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Review Article

Prolactin and Breakdown of B-Cell Tolerance: Contribution to the Pathogenesis of Rheumatic Autoimmune Diseases

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ABSTRACT

Prolactin is a hormone with various immunomodulatory activities including induction of lymphocyte proliferation, cytokine production and antibody generation. Current literature provides undoubted evidence for the contribution of prolactin in the pathogenesis of rheumatic autoimmune diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and systemic sclerosis (SSc) and female female bias of autoimmunity. In the present mini-review, contribution of prolactin to the pathogenesis of autoimmunity through breakdown of B cell tolerance will be discussed.

Key Words: Prolactin; B cell tolerance; Rheumatic autoimmune diseases

PROLACTIN AND ITS IMMUNEREGULATORY EFFECTS

Prolactin is a glycoprotein which its dominant form consists of 198 amino acids with an approximate molecular weight of 22KDa [1]. The normal level of prolactin is different based on the various factors including age, gender, menstrual cycle phase and pregnancy [2-4]. Prolactin is well-known for its role in the milk production in women [5]. Besides its role as a hormone, prolactin affects immune cells and shows various immunomodulatory activities [6,7]. Interestingly, in addition to being generated by pituitary gland, prolactin is also produced by various immune cells particularly T lymphocytes demonstrating its role as an immune mediator which affects immune responses [8]. Upon binding to its receptor, prolactin initiates a signaling cascade consists of Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway including JAK-2 and STAT-1, 3 and 5 which ultimately leads to the alteration of gene expression [9, 10].

It has been shown prolactin contributes to lymphocyte proliferation, cytokine production and antibody generation [11-15]. Prolactin induced production of various inflammatory and immunostimulatory cytokines including tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 12 (IL-12) and interferon γ (IFN-γ) from immune cells [12, 13]. Prolactin also affects lymphocyte development in the primary lymphoid organs [15]. A more detailed review of the immunoregulaotry effects of prolactin has been written by Peeva, et al [6].

PROLACTIN AND RHEUMATIC AUTOIMMUNE DISEASES

Rheumatic autoimmune diseases including, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and systemic sclerosis (SS) are the connective tissue disorders in which the immune system attaches to its own tissues especially cartilage, joints and skin resulting in various degrees of the tissue and organ injury and dysfunction[16].

SLE is a chronic systemic autoimmune disease mostly affecting skin, joints, blood, kidney and nervous system.In SLE, autoantibodies against nuclear antigens such as anti-DNA antibodies form the immune complexes which deposit within the blood vessels and tissues, activate complement system leading to an inflammatory condition observed in the disease [17]. RA is a chronic inflammatory disease mainly affecting joints and can cause cartilage and bone destruction resulting in the disability occurs in the patients [18].

The disease is one of the most prevalent chronic inflammatory diseases with an incidence of 0.5% to 1% [18]. Autoantibodies including rheumatoid factor (RF) and anti-cyclic citrullinated

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peptides (anti-CCP) antibodies are detected in many of RA patients and associated with the more severe forms of the disease [18,19]. SSc is another connective tissue disease manifested by fibrosis of skin and other internal organs as well as vasculopathy [20].Classically, anti-centromere antibodies (ACA) and anti-topoisomerase I antibodies (anti-topo I) have been used to recognize SSc patients.

Identification of autoantibody type is helpful in both disease sub-grouping and prognosis identification. ACA are associated with the limited cutaneous involvement, isolated pulmonary hypertension and a better prognosis of the disease. On the other hand, anti-topo I antibodies are linked to the diffuse skin lesions, pulmonary fibrosis and a worse disease prognosis [21]. Other autoantibodies including anti-ribonucleoprotien polymerase antibodies (anti-RNAP), anti-Th/To antibodies (anti-Th/To), anti-PM-Scl antibodies (anti-PM-Scl) and anti-U3ribonucleoprotien antibodies (anti-U3RNP) are also detected in SSc patients [21].

