Peripheral tolerance against autoreactive CD4+ T cells and CD8+ T cells is inactivated differentially by Foxp3+ regulatory T cells
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We further transferred OT II CD4+ T cells into Ivl-mOVA/Rag2KO mice, which lack both T and two-photon microscopy revealed that OT II CD4+ T cells proliferated in the skin draining nodes, while transferred OT II CD4+ T cells did not proliferate at all. We hypothesized that CD4+ T cells transfer were alive and did not manifest any skin lesions. Flow cytometric analysis showed that transferred OT I CD8+ T cells substantially expanded in the lymph nodes and infiltrated into the skin. Taken together, our study demonstrates that autoreactive CD4+ and CD8+ were handled in the periphery in different ways and that Tregs play an essential role in the induction of anergy to autoreactive CD4+ T cells.

Real-time in vivo imaging of CD8+ T cell-mediated keratinocyte apoptosis in a graft versus host disease-like murine model
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Graft-versus-host disease (GVHD) is an immunologic disorder mediated primarily by CD8+ T lymphocytes (CTLs) on epitope-nonspecific targets. However, the in vivo dynamics of keratinocyte (KC) apoptosis and KC-CTL interactions in GVHD is totally unknown. To address this, we performed intravital imaging of CD8+ T cell-mediated KC apoptosis using a novel GVHD-like model, in which membrane-bound chicken ovalbumin is expressed in KC under the control of involucrin promoter (h-mOVA). h-mOVA mice spontaneously exhibit cutaneous manifestations of GVHD-like disease both clinically and histologically after transfer of CD8+ T cells from OVA-specific T cell receptor transgenic OT-I mice. We crossed h-mOVA mice with T cell-deficient mice expressing a fluorescent protein that detects caspase activation (SCAT 3.1), an indicator of apoptosis, and subjected them to intravital two-photon microscopic analysis after the transfer of OT-I cells expressing TdTomato. We found that apoptotic KCs began to appear mainly around hair follicles, where CD8+ T cells colocalized. Time-lapse imaging revealed radial expansion of apoptotic KCs accompanied by an increase in number of CD8+ T cell infiltration. This was followed by eventual loss of activated caspase-3 signal at the completion of apoptosis and concomitant reduction in number of T cells. Image analysis showed that activated caspase-1 signals in KCs were characterized by 1) the spread to adjacent cell and 2) preceding direct contact with CD8+ T cells. Our study represents a novel model for visualisation of apoptosis in antigen-specific KC apoptosis and suggest the need for both KC-KC and T cell-KC interaction for spread of apoptosis signal.

Clinical Mechanism of Action of PRN1008, a Reversible Covalent Bruton’s Tyrosine Kinase Inhibitor in Clinical Development for Pemphigus
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BTK is expressed in B cells, innate immune cells such as macrophages, neutrophils and mast cells. Notably, both BTK and AEG-1 (aka kinase) are expressed in B cell receptor and Fc-receptors and is a promising therapeutic target for autoimmune. Unlike currently marketed BTGk, PRN1008 is a reversible covalent inhibitor designed and optimized to preferentially bind BTK versus other kinases sharing a homologous cysteine. This tailored covalent bond enables capable target occupancy with lower systemic exposures thereby reducing the potential for off-target toxicities. PRN1008 has shown rapid and durable anti-inflammatory effects in multiple animal models, via inhibition of B cell activation and blockage of antibody-mediated immune complex (ImC) activation via Fc receptor signaling blockade. In skin, PRN1008 significantly improved immune complex mediated inflammation and injury in an IgG antibody (FeR) driven acute arthus model in rats. PRN1008 inhibited mast cell activation in a murine cutaneous anaphylaxis model, supporting the potential for BTK in IgE antibody (FeR) mediated immune responses. In addition to neutralizing pathogenic antibody signaling, B cell studies demonstrated that BTK inhibition also blocked antibody-mediated immune complex-induced natural folateic, PRN1008 safely and rapidly controlled disease without corticosteroids. Overall, PRN1008 demonstrates three simultaneous MOA benefits that, combined, allow for a fast-acting and sustained response: rapid anti-inflammatory effects, neutralization of pathogenic autoantibody, and reduced antibody driven autoimmune diseases and is under investigation clinically.