Title

Type I interferon regulation in preclinical and established autoimmunity

Authors

Psarras A[1,2,4], Alase AA[1,2], Antanaviciute A[3], Carr IM[3], El-Sherbiny YM[1,2], Wittmann M[1,2], Emery P[1,2], Tsokos G[3], Vital EM[1,2]

[1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

[2]NIHR Leeds Musculoskeletal Biomedical Research Centre, Leeds Teaching Hospital NHS Trust, Leeds, UK

[3]Leeds Institute for Data Analytics, University of Leeds, Leeds, UK

[4]Division of Rheumatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA

Introduction

Type I interferons (IFN-I) –predominantly produced by plasmacytoid dendritic cells (pDCs)– are crucial mediators of antiviral immunity, but they have also recognised as key players in several autoimmune diseases including Systemic Lupus Erythematosus (SLE) and primary Sjogren's Syndrome (pSS). Although most of SLE patients are characterised by increased expression of interferon-stimulated genes (ISGs) transcripts in the peripheral blood, the source of IFN-I in autoimmunity still remains unclear.

Objectives

To investigate the role of pDCs and the dysregulation of IFN-I axis in at-risk individuals and patients with established autoimmune diseases

Methods

Patients with SLE and pSS were recruited according to the classification criteria as well as at-risk individuals (ANA +ive, 1-2 clinical symptoms, but did not fulfil criteria for any disease); age- and sex-matched healthy controls (HC) were also recruited. IFN-I activity was evaluated by measuring multiple ISGs in the PBMCs. pDCs were immunophenotyped and studied in vitro for their function to produce proinflammatory cytokines and to induce T cell responses using flow cytometry. pDCs from all groups were sorted and sequenced using high-sensitive RNA sequencing. IFN-I expression was visualised in skin biopsies using in situ hybridisation.

Results

Most of the SLE, pSS, at-risk patients had increased IFN-I activity, which was correlated with disease activity and clinical features. However, circulating pDCs were found to be low in numbers in all groups compared to HC and unable to produce IFN-a and TNF-a upon stimulation with TLR9 or TLR7 agonists. Moreover, SLE pDCs were characterised by increased telomeric erosion and they did not induce adequate T cell activation and proliferation compared to pDCs from HC. In situ hybridisation of skin biopsies revealed high expression of IFN-I in the epidermis but not in lymphocyte-infiltrating areas of SLE patients, whilst high expression of IFN-I was observed in skin biopsies of at-risk individuals without any signs of inflammation.

Conclusion

Although most at-risk individuals and patients with established autoimmune diseases (SLE, pSS) are characterised by increased IFN-I activity, their pDCs seem to be immune senescence; no production of IFN-a/TNF-a and inadequate induction of T cell responses. While pDCs appear dysfunctional, skin biopsies of SLE and at-risk patients present high expression of IFN-I. These data suggest that non-haematopoietic tissue resident cells such as keratinocytes –but not immune cells– can drive IFN-I-mediated immune responses and contribute in the initiation of human autoimmune disease.