Frequency of Regulatory T-cells in Rheumatoid arthritis

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Abstract:

T regulatory cells (Tregs) are immune cells that have important role in regulation of immune responses and preventing autoimmunity, which is when the immune system attacks the body's tissues. In rheumatoid arthritis (RA), an autoimmune disease that affects the joints, evidence suggests that Tregs are dysfunctional or reduced in number, contributing to the disease. Tregs are responsible for suppressing the activity of other immune cells, including T cells and B cells, which are involved in the inflammatory response. In RA, Tregs are less able to suppress the activity of other immune cells, leading to increased inflammation in the joints. Research has also suggested fewer Tregs in RA patients' synovial fluid and tissues, indicating a reduced ability to control inflammation in affected joints. Additionally, it has been proposed that certain genetic factors may contribute to the dysfunction of Tregs in RA. The role of Tregs in RA is an area of active research, and targeting these cells may offer a new therapeutic approach to the disease. Strategies to enhance the activity of Tregs or increase their numbers, such as adoptive cell transfer or the use of immunomodulatory drugs, are currently being investigated as potential treatments for RA.

Key Words: Immune responses; Rheumatoid arthritis; Tregulatory cells; inflammation; immunomodulation

Introduction:

The geo epidemiological data suggests that many autoimmune diseases are i) global phenomena with more or less even distribution, ii) the risk factors which contribute to the development in individuals who are genetically predisposed to RA are lifestyle, environmental factors, socio-economic status, infectious agents, pollutants, etc. (Shapira et al., 2010). Rheumatoid arthritis (RA) is a systemic autoimmune, chronic inflammatory disease affecting 0.5-1% population worldwide (Silman and Pearson 2002). Females are three times more susceptible than males to developing RA. A distinct feature of RA is that, instead of destroying its target, the synovial joints, it stimulates the proliferation of synoviocytes in the early phase of the disease (Ladner et al., 2007). This gradually leads to the dysregulated inflammatory process in the joint's synovium, resulting in damage to both cartilaginous and bony components.

Intense inflammatory infiltrates cause swelling, pain, and ultimately distortion and disability of the joint. The Pathogenesis of RA is poorly understood. Recent research has suggested the involvement of genetic components in the disease. The fact that the inflammatory process in RA is chronic revealed that immune regulation in the joint is disturbed. This disturbed regulation may be due to excessive inflammatory response, possibly due to the involvement of genes resulting in a deficiency in the mechanisms that control the immune responses. It is considered that in the pathogenesis of RA, cellular and molecular mechanisms are involved, where the role of T-cell subsets is significant.

Development and functions of T-cells:

Lymphocytes, as T-cells, are produced from the common lymphoid progenitor, which migrates to the thymus after production in the bone marrow. In the thymus, a series of differentiation steps are responsible for producing significant populations of T-cells as T-helper cells (TH) and T-cytotoxic cells (TC). Among TH, the significant cells participating in immune reactions are TH1, TH2, TH17, and TREG. All these are CD4-positive cells. The first three are pro-inflammatory and significant players of an immune response. At the same time, Treg cells are heterogenous T cells that play an essential role in tissue homeostasis and maintaining self-tolerance (Wing & Sakaguchi, 2012). Treg has been shown to possess immunosuppressive activity. The Treg cells can suppress the auto-reactivity of activated T cells, maintaining the self-tolerance of the immune system.

Tregs are instrumental in limiting anti-pathogen immunity and persistence of hepatitis C infection or other infections such as malaria or mycobacterium by restricting effector T-cell activation by clonal anergy. At the same time, they are critical in controlling the onset of autoimmunity by maintaining self-tolerance. Due to their role in mediating self-tolerance, this review was directed towards the actual implications of T regulatory cells in rheumatoid arthritis- i) status of these cells in RA; ii) the properties of T regulatory cells.

T-regulatory cells:

There are various natural subsets of Tregs in the immune systems, such as nTregs, CD8+ Tregs, and natural killer-like T (NKT) cells, and induced Treg as Tr1 and Th3 regulatory cells. NKT cells are activated by induction with glycolipids and have the property of conventional T cells called NKT cells (Godfrey DI et al., 2000). These cells secrete various types of cytokines such as IL-2 and IFN-γ, secreted by Th1 and IL-4, and IL-10, those secreted by Th1 and Th2 cells (Kawano T, 1997; Spada FM, 1998).

In differentiation/origin, Treg cells are classified as nTreg (natural) and iTreg (induced) cells. The nTreg cells develop in the thymus while iTreg develops in the periphery from naïve T cells by stimulating antigens and secretion of various cytokines. About 5-10% of peripheral CD4+ Treg cells are found in humans and mice.

