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ROLES OF SKIN-RESIDENT DENDRITIC CELLS AND T CELLS IN THE PATHOGENESIS OF CUTANEOUS LUPUS

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10.1136/lupus-2019-lsm.167

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/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 introgressing 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 differently regulated. Such specialized local regulation of autoimmunity at the tissue level has implications for developing tissue-targeted therapies without affecting systemic immunity.

Funding Source(s): NIH R01 AI080778

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RELATIVE BURDEN OF PREMATURE MORTALITY IN LUPUS

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10.1136/lupus-2019-lsm.168

Background Disease burden is the impact of a health problem on a given area, which can be used to set healthcare and research priorities and identify high-risk populations. Disease burden can be measured using a variety of indicators such as mortality, morbidity, disability, or financial cost. Analyses of 62,843 SLE deaths from the US-CDCs database showed that SLE-mortality remains high relative to general population mortality (Yen E, *et al. Ann Int Med* 2017). However, mortality rates may not adequately measure SLE burden, because among those who died, a fifth died before reaching 40 years. Premature mortality is an important way to quantify disease burden. In constructing a measure of premature death, an arbitrary limit to life is chosen, and the years of potential life lost (YPLL) is calculated.

Methods This is a population-based observational study. Death counts were obtained from the CDC-WONDER for 28 diseases, including SLE, top 15 CDCs leading causes-of-death, and 12 other autoimmune diseases. To calculate YPLL, each decedent's age at death from a specific disease was subtracted from a predetermined age of 75 years. The years of potential life lost were then added together to yield the total YPLL.

Results From 2000 through 2015, SLE was recorded as the cause of death in 28 411 women in the US. The ranking of SLE deaths relative to the CDCs official leading-causes-of-death in females showed that SLE is within the top 15 leading causes-of-death in reproductive age women (15–44 years) and tenth among women ages 15–24 years. YPLL for SLE was 304.2 thousand years in women ages 15–44 and 66.2 thousand years in women ages 15–24. SLE-YPLL ranked #14 in women ages 15–44, and #8 in women ages 15–24 above diabetes mellitus, HIV disease, septicemia, chronic lower respiratory disease, anemias, nephritis, and cerebrovascular disease. However, the NIH research funding for SLE is not commensurate with its relative premature mortality burden: NIH provided \$97 million for SLE research in comparison to \$1,084 million for diabetes mellitus and \$3,780 million for HIV in 2016. Among autoimmune diseases, SLE ranked #2 in women ages 15–44 years and #1 in women ages 15–24 years.

Conclusions SLE is among the leading causes of premature mortality burden in young women, underscoring SLE as an important public health issue. This warrants further studies on SLE disease burden, which can be used to develop and prioritize public health programs, assess performance of changes in SLE management, identify high-risk populations, and set research priorities and funding.

Funding Source(s): None

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CLINICAL AND LABORATORY FEATURES OF LATE-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS IN A CHINESE POPULATION

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10.1136/lupus-2019-lsm.169

Background Late-onset systemic lupus erythematosus (SLE) were defined as disease onset at or over the age of 50 years. Several groups have reported the differences between late-onset SLE and early-onset SLE. To further address these differences in Chinese population, we summarize the characteristics of clinical