Heliyon 9 (2023) e16977

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Interference of B lymphocyte tolerance by prolactin in rheumatic autoimmune diseases

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ARTICLE INFO

Keywords:
Autoimmune disease
B lymphocyte
B lymphocyte tolerance
Prolactin
Rheumatic autoimmune disease
Tolerance

ABSTRACT

Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and systemic sclerosis (SSc) are the most common rheumatic autoimmune diseases/disorders (RADs) that affect autologous connective tissues as a result of the breakdown of the self-tolerance mechanisms of the immune system. Prolactin, a glycoprotein hormone, has been known for its crucial role in the pathogenesis of these rheumatic autoimmune diseases. In addition to regulating lymphocyte proliferation and antibody synthesis, prolactin is also responsible for regulating cytokine production. Moreover, it contributes to the breakdown of central and peripheral tolerance mechanisms of B lymphocytes. Given the crucial role of prolactin in the pathogenesis of the mentioned RADs, prolactin may contribute to their pathogenesis by the breakdown of tolerance. In the present study, the key role of prolactin to the breakdown of B lymphocyte tolerance and its possible implication for the pathogenesis of these diseases is discussed. Current literature supports prolactin's role in the breakdown of B lymphocyte central and peripheral tolerance mechanisms, such apoptosis, receptor editing, and also anergy. Therefore, prolactin may contribute to the pathogenesis of RADs by the breakdown of B lymphocyte tolerance. However, more investigations, particularly in RA and SSc animal models, are required to precisely address the pathologic role of prolactin.

1. Introduction to prolactin

Human prolactin gene is composed of ~10 kilobase (kb) nucleotides, including four introns and five exons [1]. The mature protein form of human prolactin has 199 amino acids (aa) and a molecular weight of ~23 kilodalton (kDa) [1]. The isolation of a 23 kDa full-length prolactin (PRL) and a 16 kDa N-terminal fragment of prolactin (16 K PRL) has been documented in the human species. The complete prolactin molecule has been found to promote the formation of new blood vessels, a process known as angiogenesis. Conversely, the 16 K PRL fragment exhibits notable antiangiogenic and vasoconstrictor properties. [1], which was later called vasoinhibin and was described with different and opposite effects to the familiar prolactin [2]. Complementary deoxyribonucleic acid (cDNA) of prolactin has been isolated from all vertebrates, as well as several species. Posttranslational modifications of PRL are composed of glycosylation, phosphorylation, and proteolytic cleavage [1].

Analysis of the secondary protein structure for prolactin demonstrates it folds into non-organized loop structures [3]. Efforts to investigate the tri-dimensional configuration of prolactin with current techniques such as x-ray crystallography and nuclear magnetic

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https://doi.org/10.1016/j.heliyon.2023.e16977
Received 12 August 2022; Received in revised form 5 May 2023; Accepted 2 June 2023
Available online 3 June 2023

List of abbreviations

Bad	BCL2 associated agonist of cell death
BAFF	B cell activating factor
Bcl-2	B-cell lymphoma 2
Bcl-xL	B-cell lymphoma-extra large
CCP	Cyclic citrullinated peptides
CD20	Cluster of differentiation 20
CD40L	CD40 ligand
CRP	C reactive protein
dsDNA	Double-stranded deoxyribonucleic acid
Fc	Fragment of crystallization
IFN-γ	Interferon gamma
IL-12	Interleukin 12
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
IL-8	Interleukin 8
JAK	Janus kinase
kb	Kilobase
kDa	Kilodalton
MOG	Myelin oligodendrocyte glycoprotein
MS	Multiple sclerosis
RA	Rheumatoid arthritis
RADs	Rheumatic autoimmune diseases
RF	Rheumatoid factor
SLE	Systemic lupus erythematosus
SSc	Systemic sclerosis
STAT	Signal transducer and activator of transcription
T1B	Transitional-1 B
Th	T helper
TNF-α	Tumor necrosis factor-alpha
Trp63	Transformation related protein 63

resonance (NMR) spectroscopy have yielded limited success thus far. However, with similarity of the structure and function between prolactin and growth hormone was partly solved using the homology modeling approach [4].

