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Gene expression in regulatory T cells.

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Keywords

Gene expression, regulatory T cells, tolerance, Th2.

Context

Regulatory T cells have been shown to be important in preventing the development of autoimmune disease in animal models. Their existence has been demonstrated in humans, and their role in autoimmune disease and transplantation tolerance is being studied. They are not yet well-defined phenotypically, although they appear to reside within the subset of $CD4^+$ T cells that also express CD25 constitutively. The identification of a unique marker for this population of cells would be a substantial advance. The aim of this research was to identify genes selectively expressed by regulatory T cells *in vitro* and *in vivo*, in order to provide markers to monitor the tolerant state and give indications of potential molecular mechanisms.

Significant findings

A range of T cell lines and clones specific for male antigen were generated. These included Th1 and Th2 lines, two *in vitro*-generated regulatory-type clones, and lines derived from tolerated male skin grafts (tolerance induced by anti-CD4 and CD8 monoclonal antibodies). Naturally occurring mouse spleen $CD4^+CD25^+$cells were also purified. RNA was extracted from both resting and activated cells, for subsequent SAGE (series analysis of gene expression) analysis. A proportion of identified markers were then further analysed using flow cytometry or quantitative reverse transcriptase-polymerase chain reaction (RT-PCR).

The main candidates from the SAGE data for known genes that may be associated with the regulatory T cell clone Tr1D1 and T_{skin} cell lines were ppENK, granzyme A, GM2 ganglioside activator protein (Gm2a), cystatin F, integrin ?7, OX40, glucocorticoid-induced TNFR [tumor necrosis factor receptor] superfamily member 18 (GITR), and the cytochrome P450 enzyme Cyp11a. Immunofluorescence

demonstrated that a proportion of the resting T_{reg} and T_{skin} cells were positive for a_E integrin (CD103) and that this was maintained after activation. Of note was that 20% of the spleen $CD4^+CD25^+$ population expressed a_E integrin. This marker has previously been associated with effector cell activity of $CD8^+$ intraepithelial cells in skin and gut, and of note is that a_E-deficient mice develop autoimmune-like inflammatory skin lesions when crossed to susceptible backgrounds. Taqman quantitative RT-PCR revealed that ppENK was highly expressed and further upregulated after activation on T_{reg}, T_{skin} and $CD4^+CD25^+$ spleen cells. ppENK is a member of the opioid family and is cleaved to active enkephalin peptides by proteases. It has been reported that met-enkephalin peptides can inhibit induced chemotaxis of TH1 cells through receptor desensitisation, which may suggest a possible mechanism of local T_{reg} action. GM2a was present at high levels in resting Th2, T_{reg}, and T_{skin} lines and $CD4^+CD25^+$ cells but was lost after CD3 stimulation.

Comments

This paper demonstrates some similarities between Th2 and T_{reg} cells, although certain Th2-expressed genes are lost (eg. GATA-3 and Egr-1). A number of genes expressed by Th2 cells are further upregulated in T_{reg} clones and T_{skin} lines, as well as in naturally occurring splenic $CD4^+CD25^+$ T cells. Although no specific markers for regulatory T cells were identified, some interesting molecules such as a_E integrin were highlighted. These *in vivo* and *in vitro*correlations begin to suggest potential surrogate markers for the tolerant state.

Methods

SAGE, flow cytometry, real-time quantitative RT-PCR.

Additional information

References

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