

Early lymphocyte apoptosis and lymphopenia is responsible for CD8⁺ T cell dysfunction observed late after burn injury.

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Severe burn injury is associated with severe immune dysfunction. Rapid glucocorticoid-apoptosis of T cells in the thymus and periphery after injury forms part of the acute phase response (APR) leading to lymphopenia. We have recently observed in a mouse model of burn injury that murine T cell cycle progression increases in the periphery 14 days after burn. This time point was also associated with a burn-dependent enhancement of functional CD8⁺ T cell responses to antigen activation and accumulation of highly responsive “memory-like” CD8⁺CD44⁺CD25⁻CD62L^{hi}CD69⁻ T cells in the periphery. We hypothesized that this immune enhancement at day 14 after burn is indicative of increased T cell homeostatic proliferation. We tested this by injecting the glucocorticoid receptor inhibitor RU486 which blocks APR-induced apoptosis. Four groups of wildtype female B6 mice (n=10 per group; 1) 20% burn, 2) 20% burn + 3 daily s.c. injections of 40µg/kg RU486, 3) sham treated and 4) sham treated+RU486 treatments). Ablation of thymic apoptosis by RU486 treatment was confirmed by flow cytometry 24 hours after burn. Remaining mice were sacrificed 14 days after burn. Burn+RU486 treatment removed the hyper-proliferative responsiveness of T cells associated with burn injury at this time point compared to sham and sham+RU486 responses demonstrated by reduced IFN_γ cytokine secretion and proliferation to polyclonal stimulation. Early blockade of APR by RU486 also prevented the accumulation of peripheral CD8⁺CD44⁺CD25⁻ T cells. These data suggest that CD8⁺ T cell dysfunction after burn injury, presumably due to compensatory homeostatic proliferation, is prevented by blocking the early apoptotic events and ensuing lymphopenia.