2. Prolactin signaling pathways

Upon binding of prolactin to its receptor, signaling is initiated. The PRL receptor, a member of the class I cytokine receptor family, has widespread expression across various tissues. Three active forms of the receptor, including short, intermediate, and long forms, have been explored [5]. Janus Kinase and Signal Transducer and Activator of Transcription (JAK/STAT) is the principal signaling pathway activated by prolactin-prolactin receptor interaction. Prolactin binding causes dimerization of the receptor and JAK2 activation, a kinase that is consistently associated with the PRL receptor [6]. The process of signal transduction in the prolactin receptor is facilitated by JAK2-mediated phosphorylation of multiple tyrosine residues, which in turn allows for the recruitment and binding of signal transducer and activator of transcription (STAT) proteins [7]. Thereafter, Tyrosine-phosphorylated STAT5 undergoes dissociation from the receptor, dimerization, and subsequent translocation into the nucleus. In the nucleus, STAT5 binds to the promoters of target genes and regulates gene transcription. Therefore, the JAK/STAT pathway is one of the main downstream signaling pathways for prolactin signaling. In addition, prolactin activates multiple antigenic peptide kinase (MAPK) pathways. This pathway activation is dependent on Src, a member of the Src family kinase (SFK), and Phosphoinositide 3-kinases (PI3-Kinase) [5].

3. Prolactin physiology and immune response

As a hormone, PRL is secreted by the pituitary gland and mainly contributes to the development of the mammary glands and milk production in women [8]. Its normal level varies in accordance with a multitude of factors, such as one's age, gender, phase of the menstrual cycle, and the state of pregnancy [9–11]. In addition to its esteemed function as a hormone, PRL affects immune cell functions and imposes immune-modulating effects as well [12,13]. It is noteworthy that PRL is generated by the immune cells, particularly T lymphocytes, highlighting its function as a cytokine mediating immunomodulatory effects [14].

PRL alters lymphocyte proliferation and contributes to antibody generation and cytokine production [15–19]. It also stimulates immune cells to produce pro-inflammatory cytokines, such as interleukin (IL)-1 beta (IL-1β), IL-6, IL-8, IL-12, tumor necrosis

factor-alpha (TNF-α), and interferon-gamma (IFN-γ) [16,17]. A detailed review of the literature on PRL immunomodulatory activities has been provided by Peeva et al. [12].

Besides the immunomodulatory activities, current literature provides evidence supporting prolactin's contribution to the breakdown of tolerance mechanisms of B lymphocytes [20–24]. On the other hand, the crucial role of PRL in the pathogenesis of several rheumatic autoimmune diseases (RADs), such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and systemic sclerosis (SSc) has been shown [19,25–34]. The current mini-review delves into the significance of PRL to the breakdown of B lymphocyte tolerance and its potential implications for the development of the three momentous rheumatic autoimmune diseases.

4. Prolactin and rheumatic autoimmune diseases

A rheumatic autoimmune disease, such as SLE, RA, and SSc, is an autoimmune disorder affecting the connective tissues in which the immune system reacts against autologous antigens in tissues and organs [35]. In autoimmune diseases, self-tolerance which is the unresponsive state of lymphocytes to autologous antigens is broken [36].

4.1. Prolactin and SLE

SLE is a chronic and systemic autoimmune disease that primarily targets the integumentary, musculoskeletal, hematopoietic, renal, and neurologic systems. Different autoantibodies are detected in SLE patients, including autoantibodies against double-stranded deoxyribonucleic acid (dsDNA), ribonucleoproteins, histones, and nucleolar antigens. Immune complexes formed from the binding of autoantibodies to autoantigens deposit in the vessels and consequently trigger activation of the complement system [37]. This is followed by an inflammatory response in the different organs manifested as glomerulonephritis, arthritis, and vasculitis [38]. While hemolytic anemia, thrombocytopenia, and leukopenia are caused by the autoantibodies directed against erythrocytes, platelets, and leukocytes. Recent advances in understanding fundamental roles of the autoantibodies and autoreactive B cells in SLE pathogenies have resulted in novel therapeutic approaches such as B lymphocyte depletion using anti-cluster of differentiation (CD) 20 (anti-CD20) and *anti*-B cell activating factor (*anti*-BAFF) antibodies. BAFF is a B cell survival and growth factor. Therefore, *anti*-BAFF targets B cell survival and growth [36].

