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Role of X Chromosome Encoded miRNAs in Autoimmunity

Anura Hewagama*

Department of Internal Medicine, Division of Rheumatology, University of Michigan, Suite 7C27, SPC 5422, 300 North Ingalls Building, Ann Arbor, MI 48109, USA

Introduction

Autoimmune disorders develop when the body's immune system mistakenly attacks and destroys its own healthy tissues. Autoimmunity is believed to develop when genetically predisposed individuals encounter environmental agents that trigger the disease. Environmentally-induced epigenetic changes and, in particular, altered patterns of DNA methylation, have been implicated as a mechanism by which environment–host interactions contribute to some forms of autoimmunity [1,2]. Systemic Lupus Erythematosus (SLE) is an autoimmune disease estimated to affect about 1.5 million Americans.

Women develop lupus more frequently than men. Presence of an extra copy X chromosome has been implicated as a contributing factor to the female predisposition [3,4]. In diploid cells, females have two copies of X chromosome and males have only one copy. To neutralize the gene dosage difference of the X chromosome between the genders, one of the two X chromosomes is inactivated in females, silencing the gene expression from inactive X (Xi). DNA methylation is one of the mechanisms that contribute to repressive chromatin modifications associated with specific silencing of the genes from Xi. Despite this chromosome-wide silencing, about 15% of X-linked genes escape X inactivation in women and are expressed biallelically [5]. Previous studies have shown that the X chromosome encoded immune active genes can escape silencing on Xi due to DNA demethylation and overexpressed in women compared with men [6]. Overexpression of immune active genes can cause T cell autoreactivity, a hallmark of lupus disease manifestation. However, the escape of inactivation by miRNA transcripts and their role in disease pathogenesis remains incompletely understood. MiRNAs are approximately 22 nucleotide-long, short RNA molecules, which act as post-transcriptional regulators that blocks protein synthesis. The balance between T cell activation and subsequent modulation is required to maintain proper T cell function. MiRNA mediated downregulation of negative regulators of T cell signaling pathways could contribute to the existence of persistently activated T cells in peripheral blood and the development of autoimmunity.

Normally, T cell activity is regulated by T Cell Receptor (TCR) signaling. Ubiquitylating enzymes facilitate ubiquitylation and subsequent degradation of TCR-mediated signaling molecules to attenuate T cell activity. Using bioinformatics tools, we predicted several X-chromosome encoded miRNAs that are upregulated in lupus T cells and will downregulate CBL. Evolutionary conserved CBL family ubiquitin ligases are key negative regulators of activated tyrosine kinase-coupled receptor signalling. They provide a critical mechanism in attenuating TCR-induced signals in order to ensure an appropriate immune response [7,8]. We have experimentally confirmed that CBL is down regulated by miR-98 and miR-188-3p in healthy CD4+ T cells. Decreased levels of CBL could prevent normal down regulation of TCR signaling. This can contribute to a persistently active T cell phenotype and, subsequently autoimmunity. In addition, several X-linked miRNAs over expressed in women with lupus are predicted to target Suppressors of Cytokine Signaling (SOCS)-family proteins. SOCS family proteins form part of a classical negative feedback system that regulates cytokine signal transduction [9]. MiRNA mediated down regulation of SOCS proteins may render cytokine imbalance associated with autoimmune diseases.

We are clearly in the very early stages of understanding how X -linked miRNAs contribute to distinct immune regulatory functions. Out of 1594 annotated human miRNA transcripts, the X chromosome is reported to encode 113 (~7% of total) miRNAs and remarkably, the Y chromosome is reported to encode only 2 (miRBase Release 19: August 2012, http://www.mirbase.org/). Overexpression of X-miRNA associated with escape of X inactivation could lead to unbalanced miRNA levels between sexes. Individual miRNAs can target multiple genes and multiple miRNAs can regulate a single gene. Targeting multiple immune genes can lead to greater gender differences in T cell function and autoimmune response. The identification of X linked miRNAs targeting ubiquitinating enzymes and the SOCS family of proteins may provide us a new arena for exploration of mechanisms for female-biased autoimmunity.

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***Corresponding author:** Anura Hewagama, Department of Internal Medicine, Division of Rheumatology, University of Michigan, Suite 7C27, SPC 5422, 300 North Ingalls Building, Ann Arbor, MI 48109, USA, E-mail: anurah@umich.edu

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