Bacterial-tumor antigen cross reactive T-cells are enriched in tumors of newly diagnosed breast cancer patients

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BACKGROUND

The breast tumor immune microenvironment is characterized by a Type II signature which is an early event in breast cancer and portends more aggressive disease. We have previously demonstrated that bacteria-specific T-cells, derived from the gut, also recognize tumor antigens with which they share a high degree of homology at the level of Class II epitopes presented in MHC molecules. These peripheralized bacterial-tumor antigen cross reactive T-cells are tolerogenic, secrete high levels of IL-10 and, in mouse models, when adoptively transferred, traffic specifically to breast tumors and accelerate tumor growth.

We questioned if the Type II signature present in human breast cancer is due to these bacterial-tumor antigen (BAC-TA) cross reactive T-cells.

METHODS

Peripheral blood mononuclear cells (PBMC) and stool were collected from newly diagnosed, treatment naive breast cancer patients (n= 56) or volunteer aged matched donors (n=14). T-cells were expanded from previously identified BAC-TA epitopes that generated high IL-10 on an initial screen in PBMC. Tumor biopsies were collected from three patients at the time of surgery. Extracted DNA from the PBMC, T-cell lines and tumor biopsy was subjected to TCRb sequencing and metagenomic sequencing was performed on stool samples (Fig. 1).

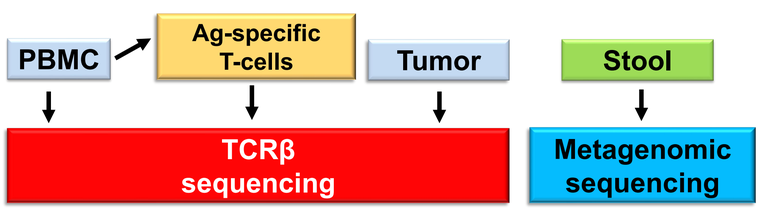

Figure 1. Graphic of samples and assays performed.

RESULTS

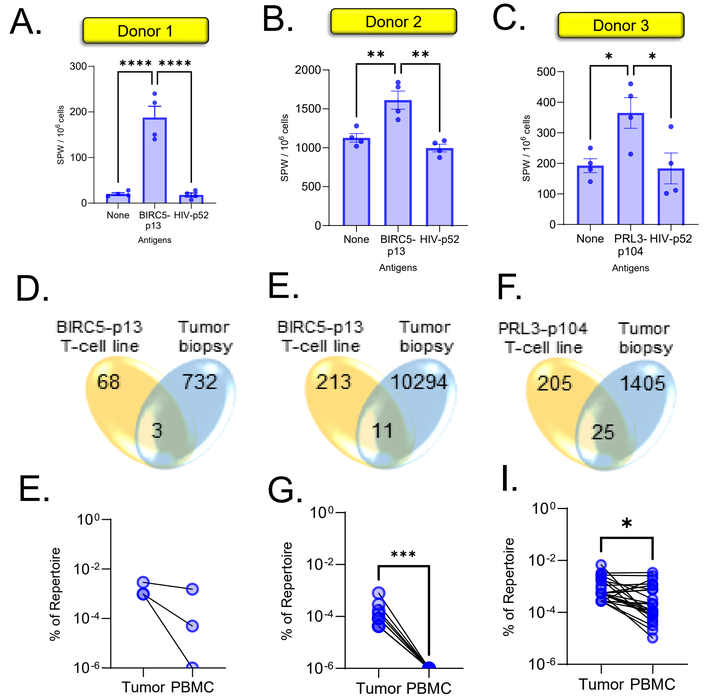

Figure 2. Bacterial-tumor antigen cross reactive-specific TCRβ are enriched in tumor biopsies of newly diagnosed breast cancer patients. Mean (±SD) IL-10 spots per well (SPW) for the indicated T-cell line from three donors (A-C). (D-F) Venn diagram for the number of TCRβ sequences in the antigen-specific T-cell line (orange) and corresponding tumor biopsy (blue). (E-I) Percent of the total TCRβ repertoire for the indicted tissue for each matching clone. *p<0.05, **p<0.01, ***p<0.001.

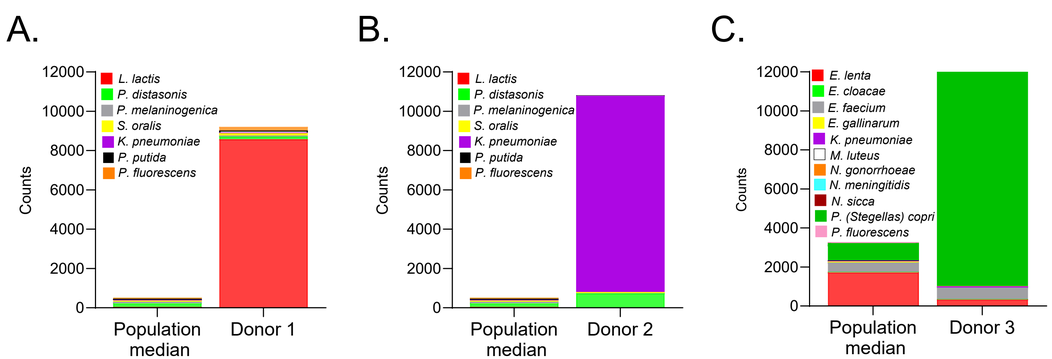

Figure 3. Bacteria with high homology to specific BAC-TA cross reactive epitopes are overrepresented in the microbiome of newly diagnosed breast cancer patients. Median bacteria counts from the stool of 52 newly diagnosed breast cancer patients and 14 volunteer donors (population median) and the exact bacterial count from the indicated donor. The bacteria species listed are >50% identical to (A, B) BIRC5-p13-27 or (C) PLR3-p104-118.

DISCUSSION

- IL-10-secreting BAC-TA T-cells can be identified infiltrating the tumor.
- Bacterial species with high homology to BAC-TA epitopes are enriched in the microbiome of the newly diagnosed breast cancer patients.
- IL-10 is a key immunosuppressive cytokine that plays a central role in dampening immune responses and maintaining immune homeostasis. IL-10 inhibits the production of pro-inflammatory cytokines such as TNF-α and IFN-γ and can limit antigen-presenting cell function, leading to the reduction of Th1, Th17 and cytotoxic CD8+ T-cell activation.

CONCLUSIONS

These data lay the foundation for a study that will follow newly diagnosed breast cancer patients correlating levels of BAC-TA cross reactive T-cells in blood with prognosis or response to therapy.

ACKNOWLEDGEMENTS

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