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Regulation of Lupus Nephritis by Stat3

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder often accompanied by nephritis, causing considerable morbidity and mortality [1,2]. Increased expression of type I Interferon (IFN) and interferon-inducible genes are frequently observed in cells from SLE patients and is associated with disease activity [3]. Activation of the interferon signaling molecules, Stat1 and Stat3, has also been reported in SLE [4,5]. Their activation levels correlated with many forms of glomerulonephritis. The reciprocal activation of these two transcription factors may have a major impact on renal inflammation. To study the role of Stat1 in a lupus model, we induced SLE-like chronic graft-versus-host disease (cGVHD) in Stat1-KO and in WT mice by intraperitoneal injection of class II-disparate bm12 splenocytes [6]. WT recipients of these alloreactive cells developed anti-dsDNA autoantibodies starting at week 2 as expected, with a decline after week 4. In contrast, Stat1-KO hosts exhibited a prolonged and significant increase of anti-dsDNA autoantibody responses compared to WT mice (week 4 to week 8). Increased autoantibody titers were accompanied by increased proteinuria and mortality in the cGVHD host mice lacking Stat1. Enhanced expression and activation of Stat3 were observed in the glomeruli of Stat1-KO host mice but not WT mice with cGVHD. Interactions between Stat1 and Stat3 thus appear to be crucial in determining the severity of lupus-like disease in the cGVHD model [6].

The interplay between Stat1 and Stat3 in this model of SLE may be important in determining the degree of target organ inflammation. Stat1 seems to regulate the activation of Stat3 in B cells and glomerular mesangial cells. Stat3 activation is crucial for diffuse B-cell activation. Stat3 expression in the kidney of Stat1-KO cGVHD mice also seems important in disease, probably via provoking inflammatory proliferation of cells. In our cGVHD model, expression of Stat3 in the mesangial cells of the Stat1-KO mice was associated with mesangial hyper-cellularity. Increased levels of IFN-γ in the glomeruli of Stat1-KO mice were associated with macrophage infiltration when cGVHD was induced [6]. Macrophage infiltration may cause further damage to the already inflamed kidney of cGVHD Stat1-KO mice.

Lupus nephritis is often treated with immunosuppression, which can cause deleterious side effects, including increased risk of severe infections and malignancy. There remains a major void in the successful management of lupus nephritis. Presently, various inhibitory strategies to block Stat signalling and function are being pursued. For example, MRL/lpr mice treated with the selective Jak2 inhibitor (AG490, which inhibits both Stat1 and Stat3) had significantly reduced proteinuria and improved renal function [7]. In this regard, inhibition of both Stat1 and Stat3 signalling may hold therapeutic potential for LN. Our studies emphasize that there are complex interactions between different Stats that need to be considered as Jak-directed therapy becomes broadly accepted, because of the wide variety of cells that express Stats and the interest in exploiting them becomes more and more tantalizing.

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