The pathologic role of PRL in SLE has been well established. A comprehensive meta-analysis for assessing PRL levels in SLE patients demonstrates the serum level of PRL is significantly higher in SLE patients compared to healthy individuals, particularly in SLE patients from Asian and European countries [25]. Moreover, a positive correlation was identified between PRL level and disease activity/-severity in SLE patients [26]. A higher level of PRL in SLE pregnant women is also associated with a poorer outcome in the pregnancy [27]. In another study, PRL level was positively associated with an increased level of autoantibodies, including *anti*-dsDNA antibodies in SLE patients, suggesting PRL could contribute to SLE pathogenesis by increasing autoantibody production [19]. Accordingly, the administration of bromocriptine, which is known to inhibit PRL secretion, has been found to be significantly associated with a reduction in the disease severity and frequency of SLE flares in human SLE patients [39], and in lupus-prone mice that were accompanied by a reduced level of autoantibodies [40,41].

4.2. Prolactin and RA

RA is the most prevalent rheumatic autoimmune disease with a prevalence of 0.5%–1% [42]. The disease is a chronic autoimmune inflammatory disease affecting different body joints, including fingers, toes, wrists, shoulders, knees, and ankles. The disease is characterized by synovial inflammation and subsequent destruction of the cartilage and bone [42].

Although the pathologic role of cellular immunity, including $CD4^+$ T helper (Th)1 and Th17, has been well recognized in RA pathogenesis, autoantibodies such as rheumatoid factor (RF) that recognizes fragment of crystallization (Fc) region of self-IgG molecules, and the presence of anti-cyclic citrullinated peptides (*anti*-CCP) antibodies has been observed in the patients and has been linked to the severity of the disease [36,42,43]. CCP molecules are generated by the enzymatic conversion of self-arginine residues to citrulline residues (citrullination of self-proteins) under environmental factors, including smoking and infections. These are foreign for the immune system and stimulate the production of *anti*-CCP autoantibodies. These antibodies enter into the joint and bind to the joint proteins containing citrulline residues, causing tissue injury by the antibody-dependent effector mechanisms, including complement system activation, antibody-dependent cellular phagocytosis (ADCP), and antibody-dependent cellular cytotoxicity (ADCC) [44]. The net result is a local inflammatory response leading to the activation of synovial cells and progressive cartilage and bone destruction. Accordingly, B lymphocyte depletion using anti-CD20 antibodies has been proven to be effective in the treatment of RA patients [36, 43].

According to a meta-analysis, the serum level of PRL was significantly higher in RA patients compared to healthy individuals [28]. Furthermore, PRL levels in serum and synovial fluid were associated with the disease severity in RA patients [29]. Interestingly, according to Seriolo et al. study, PRL level is higher in male patients with RA in comparison with males in the healthy control group, and the PRL level is significantly associated with the disease duration. Laboratory findings, including C reactive protein (CRP), and rheumatoid factor (RF) levels, also verified that a significant correlation exists between the PRL level and disease activity [30]. Due to the lower prevalence of RA in males as compared to females, these findings indicate that elevated PRL may be associated with an increased susceptibility and/or the disease severity/duration of RA. Until now, a polymorphism in the PRL gene, −1149 G/T polymorphism, has been identified that is associated with RA susceptibility, suggesting particular gene variants of PRL could predispose to RA [45]. Besides the increase of PRL, an increase in PRL receptors on the synoviocytes and synovial cells, including macrophages from

RA and psoriatic arthritis patients, has been reported indicating the higher sensitivity of the target cells to PRL effects [46]. Moreover, PRL cooperates with the pro-inflammatory signals, TNF-α and CD40 ligand (CD40L), which exist in the inflamed joints and synergistically increase macrophage activation indicating the inflammatory microenvironment of the tissues synergistically intensifies pathologic effects of PRL [46]. As expected, bromocriptine administration could effectively improve the disease course in both human patients of RA and animals in the experimental model of RA disease [47].

4.3. Prolactin and SSc

SSc is a systemic autoimmune disorder affecting the connective tissues and small vessels characterized by fibrosis and vasculopathy in the skin, and internal organs, including the lungs, heart, and gastrointestinal system [48].

A wide range of autoantibodies are detected in SSc patients and are useful tools in the early diagnosis of the disease. Moreover, the association between the autoantibodies and the disease subtypes, prognosis, and clinical manifestations has been revealed, indicating the possible pathologic role of autoantibodies in the disease course (Table 1) [49,50]. A comprehensive review discussing these associations has been presented by Kayser et al. [49]. Autoantibodies, including *anti*-topoisomerase I antibodies (ATA), anti-centromere antibodies (CENP), and *anti*-RNA polymerase I, II, and III antibodies (*anti*-RNAP), are highly specific for SSc and added to the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for diagnosis and classification of SSc [51,52]. The other detected autoantibodies include *anti*-fibrillarin antibodies (*anti*-U3RNP), anti-Th/To antibodies, *anti*-U11/U12 RNP antibodies, *anti*-U1-RNP antibodies, anti-PM-Scl antibodies, *anti*-Ku antibodies, *anti*-Ro60/SS-A antibodies, *anti*-Ro52/TRIM21 antibodies, and anti-NOR 90 antibodies [49,53].

