Molecular Immunology 47 (2009) 28–36

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Regulatory T cells and ST2 signaling control diabetes induction with multiple low doses of streptozotocin

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ARTICLE INFO

Article history:
Received 16 December 2008
Accepted 21 December 2008
Available online 7 April 2009

Keywords:
Autoimmunity
CD25
Foxp3
IFN-γ
IL-17

ABSTRACT

Several peripheral mechanisms appear to be operational in limiting autoimmune damage of the islets of Langerhans and organ-specific T cell-mediated autoimmunity in general. These include cyclophosphamide sensitive T regulatory cells (Treg cells) and Th2 derived cytokine downregulation. We used the model of multiple low doses of streptozotocin (MLD-STZ) induced diabetes in susceptible C57BL/6 mice and resistant BALB/c mice to study these regulatory mechanisms. We show that low dose cyclophosphamide (CY) sensitive $CD4^+CD25^+FoxP3^+$ Treg cell-dependent mechanisms can be demonstrated in C57Bl/6 mice susceptible to MLD-STZ diabetes induction. CY pretreatment decreased $Foxp3^+$ cell count, glycemia, glycosuria and insulitis. In contrast, CY did not overcome resistance to diabetes induction in BALB/c mice. However, in BALB/c mice, deletion of ST2, an orphan member of the IL-1R family responsible for Th2 cell signaling leads to enhanced susceptibility to diabetes induction as evaluated by level of glycemia and glycosuria, number of infiltrating cells and β cell loss. RT-PCR analysis of mRNA transcripts of diabetogenic cytokines revealed that the expression of TNF-α, and IFN-γ was significantly enhanced in pancreatic lymph nodes by day 10 after diabetes induction in ST2-deficient mice in comparison with wild type BALB/c mice while IL-17 was detected only in $ST2^{-/-}$ mice by day 21. Our results are compatible with the notion that Treg cells are involved in MLD-STZ diabetes in susceptible mice and demonstrate that ST2-mediated signaling may also be involved in limiting Th1/Th17-mediated autoimmune pathology in diabetes resistant strain.

1. Introduction

For several years, the development of autoimmune chronic inflammatory diseases has been attributed to the activity of autoreactive $CD4^+$ T helper cells. T helper cells have until recently, been grouped into Th1 cells which produce interferon-γ (Mosmann et al., 1986; Abbas et al., 1996; McInnes and Schett, 2007) and Th2 cells which are characterized by IL-4, IL-5, IL-10 and IL-13 production (review in Lafaille, 1998). While the former has been implicated in multiple sclerosis, rheumatoid arthritis and type 1 diabetes (T1D) and their experimental models in mice and rats, the latter has generally been considered to be protective in these conditions (Fiorentino et al., 1989; Ria et al., 1998; Weiss et al., 2002). Only recently, another $CD4^+$ T helper cell subset has been recognized as an independent T cell lineage distinct from Th1 and Th2 cells. This Th17 subset of cells develops from naïve T cells under the combined influence of IL-6 and TGF-β (Veldhoen et al., 2006; Bettelli et al., 2006; Mangan et al., 2006), and the transcription factors, RORγt (Ivanov et al., 2006) and STAT3 (Yang et al., 2007; Laurence et al., 2007). IL-17, the product of Th17 cells has been shown to be important in the induction of organ-specific autoimmune diseases (Bettelli et al., 2007; Weaver et al., 2007). It has been demonstrated that a member of the IL-12 family cytokines, IL-23 promotes proliferation of IL-17-producing cells in the pool of activated memory cells (Aggarwal et al., 2003; Langrish et al., 2005) and is important for maintaining the Th17 phenotype (Veldhoen et al., 2006). Additionally, it has been argued that IFN-γ is inhibitory to IL-17 in experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (Cua et al., 2003). On the other hand, studies have also shown that autoimmunity can be mediated by distinct effector populations producing both IL-17 and IFN-γ (Kroenke et al., 2008). Finally, it has been demonstrated in an adoptive transfer model that an early influx of Th1 cells is indispensable for the development of EAE while Th17 cells only enhance the pathology

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doi:10.1016/j.molimm.2008.12.023