Expansion of BCL2+ lymphocytes in cutaneous graft-versus-host disease is associated with steroid resistance and poor prognosis

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Graft-versus-host disease (GVHD) remains a major cause of mortality and alloimmune hematopoietic stem cell transplantation (HSCT) and response to first-line therapy with glucocorticosteroids is often limited. To identify novel therapeutic targets for treatment of graft-versus-host disease (GVHD), we evaluated the mechanisms underlying the expansion of BCL2+ lymphocytes. Diffuse Expression Genes (DEG) analysis on sequentially isolated T cells of HSCT recipients. In recipients who later developed GVHD, we observed early up-regulation of the anti-apoptotic molecule BCL2, which is targeted in chronic lymphocytic leukaemia with a recently approved small molecule inhibitor. Furthermore, gastrointestinal tract, liver and skin affected by acute and chronic GVHD showed higher BCL2 mRNA expression compared to matched control groups. BCL2 protein levels were elevated in overall leukocytes and pathogenic cell subsets including CD4+ T lymphocytes in peripheral blood and skin of GVHD patients. Notably, high BCL2 expression levels correlated to steroid-refractory GVHD and increased transplant-related mortality. In vitro inhibition of BCL2 in allo-reactions led to dose-dependent apoptosis of T cells and increase of CD4/CD8 ratio. Our results highlight the role of BCL2 as survival factor for GVHD-mediated lymphocytes. Selective inhibition of BCL2 may present a novel and urgently needed targeted therapy in treatment of steroid-refractory GVHD.

Targeted Inhibition of complement at the basement-membrane zone in pemphigoid diseases

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Bullous pemphigoid (BP) and mucous membrane pemphigoid (MMP) are blistering skin diseases in which autoantibodies against basal keratinocyte antigens cause loss of cell-cell adhesion leading to the formation of large, largely uninfamed blisters. Using a newly developed in vitro model of BP and MMP, we report that dominant-negative inhibitors of the classical complement activation pathway, such as the 11A10 and 11A3 mAbs, markedly reduced blister formation in this model. In addition, we show that the dominant-negative factor D inhibitor, DAF (membrane cofactor protein), dose-dependently blocked blister formation. Furthermore, we report that the monoclonal antibody 11A10 blocks the expression of the coagulation factor Xa on keratinocytes, thereby reducing fibrin deposition and reducing blister formation.

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