A meta-analysis of PRL serum levels in SSc patients revealed that PRL levels were elevated in the patients and were positively associated with the disease severity and duration [31,34]. Lymphocytes of SSc patients produce a higher amount of PRL compared to the lymphocytes from healthy individuals, implying that lymphocytes could be the possible source of excessive PRL found in SSc [32]. Polymorphism studies in SSc patients have revealed a negative association between −1149TT genotype with and the onset of the disease after the age of 45 suggesting that particular allelic variants of the PRL gene might affect the onset age of the disease [33]. Taken together, these findings provide primary evidence supporting the pathologic role of PRL in SSc.

5. Prolactin and breakdown of B lymphocyte tolerance

5.1. Tolerance of B lymphocytes and mechanisms

B lymphocytes express antigenic receptors by which they specifically recognize the target antigens. The receptors are generated during lymphocyte development in the generative lymphoid organ, bone marrow, by V(D)J recombination process. V(D)J recombination is a random DNA rearrangement process in which different gene segments localized in the receptor locus, including variable (V), diversity (D), and joining (J) gene segments are recombined (Fig. 1). The rearranged V(D)J exon encodes the variable region of the antigenic receptor that is responsible for the specific recognition of the target antigen by the corresponding B lymphocyte [36]. Although V(D)J recombination ensures the generation of a diverse repertoire of B lymphocyte clones, enabling humoral immunity

Table 1
Association of autoantibodies detected in SSc with the disease subtypes, prognosis, and clinical manifestations.

Autoantibody	SSc subtype	Prognosis	Clinical manifestation
Anti-centromere antibodies (CENP)	Limited cutaneous SSc	Good	Pulmonary arterial hypertension (PAH)
Anti-topoisomerase I antibodies (ATA)	Diffuse cutaneous SSc	Poor	Lung fibrosis Cardiac involvement
Anti-RNA polymerase I, II and III antibodies (*anti*-RNAP)	Diffuse cutaneous SSc	Poor	Sclerodermarenal crisis (SRC) PAH Tendon friction rubs and contractures Synovitis
Anti Th/To antibodies	Limited cutaneous SSc	Poor	Lung fibrosis SRC
Anti-fibrillarin antibodies (*anti*-U3RNP)	Diffuse cutaneous SSc	Poor	SRC Cardiac involvement
Anti-PM-Scl antibodies	Limited cutaneous SSc	Good	Raynaud's phenomenon Myalgia or myositis Joints contractures Calcinosis Sjogren syndrome
Anti-U1-RNP antibodies	Limited cutaneous SSc	Good	Raynaud's phenomenon Puffy fingers Mixed connective tissue disease (MCTD)
Anti-U11/U12 RNP antibodies	–	Poor	Raynaud's phenomenon Gastrointestinal involvement Lung fibrosis

PAH: Pulmonary arterial hypertension; SSc: systemic sclerosis; SRC: scleroderma renal crisis.

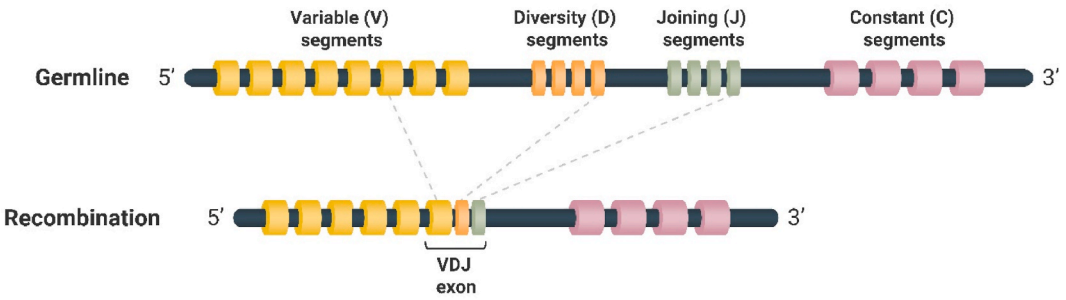

Fig. 1. A schematic representation of V(D)J recombination process for the generation of V(D)J exon. During the V(D)J recombination process, one V gene segment, one D gene segment (if it exists in the gene locus), and one J gene segment are randomly selected and rearranged to form a V(D)J exon. The rearranged V(D)J exon encodes the variable region of the antigenic receptor in B lymphocyte. D: diversity; J: joining; V: variable.

specifically recognizes a wide range of antigens, some developing B cells may express the receptors capable of recognizing self-antigens. Since the V(D)J recombination is a random process, hence the generated receptors might be autoreactive [36].