Autoimmune diseases are more prevalent in females than male almost with female: male ratio of 3:1; however, some autoimmune diseases including SLE and SSc show more female bias (female: male ratio of 9:1) [22]. Various predisposing factors, including X chromosome genes, microbiome and female sex hormones have been proposed to be involved in the female bias of autoimmune diseases through affecting humoral and cell-mediated immunity [23,24].

Given the higher level of prolactin in females than males, a great number of the studies addressed the association of prolactin with the autoimmunity. Accordingly, the findings clearly demonstrated the contribution of prolactin in the pathogenesis of autoimmune diseases especially systemic lupus erythematous (SLE) which may provide a basis for the female bias of autoimmunity.

Results of a comprehensive meta-analysis showed SLE patients have significantly higher serum level of prolactin compared to the healthy individuals especially those patients from Asia and Europe countries [25]. Another meta-analysis showed positive correlation between prolactin level and the disease activity in European, Asian, and mixed populations [26]. In pregnant SLE women, the higher level of prolactin was associated with a poor outcome in pregnancy [27]. Consistently, prolactin level was positively correlated with the increased level of IgG and IgM antibodies and autoantibodies including anti-DNA antibodies [15].

Inhibition of prolactin secretion by Bromocriptine significantly improved the disease severityin both human SLE patients and animals of the experimental model accompanied with a decrease in IgG antibody and autoantibody levels [28,29].In RA patients, a comprehensive analysis of the studies showed a significantly higher level of serum prolactin in patients with RA than the healthy control group [30]. Accordingly, an association was reported between the serum and synovial fluid prolactin level and RA disease severity [31].

Interestingly, male patients with RA showed significantly higher level of serum prolactin level compared to those of males in control group. In these patients, the level of prolactin was significantly associated with the disease duration and laboratory features of the disease activity including C reactive protein (CRP) and RF [32]. Apart from prolactin level, Tang et al. detected significantly higher level of prolactin receptors on the synovial tissues from RA and psoriatic arthritis patients especially on macrophages, the main contributors to RA pathogenesis.

They found prolactin in cooperation with the other pro-inflammatory stimuli including CD40L and TNF-α can significantly activate macrophages [33]. In line with the above-mentioned findings, a number of the studies reported efficacy of bromocriptine administration on the disease course of RA patients and in the animal models of the disease providing another evidence in contribution of prolactin in RA pathogenesis [34].

Polymorphism studies showed the -1149G/T polymorphism in prolactin gene is associated with the susceptibility to RA [35]. SSc patients also had significantly higher level of serum prolactin level compared with the healthy individuals [36]. Moreover, the prolactin status was associated to the disease severity and duration [37].

Polymorphism study for prolactin -1149G/T polymorphism in SSc patients showed no significant difference compared with the healthy control group. However, an inverse correlation between -1149TT genotype with the disease onset after 45 years was detected suggesting this prolactin genotype might be associated with the higher risk of SSc onset in the older age [38].

Interestingly, analysis of prolactin production by SSc patients showed SSc lymphocytes produce higher prolactin level than lymphocytes from the healthy individuals suggesting SSc lymphocytes may contribute to the elevated level of prolactin in these patients and also might be the target of immunoregulatory activities of prolactin [39]. Altogether, these findings provide evidence in the contribution of prolactin in the pathogenesis of SLE, RA and SSc.

PROLACTIN AND BREAKDOWN OF B CELL TOLERANCE

Autoreactive B cells are eliminated or inactivated by central and peripheral tolerance mechanisms including receptor editing, deletion and anergy [40] . In receptor editing, immature B cells recognizing selfantigens with high avidity in the generative lymphoid organs produce a new light chain. Therefore, receptor editing process generates a B cell receptor (BCR) with new specificity resulting in the elimination of self-reactive B cells from lymphocyte repertoire. Failing in the receptor editing results in lymphocyte apoptosis (deletion). Recognition of self antigens with low affinity induces an unresponsive state in the immature lymphocytes (anergy). In central tolerance, mature B cells recognizing self antigens in the peripheral tissues become anergic or die by apoptosis [40].

