

Prolactin May Promote the Development of Psoriasis: Reawakened Issue

Kanda N^{1,2*}, Hau CS^{2,3}, Tada Y¹⁻³ and Watanabe S²

¹Department of Dermatology, Kosei Hospital, Tokyo, Japan

²Department of Dermatology, Teikyo University School of Medicine, Tokyo, Japan

³Department of Dermatology, Faculty of Medicine, University of Tokyo, Tokyo, Japan

Abstract

Psoriasis is a chronic inflammatory dermatosis characterized by the hyperproliferation and impaired differentiation of keratinocytes, the abnormal activation of type 17 helper T (Th17), Th22, Th1 cells, dendritic cells or neutrophils, and enhanced angiogenesis in the dermis. A polypeptide hormone, prolactin is mainly produced in the anterior pituitary gland; however, it can also be produced in extra pituitary sites and is detected in the skin. Prolactin is a member of the type I cytokine superfamily and exerts a variety of immunostimulatory effects. It has been indicated that prolactin may be involved in the pathogenesis of psoriasis. The aim of this review is to overview the clinical and experimental data which support the promoting effects of prolactin on the development of psoriasis, including our recent experimental results.

Keywords: Prolactin; Psoriasis; Keratinocyte; Th17; Th22; Th1; Imiquimod

Abbreviations: PRL: Prolactin; Th17: Type 17 Helper T; pDC: Plasmacytoid Dendritic Cell; TIP-DC: TNF- α and iNOS-Producing Dendritic Cell; JAK: Janus Kinase; STAT: Signal Transducer and Activator of Transcription; MAPK: Mitogen-activated Protein Kinase; AP-1: Activator Protein-1; NF- κ B: Nuclear Factor- κ B; PI3K: Phosphoinositide 3-Kinase; IMQ: Imiquimod

Introduction

Psoriasis is a chronic inflammatory dermatosis. The pathogenesis of psoriasis involves a variety of genetic factors like *HLA-C* genes and environmental factors like infection, stress, food, or drugs [1,2]. A polypeptide hormone, prolactin (PRL) may be one of the risk factors to trigger or accelerate psoriasis [3]. In this article, we will overview the clinical and experimental data supporting the promoting roles of PRL in the pathogenesis of psoriasis, including our recent experimental results.

Abnormal Immune Responses in Psoriasis

Psoriasis is characterized by the hyperproliferation and impaired differentiation of epidermal keratinocytes, hyperactivation of inflammatory cells like T cells, dendritic cells, or neutrophils, and enhanced angiogenesis in the dermis (Figure 1) [1,2,4,5]. In the early phase of psoriasis, certain stress or scratch on keratinocytes induces the release of an antimicrobial peptide, LL-37 which is complexed with self DNA derived from apoptotic keratinocytes [1,2]. The complex activates plasmacytoid dendritic cells (pDCs) in the dermis to secrete IFN- α which further activates dermal dendritic cells to become TNF- α and iNOS-producing dendritic cells (TIP-DCs) secreting a proinflammatory cytokine TNF- α , IL-20 enhancing proliferation of keratinocytes, or IL-23 inducing the differentiation or survival of type 17 helper T (Th17) cells producing IL-17A/F or IL-22 or Th22 cells producing IL-22 [1,2,6-8]. The activated TIP-DCs enter regional lymph nodes and induce the differentiation of Th17, Th22 cells and Th1 cells producing IFN- γ via direct cell-cell interaction or cytokines [9-11]. Th17 and Th22 cells express CCR6 on their surface and are chemoattracted by its ligand CCL20 [12]. Th1 cells express CXCR3, and are chemoattracted by its ligands CXCL9/10/11 [9,10]. In the acute phase of psoriasis, TNF- α from the TIP-DCs in the dermis acts on epidermal keratinocytes to produce vascular endothelial growth factor which enhances the proliferation of endothelial cells and promotes angiogenesis, and a chemokine CXCL8 attracting neutrophils, a chemokine CXCL10

