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Short Commentary

# Action of the Proteasome Activator REGγ in Autoimmune Diseases

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*# Equal contribution*

Systemic lupus erythematosus (SLE) is a common autoimmune disease with multiple systems and organs damaged [1]. Lupus Nephritis (LN) is one of the most serious complications in SLE and almost all SLE patients have varying degrees of renal lesions which directly affect the prognosis of SLE [2]. About 60% of SLE patients have LN, and 10%~30% of patients eventually develop renal failure [3]. The pathogenesis of SLE is complex and has yet to be clearly explained, resulting in a lack of effective targeted therapy in clinical practice.

Several studies have shown that $CD8^+$ T cells, Dendritic cells (DCs) and immunoproteasomes play crucial roles in autoimmune diseases. In SLE patients, the number of $CD8^+$ T cells are expanded [4,5] and the expression of costimulatory molecules CD40/CD86 on DC are increased [6,7]. Mice depleted the proteolytic β subunits of immunoproteasome LMP2, LMP7, or MECL1 have a significantly decrease in the generation of MHC class I ligands [8]. In contrast, depletion of $CD8^+$ T cells ameliorates symptoms in experimental autoimmune glomerulonephritis, experimental autoimmune myasthenia gravis and several rheumatoid arthritis (RA) models [5,9]. Inhibition of the immunoproteasome also ameliorates symptoms in SLE and RA models [10,11].

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The activity of the proteasome is drastically enhanced by three classes of proteasome activator complexes: 19S (or PA700), 11S (or PA28) and PA200 [12]. 11S proteasome activator, which contains three family members with molecular weight of 28kDa: REGα, REGβ and REGγ, is involved in ubiquitin- and ATP-independent protein degradation pathway [13,14]. While REGα and REGβ has been shown that control immunoproteasome to process antigens for MHC class I ligands presentation [15-18], the biological functions of REGγ in immune system has not been fully characterized. Until recently, Dr. Li's research group at East China Normal University has reported for the first time that REGγ plays a regulatory role in autoimmune diseases by inhibiting immunoproteasome [19]. This work, entitled "The proteasome activator REGγ counteracts immunoproteasome expression and autoimmunity", has been published in Journal of Autoimmunity.

In this article, the authors demonstrate that REGγ functions as an inhibitor of immunoproteasome using samples from REGγ-deficient mice and lupus nephritis patients. Mice lack of REGγ have elevated $CD8^+$ T cells, DCs, and develop age-related spontaneous autoimmune symptoms, which are exacerbated in the Pristane-induced lupus model. Mechanistically, REGγ interacts with phosphorylated STAT3 and leads to its degradation in an ubiquitin-independent manner, inhibiting the transcription of its downstream target genes LMP2/LMP7 and eventually attenuating MHC class I-restricted antigen presentation by DCs. Inhibition of STAT3 significantly diminishs LMP2/LMP7 expression and antigen presentation in $REG\gamma^{-/-}$ DCs, while treatment with STAT3 or LMP2/7 inhibitors results in less accumulation of immune complexes in kidneys from REGγ KO mice. In addition, the authors have revealed an inverse correlation between REGγ (low) and phosphorylated STAT3, LMP2, and LMP7 (high) in human Lupus Nephritis in clinical samples.

Recently, the same group has published a second report that REGγ-mediated regulation of DCs controls the differentiation of Th17 cell and the pathogenesis of experimental autoimmune disease [20], indicating again that REGγ deficiency is associated with autoimmune diseases. The function and mechanism of REGγ in other autoimmune diseases deserve further investigation.

Taken together, it has been shown for the first time that the proteasome activator REGγ is a new regulator for antigen presentation and autoimmunity. PR-957, a promising LMP7 specific inhibitor, has been validated in several autoimmune disease mice models [21,22], demonstrating importance of immunoproteasome in autoimmunity. The current results suggest that targeting REGγ-proteasome abnormalities, rather than direct intervention in systemic immunity, may be an important and feasible strategy for the treatment of LN, providing a new idea for targeted therapeutic options for LN.

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