In addition to the various immunostimulatory effects, recent studies have shown prolactin may contribute to autoimmunity through breakdown of B cell tolerance. Flores-Fernández et al. showed interaction of prolactin with its receptor on immature B cells including WEHI-231 B cell line and immature B cells from lupus prone MRL/lpr mice lead to the decreased apoptosis.

Consequently, self-reactive B cells rescued from cell death can be matured and survived contributing to the onset of autoimmune diseases. Mechanistically, decreased apoptosis was mediated through the increased level of anti-apoptotic proteins, B-cell lymphoma-extra large (Bcl-xL) protein, and the decreased level of pro-apoptotic proteins, BCL2 associated agonist of cell death (Bad) [41].

In another study, Ledesma-Soto et al, showed differential expression of prolactin receptors on B cells during various developmental stages including transitional (immature) and mature B cells with the higher level of prolactin receptors on transitional B (TB) cells. Besides, B cells in various developmental stages differentially affected by prolactin. Interestingly, transitional1 B (T1B) cells from MRL/lpr and MRL mice which are prone to SLE disease had higher level of prolactin receptors compared to C57BL/6 mice [42]. Accordingly, Legorreta-Haquetet al. showed B cells from lupus prone mice highly express prolactin receptors in their early development including pro-B cells and immature B cells stages. Analysis of baculoviral inhibitor of apoptosis repeat containing 5(BIRC5) (survivin), an anti-apoptotic protein involved in the progression of cell cycle and inhibition of apoptosis, showed increased expression in these immature cells. These results suggest increased expression of anti-apoptotic genes during early B cell developmental stages in response to prolactin led to escape of autoreactive B cells from tolerance mechanisms and consequent production of autoantibodies observed in SLE disease [43].

The similar findings were reported by Saha et al. They showed prolactin decreased apoptosis of T1B cell subset of TB cells upon engagement of BCR. Mechanistically, up-regulation of interferon-gamma receptor type II which mediates anti-apoptotic signaling in TB cells and down-regulation of transformation related protein 63 (Trp63), a pro-apoptotic protein, was observed. Furthermore, a dysregulation in receptor editing and altered threshold for activation of anergic B cells was detected suggesting prolactin contribution to the breakdown of B cell tolerance is not solely mediated by apoptosis disruption [44].

Contribution of prolactin in promotion of B cell autoreactivity was reported in another autoimmune disease, multiple sclerosis (MS) by Correale et al. Evaluation of prolactin level showed higher level of prolactin in MS patients in both remission and exacerbation stages of the disease. Prolactin decreased B cell threshold for activation and increased the number of autoreactive B cells secreting autoantibodies against *myelin oligodendrocyte glycoprotein* (MOG) which is a main autoantigen targeted by immune system in MS. The patients had higher level of B cell activating factor (BAFF) cytokine which its over-expression positively correlates with the risk of autoimmune diseases through increasing activation of B cells and antibody production [45].

In addition, an up regulated expression of B-cell lymphoma 2 (Bcl-2) expressions, an anti-apoptotic protein, and down-regulated expression of Trp63 was detected in B cells suggesting prolactin increases survival of auto reactive B cells. These results suggest that contribution of prolactin in promotion of B cell auto reactivity in MS patients is mediated through various mechanisms including activation of B cells, increased production of antibody and B cell survival [46]. Altogether, the obove-mentioned studies demonstrate implication of prolactin in the breakdown of B cell tolerance mechanisms including apoptosis, receptor editing and energy.

CONCLUSION

Current literature provides evidence for the contribution of prolactin in the pathogenesis of rheumatic autoimmune diseases including SLE, RA and SSc. In addition to its various immunostimulatory effects, prolactin may contribute to the pathogenesis of autoimmunity through breakdown of B cell tolerance mechanisms including apoptosis, receptor editing and anergy.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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