attracting Th1 cells, and a chemokine CCL20 attracting Th17 and Th22 cells. Thus neutrophils infiltrate the epidermis, composing Munro's microabscess, and Th1, Th17 and Th22 cells are also induced to infiltrate, and secrete IFN- γ , IL-17A/F, and IL-22, respectively, and act as effector T cells. In the chronic phase of psoriasis, IL-17A/F from Th17 cells acts on keratinocytes and induces their production of CXCL8 and CCL20; IL-22 from Th22 cells and IL-20 from TIP-DCs enhance the proliferation of keratinocytes and induce the acanthosis; IFN- γ from Th1 cells enhances the production of chemokine CXCL10 in keratinocytes [9,10,12-14]. IL-17 A/F, IL-22 and IFN- γ enhance the production of cytokeratins K6/16/17 which induce the abnormal hyperproliferation and impaired differentiation of epidermis and also enhance the production of antimicrobial peptides including LL-37 in keratinocytes [11,13,15]. LL-37 produced may newly trigger the initiation of psoriatic lesion by stimulating pDCs.

The Functions of PRL

Prolactin is a 24 kDa polypeptide hormone, and is mainly produced in the anterior pituitary gland; however, it can also be produced in extrapituitary sites such as mammary gland, prostate, or neurons [16]. Prolactin induces the differentiation and proliferation of mammary gland cells, the production and secretion of milk, and also modulates the differentiation, proliferation, or survival of spleen islet β -cells, adipocytes, or T cells [17].

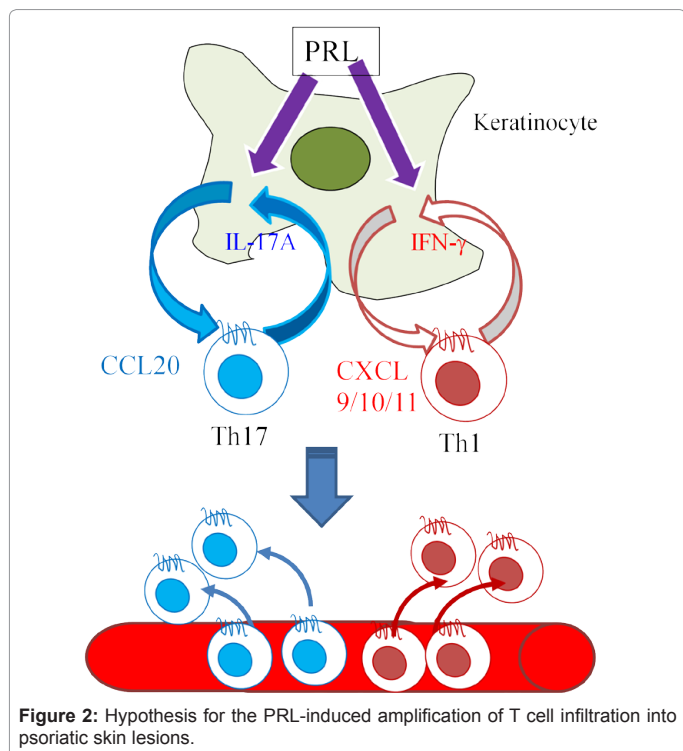
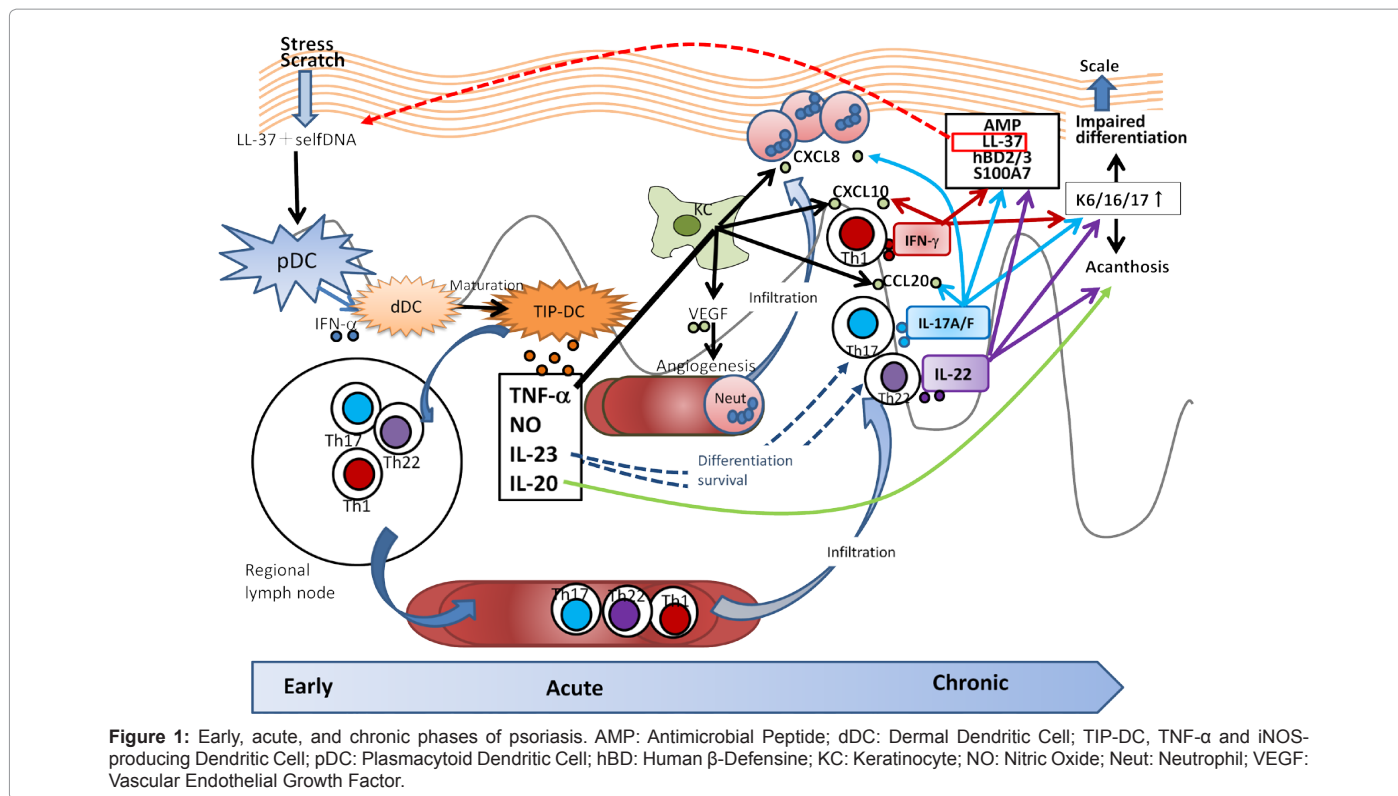
Prolactin is a member of the type I cytokine superfamily and exerts a variety of immunomodulatory effects; it induces the expression of γ/δ T cell receptors on rat pre-T lymphocyte Nb2 cells, enhances the production of IFN- γ in T cells or natural killer cells, promotes IL-4/13 production in Th2 cells, and enhances the expression of MHC class II, CD40, CD80, or CD86 on antigen-presenting cells [16,18-20]. On

