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CD137 signaling in regulatory dendritic cells is required for suppressing a systemic inflammation in the bm12-inducible model of systemic lupus erythematosus.

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Objectives: Although CD137 is well known as a costimulatory receptor in T cells, limited information is available for its immunoregulatory function. Here, we report that CD137 signaling maintains $CD11b^+$ regulatory dendritic cells (DCs) that can suppress activation of donor T_H1 and T_H17 $CD4^+$ T cells in chronic graft-versus-host disease (GVHD).

Methods: Chronic GVHD can be induced by mouse BMT models in which donor and recipient strain combination is MHC class I identical but MHC II mismatched. This chronic GVHD model recapitulates human SLE.

Results: The deletion of CD137 in recipient mice shifted the disease phenotype toward acute GVHD, which was caused by the activation of donor T cells. $CD137^{-/-}$ recipients had had characteristic changes associated with acute GVHD: 1) there were defects in differentiation of T follicular helper (T_{FH}) cells, germinal-center B cells, and plasma cells, and production of anti-DNA IgG_1 autoantibody; 2) their splenic DCs showed dysregulated expression of DC-specific transcription factors and pro-inflammatory genes, and 3) there were strong activation of donor T cells but decreased Treg cells in the $CD137^{-/-}$ recipient spleen. $CD11b^+$ splenic DCs stimulated with agnostic anti-CD137 antibody and CpG markedly increased expression of immunomodulatory genes, and such regulatory DCs inhibited acute GVHD in $CD137^{-/-}$ recipients. Their suppressive action was mediated through IL-10 that is indispensable for the induction and expansion of peripheral of Treg cells.

Conclusions: Our study identifies CD137 signaling in DCs as an important braking point to prevent systemic inflammation, and this control system may be considered as a therapeutic strategy for a variety of inflammatory and autoimmune diseases.