Cutaneous barrier leakage and gut inflammation drive skin disease in Omenn Syndrome

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Patients with Omenn Syndrome (OS) suffer from early-onset inflammatory skin disease characterized by erythroderma, hyperkeratosis and massive dermal infiltration of oligoclonal activated T cells. Gut inflammation with prominent T cell infiltrates is also seen in OS. Peripheral blood CD45R0+ memory T cells from OS patients express the skin homing receptors Cutaneous Lymphocyte Associated Antigen (CLA) and CCR4 at high levels, and serum levels of CCL17 and CCL22 chemokines as well as LPS are elevated in OS patients. We employed the Rag2R229Q mouse model of OS to examine whether intestinal inflammation, dysbiosis and abnormalities of gut permeability contribute to the pathogenesis of skin disease. We found high frequencies of T cells co-expressing the skin- and gut-homing receptors CCR4 and CCR9 in the spleen, mesenteric and peripheral lymph nodes of mutant mice. Boosting colitis with chronic DSS treatment results in increased frequency of CCR4+ splenic T cells and worsening of skin inflammation in Rag2R229Q mice, as indicated by epidermal thickening, enhanced epithelial cell activation and dermal infiltration by Th1 effector T cells. Increase of cutaneous inflammatory response occurred also in response to systemic LPS. These results support the existence of a communication axis between gut and skin that can sustain skin inflammation in OS.