Prevalence of TIGIT expression in normal tissues, inflammation, and cancer.

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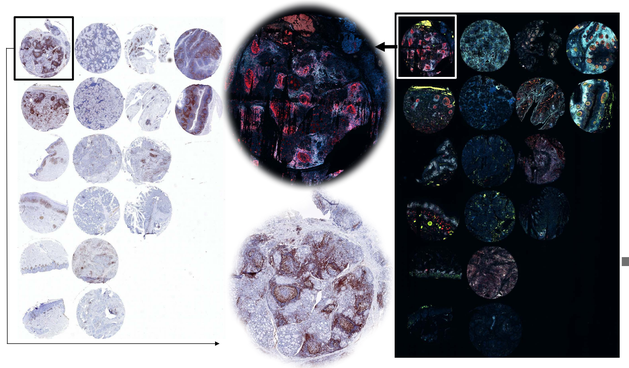
Introduction and Objectives

TIGIT (T-cell immunoreceptor with Ig and ITIM domains) is an immune checkpoint protein expressed on subsets of T lymphocytes. TIGIT inhibiting drugs are currently under developed. The purpose of this study was to investigate the patterns and levels of TIGIT expression in normal, inflamed and cancerous tissues.

Materials & Methods

Mouse monoclonal antibodies were used for immunohistochemical TIGIT (Dianova, Hamburg, Germany) and PD-1 (Abcam, Cambridge, UK, ab52587) analysis of formalin fixed paraffin embedded tissue sections from normal lymphatic tissues as well as selected inflammations and cancers. „Microenvironment (ME) TMAs“ were constructed from 4 mm tissue spots containing inflammation or cancer and adjacent areas of nomal tissue. Fluorescence images were taken and analyzed with a Leica Aperio Versa 8 automated microscope system equipped with Leica Image Scope analysis software.

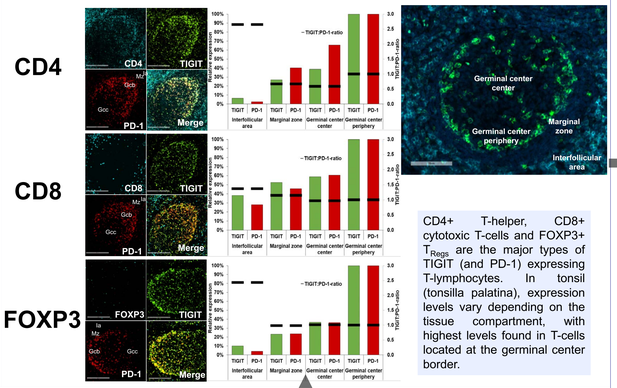
Microenvironment TMA



Example of a Microenvironment TMA constructed from 4 mm tissue spots of tonsil, synovialitis, Crohn's disease, sarcoidosis, Hashimoto thyroiditis, lichen sclerosis and skin eczema.

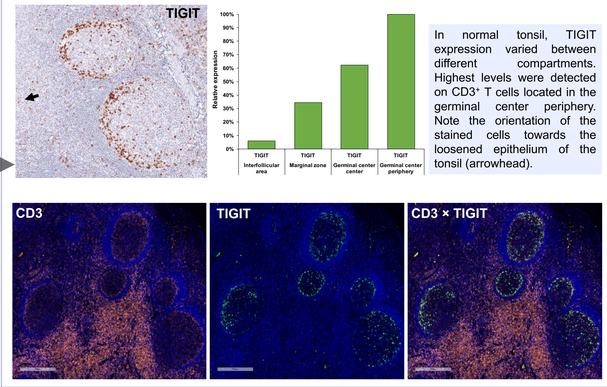
RESULTS

TIGIT expression parallels that of PD-1 in T-cell subtypes



CD4+ T-helper, CD8+ cytotoxic T-cells and FOXP3+ T_{Regs} are the major types of TIGIT (and PD-1) expressing T-lymphocytes. In tonsil (tonsilla palatina), expression levels vary depending on the tissue compartment, with highest levels found in T-cells located at the germinal center border.