The most widely studied human nTregs are CD4 and CD25 (a-chain of IL-2R) positive, known to have an essential role in autoimmune pathology. Known earlier as suppressor T-cells (Gershon et al., 1972), these cells maintained self-tolerance in mice models (Asano et al., 1996; Sakaguchi et al., 1995; Wildin et al., 2001). Their transcription factor forkhead box P3 (Foxp3) was known to control and maintain the functionality of murine Treg (Khattri et al., 2003; Hori et al., 2003). In humans, immune dysregulation poly-endocrinopathy enteropathy X-linked (IPEX) syndrome has mutations in Foxp3 leading to autoimmunity.

These cells constitutively secrete several activation markers like glucocorticoid-induced TNFR (GITR) family-related protein, L-selectin, and cytotoxic T-lymphocyte antigen (CTLA4) (Birzele et al., 2011; Asano et al., 1996; Sakaguchi et al., 1995) have shown that 10% of CD4+ CD25+ cells were essential for maintaining self-tolerance in mice. However, identifying the CD25 marker on Treg cells for screening purposes is not very reliable because it is also produced by activated T cells. The other factor, Foxp3, is an intracellular protein that is difficult to screen. Despite controversies in selecting an appropriate marker-based method for effectively evaluating Treg cells, many studies have reported Treg cells in RA using combinations of Treg markers.

Frequency of Treg in RA:

Circulating Treg frequencies are shown to be decreased, increased, or unaffected in RA (Liu et al., 2004; Amelsfort et al., 2004; Ehrenstein et al., 2004; Mottonean et al., 2005; Nie et al., 2013). In well-managed RA, a normal frequency of Treg was found, but a lower frequency was shown in patients with early active RA (Cao et al., 2004).

Multiple studies in RA reported no defects in Treg cells while measuring CD4pos CD25pos cells (Amelsfort et al., 2004) reported a high frequency of CD4posCD25pos cells in RA. In a meta-analysis done by Morita et al., 2016, they found no statistically significant differences in the percentage of Tregs within CD4+T-cells in PB of RA patients compared to the control. However, many studies further reported a higher percentage of Tregs in control as discussed in Morita et al., 2016) while many others reported higher percentage in RA. Multiple studies in RA reported no defects in Tregs while measuring CD4pos, CD25pos/high cells (Amelsfort et al., 2004; Ehrenstein et al., 2004; Mottonean et al., 2005; Nie et al., 2013; Cao et al., 2004; Lawson et al., 2006; Putnam et al., 2005). However, these cells had limited ability to reduce the proliferation of autoreactive cells.

Fine analysis done by Morita et al. 2016, showed that when CD25high was used to define Treg cells, its proportion was significantly reduced in PB in RA subjects (REM-1.04; [-1.85 to 0.24; I2=84.2% p<0.0001). However, the studies which defined Treg cells by CD25pos and

CD127neg (Cribbs AP et al. 2014; Moradi B et al. 2014; Huang ZX. et al. 2009) (REM -0.23 [-1.01 to 0.54] or Foxp3 alone (Ji L et al., 2014; Furuzawa-Carballeda J et al. 2011; Loza MJ et al., 2011) (REM 0.72; [-0.72 to 2.16; I2=86.5%, p=0.0006) showed no significant difference in PB in RA patients versus control.

Whereas other reports showed normal (Walunas et al., 1994; Ehrenstein et al., 2004; Mottonean et al., 2005; Nie et al., 2013) levels or decreased frequency of Tregs after analyzing Foxp3 pos or CD127neg cells. Removing CD127POS cells help remove the activated effector T-cell contamination. In these studies, Cribbs et al. showed nTregs (presence of fully demethylated TSDR) whose activity was largely reduced.

However, when CD25-high (gating strategy was used to define Treg) were used, they were found to be Foxp3+ (cut off for defining CD25high was clear to eliminate naïve Tregs and non-Tregs) in PB. These were significantly reduced in RA patients as compared to the control. Thus, CD25+Foxp3+ double positive cell percentage was significantly lower in RA subjects than in control. There was a significant reduction of these in PB of RA patients (REM -1.03 [-1.42 to -0.63]), while their proportion was higher in synovial fluid of RA patients as compared to PB (Morita et al. 2016).

Conclusion: RA is an aggressive autoimmune disease, where regulatory aspects of immune system are severely compromised. The Tregulatory cells are reduced and thus lead to inflammation in the synovial joint. More studies are required to elucidate the role of immune cells in autoimmunity and RA to develop effective diagnostic and therapeutic targets.

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