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Drivers of the immunopathogenesis in systemic lupus erythematosus

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A B S T R A C T

This review summarises a number of current insights into the pathogenesis of SLE. On the basis of the interaction of environmental factors within a predisposed host, a chronic autoimmune process gains function with a positive feed-forward loop between innate and adaptive immunity. A current focus of SLE pathogenesis is on the enhanced production of certain cytokines, such as type I interferons and BLyS/BAFF, suggesting continuous plasmacytoid dendritic and myeloid cell activity together with disturbances of B lineage cells (increased autoantibodies, including anti-dsDNA and plasmablasts, which correlate with SLE activity and memory B-cell abnormalities). Recent studies provided evidence that $CD4^+$ and $CD8^+$ T cells and B cells are hyporesponsive in SLE, likely reflecting their 'post-activation status'. Data of enhanced protein tyrosine phosphatase activity of lymphocytes in SLE require consideration if they represent a disease characteristic. Better understanding of the chronic autoimmune phase is needed in addition to those phases during flares and will permit improved treatment of SLE.

Introduction

Systemic lupus erythematosus (SLE) is a prototypic, systemic autoimmune disease with a wide clinical spectrum that ranges from typical organ manifestations, such as joints, skin and kidneys to

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infrequent manifestations, e.g. shrinking lung syndrome [1]. The clinical heterogeneity of SLE is accompanied by complex disturbances in the immune system, with the hallmark of characteristic autoantibodies and an enhanced type I interferon (IFN) and B-cell activating factor (BAFF)/B lymphocyte stimulator (BlyS) system [2]. A number of alterations in SLE have been targeted in clinical trials in the last decade, but so far, only belimumab obtained FDA and EMA approval [3]. Owing to the various abnormalities in the innate and adaptive immune system, unspecific inhibition with NSAID, glucocorticoids, antimalarials, methotrexate, cyclophosphamide or mycophenolate mofetil remains the first choice to control lupus activity. Prior successes and failures of certain targeted therapies in SLE, however, have permitted deeper insights into the mechanisms of the disease. For example, as IFNs have pleiotropic effects on the immune system, anifrolumab, a monoclonal antibody against the IFN receptor, holds promise as another targeted immune therapy and is in advanced development followed by many other [3].

SLE pathogenesis can only be incompletely explained by a single cause, and it is believed that a complex interplay of environmental factors (e.g. sex hormones, UV light and smoking), genetic and epigenetic factors contributes to SLE pathology. The idea of a complex interplay of various factors led to the concept of an 'exposome' affecting healthy but genetically predisposed individuals [4] (Fig. 1). This concept has been addressed in Gene, Environment Association Studies [5] that will provide further insights in the interaction between host and environment.

Environmental risk factors

Environmental factors, such as exposure to silicates, smoking, UV light and certain medications; vitamin D deficiency; viral infections; and oestrogens are considered potential risk factors in the

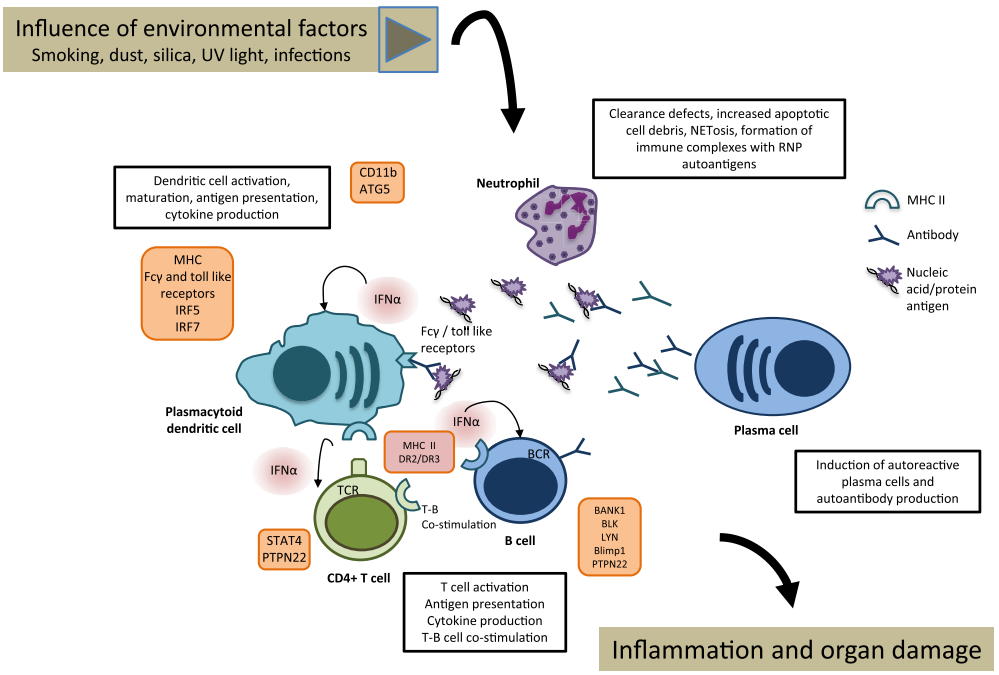

Fig. 1. Scheme of the potential positive forward loop in the pathogenesis of SLE (adapted from Ref. [2]). Certain environmental factors are able to induce immune activation in a predisposed host (relevant genetic risk factors of certain immune cells are shown). Upon activation, enhanced production of type I interferon and formation of immune complexes by anti-RNP autoantibodies (and other specificities) lead to continuous activation of a circuit and/or network of the depicted cells. As a result, chronic and acutely enhanced immune activation arrive at tissue and/or organ damage in SLE.

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