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Mini Review

Failure of Tolerance to Autoimmunity, Systemic Lupus Erythematosus

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Abstract

Systemic Lupus Erythematosus (SLE), the well-known autoimmune disorder, is mostly denoted by the presence of auto-antibodies. The failure of tolerance to autoimmunity, body cell surface molecules and self-nuclear substances results in SLE. The etiology of disease is still not known but it is suspected that it is an inter relation between the environmental and genetic factors. The things which are observed in SLE patients are the hyperactivity of B cells; autoimmunity, the abnormal production and regulation of $CD4^+$ T cells. FOXP3, which is an important transcriptional Factor of Regulatory T cells (Tregs), thought to be involved in the dysregulation of T cell production and functional abilities. It is hypothesized that mutation in exon 2 of FOXP3 is involved in causing SLE.

Keywords: Systemic Lupus Erythematosus (SLE); Tregs: Regulatory T cells; FOXP3 gene; Tolerance failure; Autoimmunity; Auto-antibodies

Abbreviations

SLE: Systemic Lupus Erythematosus; Tregs: T regulatory cells; FOXP3: Fork Head Box P3; ANA: Anti-Nuclear Antibody

Introduction

Tolerance to autoimmunity, immunological tolerance, is the process of differentiating the self-antigens from non-self-antigens [1]. One of the significant mechanism of self-tolerance is exclusion of self-antigens. Deletion of body's self-antigen is done to prevent the autoimmune diseases [2]. The dysregulation of immune system causes autoimmune disorders. One of the deadly autoimmune disorder is Systemic Lupus Erythematosus (SLE). The etiological reasons of SLE are genetic factors having collaboration with environmental ones. The indications of the disease which have their role in maintenance and progression are have extreme variability. Genes have the major role in development of disease, environmental factors just stimulate them in the unlucky individuals. The mechanism of central tolerance followed by the peripheral tolerance control the autoimmunity in the body. These mechanisms prevent the exposure of self-antigens to body. Mutation in any of them results in establishment of autoimmunity [3]. Once the autoimmunity hits the individual, the leucocytes, chemokines and cytokines which have their initial role in the protection of body from invading foreign particles, produce inflammatory events in infected individual [4]. The disease is usually designated by the presence of autoantibodies in the body; high levels of ANA serum and abundance of B cell activation. Not only the B cells are involved in hyperactivity of immune system, but the T cells have the side by side role. Failure in the tolerance mechanism of T cells results in Systemic Lupus Erythematosus. The neutrophils role in SLE is significant. The pediatrics SLE is due to the exposure of nuclear content of neutrophils [5]. The occurrence rate of the disease is double or triple in Africans as compared to the Asians. The chances of occurrence are also high in the siblings and the 1st relative of patient with the respect to that of general population. [6].

FOXP3, (Forkhead box P3) the center of regulation of T cell production and progression, has a major role in causing autoimmune disorder. The body's immune homeostasis is regulated by the Tregs; $CD4^+CD25^+$ T cells. Almost 5-10% of Tregs is of $CD4^+$Tcells. These $CD4^+CD25^+$T cells of FOXP3 show suppressing behavior [2]. In T cell immunity, FOXP3 regulation is maintained to prevent the auto-aggressiveness of T-cells [7]. The dysregulation in the Regulatory T cells (Tregs) in FOXP3 inserts a risk to induce autoimmunity in body, leading towards autoimmune disorders like SLE [2]. In SLE, $CD4^+$ FOXP3 T cells expression suppresses the expression of $CD25^+$FOXP3 T-cells, the resultant phenotype observed is $CD4^+$ CD25- $FOXP3^+$ T cells [8]. Destruction of Tregs is the major indication of Lupus [5]. The epigenetic mechanism has the role in the methylation of $CD4^+$ DNA. The exact mechanism of it is still unknown [6].

The deletion of exon 2 of FOXP3 results in exhibition of failure of tolerance to autoimmunity, leading the development of notorious disease SLE in mouse [9]. The studies showed that an association is present between the FOXP3 and SLE in humans too. The Treg cells production seems to be very different in SLE patients, which exhibits a relation of FOXP3 with autoimmune disease; Lupus. The Exon 2 seems to be lie in the repression domain of FOXP3. Mutation in the Exon 2 might involve in the dysregulation of Tregs.

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