The role of skin tissue in initiation of SLE

Antonios Psarras, Adewuonola Alase, Md Yuzaiful Md Yusof, Mohammed Shalbaf, Paul Emery, Miriam Wittmann, Edward MJ Vital

Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds
NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust

Background

Prior to a diagnosis of SLE there is an At Risk stage, characterised by ANA and elevated type I interferon (IFN-I) scores with either no symptoms or mild suggestive symptoms not meeting diagnostic criteria. We previously showed that clinical symptoms and routine immunology tests were not predictive of progression, but that an IFN score was strongly predictive[1]. We therefore evaluated the dysregulated production of IFN in this group. We first studied plasmacytoid dendritic cells, which are considered to be the dominant source of IFN-I in acute viral infections or stimulation of healthy blood. We found that these cells were exhausted in both established SLE and At Risk patients. Skin is the most commonly affected organ in SLE, may be infiltrated by immune cells, and keratinocytes and fibroblasts can also produce inflammatory mediators including interferons.

Objectives

To evaluate skin of At Risk individuals for production of IFN by either infiltrating immune cells or skin resident cells, compared to healthy individuals and SLE patients.

Methods

We obtained skin biopsies from lesional and non-lesional skin of SLE patients, SLE patients before and after UV provocation, sun-exposed non-lesional skin of At Risk individuals, and healthy controls. Previously validated scores of IFN-I stimulated genes were measured in whole skin biopsies and PBMCs using Taqman. IFN-alpha (*IFNA2*) and IFN-kappa (*IFNK*) mRNA in infiltrating lymphocytes, keratinocytes and dermal fibroblasts was evaluated using RNAScope in-situ hybridisation. Keratinocytes were cultured

Results

IFN Scores was increased in skin and blood of At Risk individuals compared to healthy controls but the fold difference in skin was markedly greater than in blood suggesting local IFN production. Fold difference (95% CI) was 29.5 (1.3 - 635.0) in skin and 2.2 (2.0 – 2.3) in PBMCs.

Skin biopsies from healthy controls with minimal IFN Score in blood showed no expression of either *IFNK* or *IFNA2.* In contrast, active skin lesions from SLE patients with high IFN Score demonstrated diffuse expression of *IFNK* in the epidermis. The epidermis of at-risk individuals with high IFN Score in blood was also characterized by diffuse expression of *IFNK*, but unlike SLE patients, there were no clinical or histopathological features of inflammation. Before UV provocation, a patient had low *IFNK* expression in the epidermis but a striking increase in expression after UV provocation. We detected *IFNA*2 expression in the dermis, but not in areas of lymphocyte infiltration.

We isolated human keratinocytes and dermal fibroblasts from healthy controls (n = 3), at-risk individuals (n = 5) and SLE patients (n = 5). Cells were cultured and triggered by TLR3 or RIG-I stimuli, Poly(I:C) (1 μg/mL) or Poly(dA:dT) (100 ng/ml) respectively, for 6 and 24 hours before the expression of *IFNK* was measured by qRT-PCR. At baseline, without exogenous stimulation, keratinocytes from both at-risk and SLE patients showed higher expression of *IFNK*; after stimulation with Poly(I:C) or Poly(dA:dT), the expression of *IFNK* was significantly increased.

Conclusions

At the At Risk stage, production of IFN-I, a key pathogenic process that predicts progression to SLE, is mediated by keratinocytes and not haematopoietic immune cells. This suggests that organs such as the skin are not merely passive targets for autoimmunity but play an active role in initiating disease.

[1] Md Yusof et al. ARD 2018.