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of the of the Concerned Biology 4 May Describe the mechanisms that contribute to the development of autoimmunity. How may the role of regulatory T cells be altered in patients suffering from autoimmunity? Mechanisms of autoimmunityNormally, immune system of the body is programmed to identify and attack foreign antigens and spare self tissues. This inbuilt mechanism is described as self tolerance. Autoimmunity is a disorder of the immune system when the self tolerance is abolished and immune system starts targeting self tissues. To understand the mechanism behind autoimmunity, it is imperative to understand the mechanism behind self tolerance. Immunological tolerance can be central or peripheral (Mitchell et al 2006). In central tolerance, immature T cells which recognise self tissues are destroyed in the thymus and similar B cells are destroyed in the bone marrow. Peripherally, mature lymphocytes which are autoreactive and escape developmental deletion in thymus and bone marrow, are either destroyed or inactivated by various methods such as anergy, clonal deletion by apoptosis and suppression by regulatory T cells (Mitchell et al 2006). Extensive research has been conducted in this field to understand the mechanisms that allow tolerance to be bypassed, allowing autoreactive lymphocytes to escape and thereby, contribute to the pathogenesis of autoimmunity. It has been demonstrated that a combination of genetic and environmental factors is responsible. The following mechanisms have been proposed: 1) Genetic factors – The role played by genetic factors in the development of autoimmunity can be easily explained by single gene disorders in which there is direct correlation between the genetic variant and

the disease, for example, gene for insulin in type 1 diabetes and AIRE (autoimmune regulator) in APS 1(autoimmune polyendocrine syndrome). In both these disorders, there is lack of thymic expression and autoreactive T cells escape tolerance. One more example is of foxp3 gene whose mutations leads to development of autoimmune disease by T regulator cell dysfunction. Also, Fas mutation causes autoimmune lymphoproliferative syndrome, as autoreactive T and B cells fail to undergo apoptosis. Thus, different mechanisms of anergy, T cell regulation and apoptosis of autoreactive lymphocytes appear to be involved here (Rioux & Abbas 2005). However, these single gene autoimmune disorders are infrequent and most commonly, autoimmune disorders are multi-genetic diseases. Sequence variations and single nucleotide polymorphism in genomic mapping have been found for diseases such as type 1 diabetes (genetic locus is in the major histocompatibility complex), Crohn’s disease, rheumatoid arthritis and SLE. These genetic variants determine the susceptibility of an individual to the development of an autoimmune disease mainly by T cell modulation (Rioux & Abbas 2005). Autoimmune disorders are predominantly seen in females. Mechanisms such as X- chromosome linked genetic susceptibility have been proposed as an explanation. 2) Environmental factors- External factors which have been correlated with the onset of some autoimmune diseases are infections. Infectious agents may have epitopes similar to those of body cells; hence, body cells are destroyed by a concept of molecular mimicry. Also, there may be upregulation of expression on antigen presenting cells (APCs) with infection. This can inactivate peripheral tolerance (Mitchell et al

2006). Regulatory T cells and autoimmunityRegulatory T cells may inactivate autoreactive T cells by two principle mechanisms. Either cytokines such as TGF-β and IL-10 may be used as effectors or a cytokine independent, contact-dependent mechanism may be used (Kronenberg & Rudensky 2005). The ability of regulatory T cells (Treg) to suppress responder T cells (Tresp) is largely dependent on the strength of the stimulus activating Tresp. A high degree of TCR signal strength and costimulation, and presence of growth promoting cytokines makes Tresp resistant to suppression by Treg. This is clearly evident in and probably forms the pathogenesis of an autoimmune disorder. As Tresp cells in inflammatory environment have a low threshold for activation, thus, self reactive Tresp cells can't be suppressed by Treg in autoimmune diseases. Additionally, it has also been shown that CD4-+CD25high Treg are functionally defective in many autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and type 1 diabetes. While HLA-DR+ Treg inhibit both proliferation and cytokine release in Tresp, HLA-DR- Treg, before inhibiting proliferation, causes release of cytokines in Tresp. Decreased foxp3 levels caused by a mutant gene have been demonstrated in patients with IPEX, which is an autoimmune disorder of endocrine organs. Further investigations exhibited that transcription factor foxp3 is important for the functioning of Treg. Consecutively, foxp3+CD25+CD4+ T cells have been termed as ' professional Treg' (Costantino et al 2008). Polymorphism of genes such as IL-2 and Cd25 has been seen in many autoimmune diseases and has been implicated in Treg dysfunction (Sakaguchi 2008). In vivo, CD25+CD4+ Treg TCRs have been determined to have specificity for self

peptide- MHC. This is a possible mechanism for breakdown in self tolerance (Kronenberg & Rudensky 2005). As experiments in mice have shown that depletion of a subset of T cells can lead to development of autoimmune diseases, it becomes clear that, in spite of other genetic and environmental factors playing a role in maintenance of self tolerance, Treg independently play a key role. These are, therefore, being targeted and investigated so that they can be exploited for clinical and therapeutic applicationReferencesCostantino, CM, Baecher-Allan, CM & Hafler, DA 2008, ' Human regulatory T cells and autoimmunity', European Journal of Immunology, vol. 38, pp. 921-24Kronenberg, M & Rudensky, A 2005, ' Regulation of immunity by self-reactive T cells', Nature, vol. 435, no. 2, pp. 598-604Mitchell, NR, Kumar, V, Abbas, AK & Fausto, N 2006, Pocket companion to Robbins and Cotran pathologic basis of disease, 7th edition, Saunders, Philadelphia, pp. 129-30 Rioux, JD & Abbas, AK 2005, ' Paths to understanding the genetic basis of autoimmune disease', Nature, vol. 435, no. 2, pp. 584-89Sakaguchi, S 2008, ' Regulatory T cells in the past and for the future', European Journal of Immunology, vol. 38, pp. 901