The elimination or inactivation of autoreactive B cells is a crucial aspect of maintaining immune tolerance. This process is governed by a combination of central and peripheral tolerance mechanisms, which include receptor editing, deletion or apoptosis, and anergy state (Fig. 2A) [36]. In the receptor editing, a developing B cell that recognizes a self-antigen with high avidity in the bone marrow generates a new antigenic receptor by inducing a new DNA rearrangement in the light chain of the receptor. This allows the lymphocyte to express a receptor with a different specificity that is not self-reactive. Failure of the receptor editing process in the developing lymphocyte may lead to lymphocyte death, called apoptosis. Developing lymphocytes that recognize self-antigens with low avidity undergo anergy, which is an unresponsive state of the lymphocytes to self-antigens (Fig. 2A). On the other hand, peripheral tolerance mechanisms, including anergy, deletion, and engagement of inhibitory receptors, lead to the elimination or inactivation of mature autoreactive B lymphocytes recognizing autoantigens present in non-generative lymphoid organs (the periphery). Herein, mature autoreactive B lymphocytes become anergic or die by apoptosis upon recognition of self-antigens (Fig. 2B) [36].

5.2. *Breakdown of B lymphocyte tolerance by prolactin*

Besides its immunomodulatory activities, PRL contributes to the breakdown of B lymphocyte tolerance and consequently might be involved in the pathogenesis of autoimmune diseases (Fig. 2).

It has been shown B lymphocytes in different developmental stages are differentially affected by PRL, so that the developing lymphocytes are more sensitized to the PRL effects. Correspondingly, the developing B lymphocytes, transitional-1 B (T1B) cells, express a higher number of PRL receptors on their surfaces compared to the mature lymphocytes. More interestingly, T1B cells derived

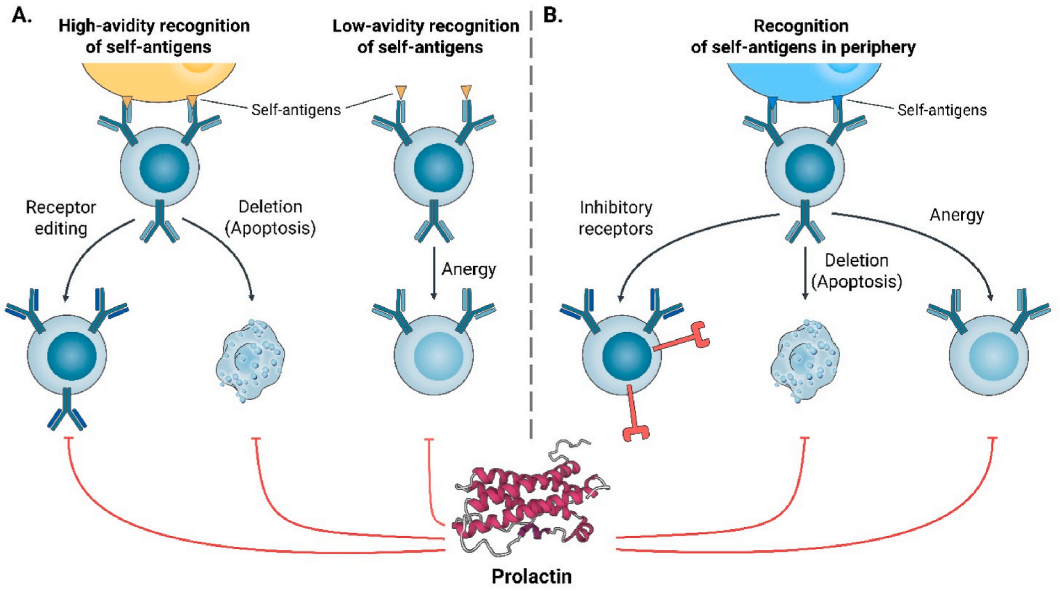

Fig. 2. Tolerance mechanisms of B lymphocytes and their breakdown by prolactin. A. Central tolerance mechanisms of B lymphocytes B. Peripheral tolerance mechanisms of B lymphocytes.