Localization dependent TIGIT expression in normal tonsil

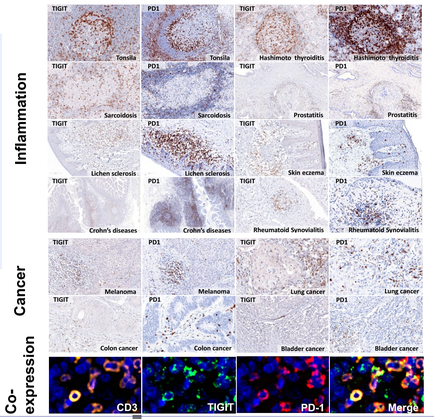


In normal tonsil, TIGIT expression varied between different compartments. Highest levels were detected on CD3⁺ T cells located in the germinal center periphery. Note the orientation of the stained cells towards the loosened epithelium of the tonsil (arrowhead).

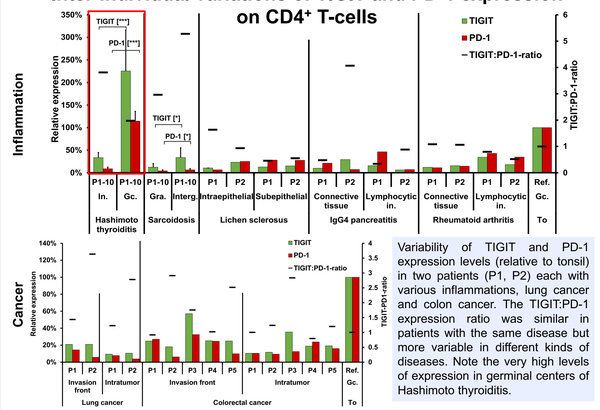
TIGIT is co-expressed with PD-1 in inflammation and cancer

Immunostaining using a novel commercial mouse anti-TIGIT primary antibody in routine formalin fixed paraffin embedded tissue samples from selected inflammations and cancers to evalutate compartment specific TIGIT and PD-1 expression levels.

Variable expression levels of both are apparent, with strongest expression in lymph follicles.

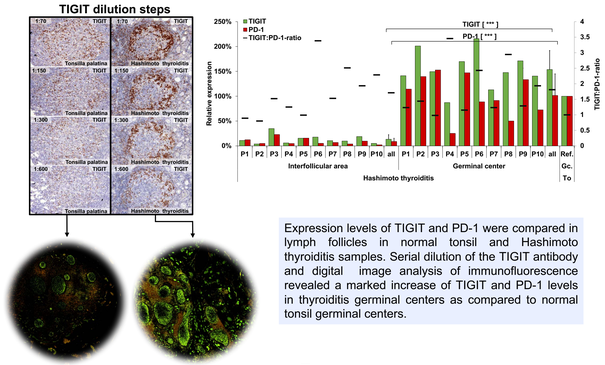


Inter-individual variations of TIGIT and PD-1 expression on CD4⁺ T-cells



Variability of TIGIT and PD-1 expression levels (relative to tonsil) in two patients (P1, P2) each with various inflammations, lung cancer and colon cancer. The TIGIT:PD-1 expression ratio was similar in patients with the same disease but more variable in different kinds of diseases. Note the very high levels of expression in germinal centers of Hashimoto thyroiditis.

Supramaximal upregulation of TIGIT and PD-1 in Hashimoto thyroiditis on CD4⁺ follicular T helper cells



Expression levels of TIGIT and PD-1 were compared in lymph follicles in normal tonsil and Hashimoto thyroiditis samples. Serial dilution of the TIGIT antibody and digital image analysis of immunofluorescence revealed a marked increase of TIGIT and PD-1 levels in thyroiditis germinal centers as compared to normal tonsil germinal centers.

Conclusions

- TIGIT expression is highly variable between histologically defined tissue compartments in normal lymphatic tissues, inflammatory conditions and cancers.
- Expression patterns of TIGIT resemble those of PD-1 in inflammatory tissues and cancers.
- Highest levels of TIGIT and PD-1 are found in follicular T-helper cells and in Hashimoto thyroiditis.
- TIGIT's frequent co-expression with PD-1 in cytotoxic T cells is consistent with TIGIT representing a clinically relevant druggable immune checkpoint regulator that potentially could be targeted in combination with PD-1.

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