***Corresponding author:** Dr. Naoko Kanda, Department of Dermatology, Kosei Hospital, 5-25-15, Yayoi-Cho, Nakano-Ku, Tokyo-164-8617, Japan, Tel: +81-3-3383-1281; Fax: +81-3-3382-8972; Email: nmok-kosei-hp.or.jp

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the other hand, the effects of PRL on Th17 or Th22 cells have not been precisely investigated.

The binding of PRL to cell surface receptors induces the activation of Janus kinase (JAK) 2/signal transducer and activator of transcription (STAT) 1/3/5 signaling pathways and induces the STAT-dependent gene expression [20-22]. Prolactin also activates the other signaling

pathways like *src* kinase, phosphoinositide 3-kinase (PI3K)/Akt or mitogen-activated protein kinase (MAPK), leading to the activation of other transcription factors like activator protein 1 (AP-1), cAMP responsive element binding protein, or activating transcription factor [23-26]. Which of these signals are dominant may differ with target cells or co-stimuli, and thus the final effects of PRL, either stimulatory or inhibitory, may vary with different organs.

Prolactin and Autoimmune Diseases

It is reported that hyperprolactinemia frequently occurs in patients with autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus, or multiple sclerosis, and it is hypothesized that PRL may be involved in the pathogenesis of these diseases [27-31]. It is also reported that treatment with bromocriptine, which suppresses the release of PRL from pituitary, improves the symptoms of these diseases, supporting the pathogenic roles of PRL [31].

