

proteasome inhibitor, was recently approved in the US and Canada for use in combination with lenalidomide and dexamethasone in patients with multiple myeloma who have received at least 1 prior therapy. The Keyhole limpet hemocyanin (KLH) model of T cell-dependent antigen response was used to determine if ixazomib depletes plasma cells resulting in a reduction of antibodies.

Methods Briefly, rats were immunised with KLH and Titer-Max adjuvant then treated with ixazomib twice weekly until study termination.

Results Treatment with ixazomib significantly inhibited anti-KLH antibodies by 34% ($p < 0.05$) versus vehicle. Additionally, KLH plasma cells quantified by ELISpot were decreased 78% ($p < 0.01$) in the spleen and 53% ($p < 0.01$) in the bone marrow compared to control. To gain some understanding of the selectivity of plasma cell depletion total White Blood Cells, Red Blood Cells (RBC) Platelets, Neutrophils, and total Lymphocytes were quantified with small a reduction only seen in RBCs and platelets.

Conclusions Ixazomib depleted plasma cells resulting in reduced antibodies suggesting further preclinical studies are warranted in diseases with pathogenic antibodies such as SLE, RA, SS and solid organ transplant rejection.

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ABSENCE OF HOST CD137 SIGNALLING CONVERTS CHRONIC GVHD TOWARD ACUTE GVHD

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Background and aims CD137 functions mainly as a costimulatory molecule for T cell activation. However, its functions have been found in a variety of other immune and nonimmune cells. Transfer of BM12 CD4⁺ T cells into unirradiated, MHC II-mismatched C57BL/6 mice induces lupus-like chronic GVHD, which occurs because donor CD4⁺ T cells break host B cell tolerance with help from host CD4⁺ T cells.

Methods cGVHD was induced by transferring 8×10^7 cells/mouse BM12 spleen/lymph node cells into C57BL/6 and CD137^{-/-} mice. Serum samples were collected 2 wk after disease induction and assayed by ELISA for IgG1 anti-DNA autoantibody. Mouse body weight measured two times a week. Splenocytes were harvested 10 days after disease induction. After counting the number of total spleen and analysed by flow cytometry. Pathological scores of colons and livers. Colons and livers were harvested 10 days after disease induction.

Results We found that chronic GVHD was inhibited when CD137^{-/-} mice were used as the host in this chronic GVHD model. Instead, they exhibited evident loss of body weight, indicating that they had acute GVHD. Indeed, their splenocytes were markedly depleted and they had severe intestinal and liver GVHD. Consistent with these phenotype changes, there were increased numbers of Th1 and Th17 cells but decreased numbers of Treg cells in the spleen of CD137^{-/-} recipient mice 10 days after disease induction.

Conclusions Our results indicate that host CD137 signalling is a key factor to determine the fate of donor CD4⁺ T cells during GVHD course.

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EXPRESSION OF LY6C/6G DEFINES A NOVEL AIRE-DEPENDENT SUBSET OF MEDULLARY THYMIC EPITHELIAL CELLS WITH TOLEROGENIC FUNCTION

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Medullary thymic epithelial cells (mTECs) are a heterogeneous population in terms of the spectrum of tissue-restricted Ags (TRAs) expressed from each cell for ensuring the elimination of autoreactive T-cells. Additionally, mTECs comprise cells at different developmental stages and/or in various activation conditions. Because of these heterogeneities, it is unclear whether mTECs are composed of any particular subsets possessing unique properties for their developmental pathway and/or immunological function. Here, we report a distinct mTEC subset characterised by expression of Ly6 family protein prior to and concomitant with Aire expression during its differentiation. Ly6C/6G⁺ mTECs, constituting 5%–15% of mature mTECs, were preferentially localised at the cortico-medullary junction, and expressed high levels of TRAs and thymocyte-attracting chemokines. Remarkably, Ly6C/6G⁺ mTECs were absent in Aire-deficient mice, suggesting that this subset requires Aire and/or Aire⁺ mTECs for its production. Uniquely, Ly6C/6G⁺ mTECs lack a post-Aire stage because of a tendency to die after Aire had been expressed. With a TCR-transgenic model in mice, we found that *in vivo* depletion of Ly6C/6G⁺ mTECs frequently induced organ-specific autoimmunity. We suggest that Ly6C/6G⁺ mTECs serve as an important source of TRAs for efficient cross-presentation during establishment of self-tolerance.

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INCREASED APOPTOSIS AND ABERRANT APOPTOSIS SIGNALLING PATHWAYS OF NATURAL CD4+CD25+FOXP3+ REGULATORY T CELLS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background and aims Systemic Lupus Erythematosus (SLE) is a prototype of autoimmune disease. Decreased cell numbers and suppressive defects of naturally occurring CD4⁺CD25⁺FOXP3⁺ regulatory T cells (Tregs) play an important role in the breakdown of SLE immune tolerance. We have previously observed significantly increased apoptosis of peripheral blood CD4⁺T cells in SLE patients. Our objective here was to detect the apoptosis of Tregs in SLE patients to see if it could contribute to reduced suppressive activity of Tregs, and further elucidate the genes and signalling pathways which trigger the apoptosis in these cells.

Methods The cell number and apoptosis rates of Tregs was respectively evaluated in SLE patients and normal controls (NCs) by FACS. The suppressive activity of Tregs was measured by coculture with CD4⁺CD25⁺CD127^{dim}/T cells. The relationship of abnormal Tregs apoptosis with clinical parameters was analysed by correlation analysis. Gene expression profiles of unstimulated Tregs from active SLE patients and NCs were generated by microarray analysis. Differential genes expression were verified by real time-PCR.