Background Pathogenesis of cutaneous lupus is unclear. Skin harbors at least three subsets of dendritic cells (DC): langerhans cells (LC) that reside in the epidermis, langerin-expressing dermal DC that reside in the dermis (LangdDC), and langerin-negative dermal DC. Skin also contains T cells including skin-resident T cells called dendritic epidermal T cells (DETC). Here, we investigated the roles of skin-DC subsets and DETCs in the pathogenesis of cutaneous lupus. To allow investigations into early events leading to cutaneous lupus, we used animal models.

Methods We used MRL-Fas+/+(MRL+/+) mice that develop lupus ~10 months of age and MRL-Fas/lpr (MRL-lpr) mice that develop lupus ~4 months. We applied fluorophores to the skin of these and MHCII-matched control mice to track in vivo migration of skin-DC to skin-draining lymph nodes. To be able to track skin-DC in steady state (without any external manipulation), we generated langerin-driven eGFP knock-in MRL+/+ and MRL-lpr mice by introducing the knock-in mutation from the stock B6 background (kindly provided by Bernard Malissen). We used in situ assays to identify potential sites of defect in skin-DC migration in lupus. We treated MRL mice with glycolipid GalCer that ameliorates cutaneous lupus and determined its effect on skin-DC migration, and investigated mechanisms of skin-DC migration using TCR/ and CD40 L/mice. Finally, to directly test the role of skin-DCs in cutaneous lupus, we used DTR knock-in MRL mice to conditionally deplete LC and/or LangdDC.

Results Lupus-prone mice exhibit reduced LC migration but increased LangdDC trafficking to skin-draining lymph nodes. Such altered migration of these two skin-DC subsets was corrected by GalCer treatment. However, GalCer did not increase LC migration through its well-known target iNKT cells but increased DETCs that were otherwise reduced in lupus mice compared to controls. DETCs increased LC migration in vitro. The role of DETCs in modulating LC migration was confirmed using mice. CD40L deficiency or antibody blockade abrogated the ability of DETCs to enhance LC migration. Finally, conditional ablation of LC worsened cutaneous lupus; this effect was abrogated when both LC and LangdDC were ablated together. LC depletion or GalCer treatment did not affect anti-DNA antibodies or lupus nephritis.

Conclusions Skin-DCs regulate the development of cutaneous lupus, but don’t affect systemic disease. Different skin-DC subsets play different roles in the pathogenesis of cutaneous lupus and are differentially regulated. Such specialized local regulation of autoimmune at the tissue level has implications for developing tissue-targeted therapies without affecting systemic immunity.

Funding Source(s): NIH RO1 AI080778