from MRL/lpr and MRL mice, the animal models of SLE, exhibit a significantly higher expression of PRL receptors compared to the cells from C57BL/6 mice that are not susceptible to SLE [20]. Accordingly, hyperprolactinemia induced an increase in the number of the developing B lymphocytes, but not the mature ones in the lupus-prone mice and caused the acceleration of the disease onset [20]. Therefore, the developing B lymphocytes from lupus-prone animals are more sensitive to the PRL effect, which might be due to the higher number of PRL receptors expressed on the developing lymphocytes compared to the mature ones. A similar finding was detected by Legorreta-Haquetet al., and the developing B cells, including immature B cells and pro-B cells from lupus-prone mice, had a higher level of PRL receptors. The developing B cells upregulated the level of an anti-apoptotic protein baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5), which inhibits apoptosis and promotes the cell cycle progression. These findings suggest PRL inhibits cell deletion and apoptosis, allowing autoreactive lymphocytes intended for elimination from the lymphocyte repertoire by apoptotic death to survive [21]. Accordingly, Flores-Fernández et al. found PRL binding to its receptors on the developing B lymphocytes from lupus-prone mice decreased apoptosis. In this instance, B-cell lymphoma-extra large (Bcl-xL) protein, another anti-apoptotic protein, was responsible for the reduction in apoptosis. Additionally, the level of the pro-apoptotic protein BCL2-associated agonist of cell death (Bad) was reduced [22]. Taken together, these findings suggest PRL could break a central tolerance mechanism, apoptosis, in SLE by disrupting the balances of pro-apoptotic and anti-apoptotic proteins in favor of apoptosis reduction and consequently contribute to SLE pathogenesis.

Despite the PRL's contribution to B cell tolerance collapse in SLE, the same contribution has not been directly established for two other rheumatic autoimmune diseases, RA and SSc. However, the action of PRL in the promotion of B lymphocyte autoreactivity was detected in a non-rheumatic autoimmune disease of the nervous system, multiple sclerosis (MS). Correale et al. found a higher level of PRL in MS patients, which reduced the activation threshold of anergic B lymphocytes. The end result was an increase in the number of autoreactive B lymphocytes that secreted autoantibodies against myelin oligodendrocyte glycoprotein (MOG), the primary auto-antigen in MS. Moreover, PRL activated autoreactive B lymphocytes by stimulating the secretion of the BAFF cytokine [23,54]. PRL also induces in B lymphocytes the upregulation of an anti-apoptotic protein, B-cell lymphoma 2 (Bcl-2), and the downregulation of a pro-apoptotic protein transformation-related protein 63 (Trp63). Therefore, PRL could break two peripheral tolerance mechanisms, including anergy and apoptosis in B lymphocytes of MS patients, and by this way contributed to the disease pathogenesis [23].

Besides the tolerance breakdown of B cell in autoimmune diseases, Saha et al. revealed that PRL accelerates apoptosis of the developing B lymphocytes, T1B cells, from healthy mice when antigenic receptors are stimulated [24]. The increased apoptosis was attributed to the downregulation of Trp63, and the upregulation of type II interferon-gamma receptor which is responsible for mediating an anti-apoptotic signaling cascade [55]. Furthermore, PRL caused dysregulation of the receptor editing and decreased the activation threshold of anergic B cells [24]. These findings reveal that PRL predisposes for autoimmune diseases not only in the genetically susceptible subjects, but also in the non-susceptible ones by impairment of both the central and peripheral mechanisms, encompassing processes such as deletion or apoptosis, receptor editing, and induction of anergy, implying the possible contribution of PRL in the breakdown of B cell tolerance in RA, and SSc. However, more investigations are required to precisely address the issue in RA and SSc.

6. Conclusions

Current literature provides evidence supporting prolactin's contribution to the disruption of both central and peripheral tolerance mechanisms of B lymphocytes, refer to apoptosis, receptor editing, and induction of anergy. Given the pivotal involvement of PRL in the pathogenesis of several rheumatic autoimmune disorders, including SLE, RA, and SSc, prolactin may contribute to their pathogenesis by causing the breakdown of B lymphocyte tolerance. However, more investigations particularly in RA, and SSc animal models, are required to precisely address the pathologic role of PRL via the breakdown of B cell tolerance.

Declarations

The authors declare that there are no conflicts of interest.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Declaration of competing interest

The authors declare that they have no competing interests.

Funding

Not applicable.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Not applicable.

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