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$CD4^{+}CD28^{+}$ regulatory T cells in Sjogren's syndrome

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Keywords

CD4 T cells, CD28, regulatory T cells, Sjogrens syndrome

Context

SS is a chronic autoimmune exocrinopathy chiefly affecting the salivary and lachrymal glands. The authors have previously established a murine model for SS in NFS/sld mice thymectomised 3 days after birth. The a-fodrin protein was identified as an organ-specific autoantigen in salivary gland tissue. In this study the authors investigate a mechanism of active suppression mediated by regulatory T cells in their model of SS. The authors identify a novel population of regulatory T cells expressing CD28; this key co-stimulatory molecule is expressed on the T cell surface and interacts with ligands B7.1/B7.2 (CD80/86) expressed on the surface of antigen presenting cells (APCs). CD28 delivers the critical 'second signal' to T cells following ligation of the T cell receptor 'first signal'. A number of studies have demonstrated that CD28 co-stimulation of T cells is involved in development of collagen-induced arthritis and experimental autoimmune encephalomyelitis. To investigate active suppression mediated by regulatory T cells involved in autoantigen-specific inhibition of immune responses in a murine model of SS.

Significant findings

Spleen cells from SS mice showed significant autoantigen-specific proliferation in response to fodrin before disease onset, and T cells showed increased expression of activation markers. *In vitro* stimulated T cells from SS mice showed high levels of interleukin (IL)-4, but low IL-2 and interferon (IFN)-? production before disease onset. A subset of splenic $CD4^+$ T cells expressing low-level CD28; these were present only before disease onset and were $CD25^-$. Addition of anti-CD28 stimulatory antibodies inhibited the splenic T cell response to fodrin. Culture supernatants from unstimulated splenic T cells isolated before disease onset also inhibited proliferation to fodrin autoantigen. Similarly, neutralising antibodies to IL-4 and IL-10 blocked the T cell response to fodrin. As detected by RT-PCR, $CD4^+CD28^{low}$ T cells showed increased expression of IL-4, IL-10, IFN-? and transforming growth factor (TGF)-?. Intraperitoneal injection of $CD4^+CD28^{low}$ T cells into SS mice was effective in preventing autoimmune lesions, and resulted in decreased titres of autoantibody to fodrin. Splenic $CD4^+$

T cells from SS mice transferred with $CD28^{low}$T cells showed decreased expression of activation markers.

Comments

A number of studies have shown that autoreactive T cells frequently escape deletion in the thymus and are not tolerized in peripheral lymphoid tissues, but rather persist in the periphery in a state of unresponsiveness. A number of regulatory $CD4^+$ T cell subsets, which are believed to control the autoreactive T cells, have now been described by different groups. Here the authors thymectomise neonatal mice, a technique which is known to impair the migration of regulatory T cells to the periphery (see Additional information), in order to generate a murine model of Sjogren's syndrome (SS). They describe a population of autoantigen-specific peripheral regulatory T cells, identified by low-level CD28 expression. These cells emerge during the first 4 weeks of life and exhibit an immunoregulatory phenotype. The development of disease corresponds with their disappearance. This study raises interesting questions regarding how the $CD4^+CD28^{low}$ regulatory T cell subset emerges and why it ultimately fails.

Methods

The animal model for SS was established in NFS/sld mice thymectomised 3 days after birth (3d-Tx), in which autoimmune lesions develop at >4 weeks age. Histology was graded on the White and Cassarett scale. Flow cytometric analysis of cells was by standard protocols, as were proliferation assays performed with spleen cells cultured at 5×10^6 cells/well. Cytokine production was assayed by ELISA, intracellular FACS analysis or by RT-PCR. Cell transfer studies were carried out in 3d-Tx NFS/sld mice at 4 weeks of age ($n = 7$). $CD4^+CD28^{low}$ T cells were FACS-sorted from spleen and 5×10^6 cells transferred intraperitoneally in cell transfer experiments.

Additional information

Shevach EM: **Regulatory T cells in autoimmmunity.**

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References

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