correlated with patient outcome data. We used mouse models, flow cytometry and single cell RNA sequencing to analyse T-IELs in different regions of the gastrointestinal tract. In addition, targeted deletion of transcriptional regulators in $\gamma\delta$ T-IELs was used to interrogate the function of $\gamma\delta$ T-IELs in controlling tumor growth.

Results

We show that cytotoxic molecules important for defense against cancer, were highly expressed by T-IELs in the small intestine. In contrast, abundance of colonic T-IELs was dependent on the microbiome, displayed higher expression of TCF-1/TCF7 and a reduced effector and cytotoxic profile, including low expression of granzymes. Targeted deletion of TCF-1 in $\gamma\delta$ T-IELs induced a unique T-IEL effector profile and reduced colon tumor formation in mice. Finally, TCF-1 expression was significantly reduced in $\gamma\delta$ T-IELs present in human CRCs compared to normal healthy colon, which strongly correlated with an enhanced $\gamma\delta$ T-IEL effector phenotype and improved patient survival.

Conclusions

Our findings highlight the exciting potential for exploiting colon-resident T cells subsets, including $\gamma\delta$ T-IELs in the development of new immunotherapy strategies to treat CRC.

REFERENCES


Ethics Approval

Use of human samples were approved by the Austin Health Human Ethics Committee (Heidelberg, Australia protocol H2013/050777). Informed consent was obtained from all patients. All mice used in accordance with Austin Health Animal Ethics Committee or the James Cook University Animal Ethics Committee, Australia.

Consent

None of the patient data in this abstract is identifiable.