Prolactin and Psoriasis

It is reported that hyperprolactinemia frequently occurs also in patients with psoriasis, and that the serum PRL levels are correlated with the disease severity and it has been suggested that PRL may promote the development of psoriasis [3,32-37]. Psoriasis is frequently associated with extracutaneous inflammation like arthritis or uveitis [38]. Psoriatic patients also frequently manifest obesity and metabolic syndromes like hypertension, dyslipidemia, or diabetes [39]. Hyperprolactinemia associated with psoriasis may be caused by the overactive somatotrophin signaling axis or prolactinoma [3]. It is reported that dopamine agonists like bromocriptine or cabergoline, suppressing PRL release, alleviate uveitis, arthritis, and metabolic syndromes as well as the improvement of hyperprolactinemia and psoriatic eruption [29,40]. Such causal relationship indicates that PRL may promote the development of psoriatic co-morbidities like arthritis, uveitis, and metabolic syndromes since PRL promotes endothelial

dysfunction and insulin resistance [41]. Thus hyperprolactinemia may link the development of psoriasis with that of the psoriatic comorbidities like extracutaneous inflammation or metabolic syndromes.

An antipsoriatic drug cyclosporine A suppresses the binding of PRL to its receptors on T or B cells; another antipsoriatic drug *all-trans* retinoic acid suppresses the release of PRL from pituitary and the expression of PRL receptors on breast carcinoma cells; an antipsoriatic drug propylthiouracil reduces serum PRL levels in association with the improvement of lesional acanthosis in psoriatic patients [21,42-44]. Thus to suppress the production and/or functions of PRL may be one of the mechanisms for therapeutic efficacy of these antipsoriatic drugs.

Certain stressors induce the secretion of PRL-releasing factors from hypothalamus, which stimulates anterior pituitary gland to release PRL [45]. Thus PRL may be involved in the stress-induced exacerbation of psoriasis [46,47]. The suckling stimulus promotes the release of PRL, which may be related to the acceleration of psoriasis after delivery in female patients [48].

Prolactin in the skin may be mainly leaked from the circulation, however, may be produced in the sweat glands or hair follicles and it is also possible that T cells infiltrating the skin may produce PRL [49-52]. A recent paper reports that prolactin level is elevated in the lesional skin, indicating that locally produced prolactin may promote the development of psoriasis [53]. Prolactin *in vitro* enhances the proliferation of epidermal keratinocytes indicating that PRL may be related to the hyperproliferation of epidermal keratinocytes in psoriatic lesions. It is also reported that PRL promotes the expression of keratins K5, K14, K15 and K19 in hair follicle keratinocytes [54,55]. A recent paper reports that PRL and PRL receptors are detected in human epidermal keratinocytes as well as hair follicles, and that PRL enhances the phosphorylation of STAT5 in the epidermal keratinocytes, indicating functionality of PRL receptor-mediated signaling in human epidermis [56]. In hair follicle outer root sheath keratinocytes, PRL expression is increased by IFN- γ while decreased by TNF- α [57]. Such modulation indicates that the local balance of inflammatory cytokines may influence PRL expression in the skin, especially in psoriatic lesions.

In vitro Effects of PRL on Keratinocyte

We have found that PRL *in vitro* acts on human keratinocytes and enhances their production of chemokines attracting Th1 or Th17 cells [57,58].

The enhancement of CXCL9/10/11 production by PRL

Prolactin *in vitro* enhances IFN- γ -induced secretion and mRNA expression of CXCR3 ligands, CXCL9/10/11 in human keratinocytes though PRL alone is ineffective [57]. Prolactin enhances the IFN- γ -induced transcriptional activities of nuclear factor- κ B (NF- κ B), STAT1, or interferon regulatory transcription factor-1 conferring the expression of *CXCL9/10/11* genes [57]. Thus PRL may promote the IFN- γ -induced production of CXCL9/10/11 via the activation of these transcription factors in epidermal keratinocytes.

The enhancement of CCL20 production by PRL

Prolactin *in vitro* enhances basal and IL-17A-induced secretion and mRNA expression of CCL20 in human keratinocytes [58]. The expression of CCL20 depends on NF- κ B and AP-1. Prolactin alone promotes the expression of AP-1 components, c-Fos and c-Jun and enhances the transcriptional activities of AP-1 while IL-17A does not enhance AP-1 activities though moderately enhances the expression of c-Fos in human keratinocytes. Prolactin alone moderately enhances the activities of NF- κ B while the activities are remarkably enhanced by

IL-17A, and the addition of both results in the synergistic activation of NF- κ B. Thus PRL mainly activating AP-1 may promote the production of CCL20 in concert with IL-17A mainly activating NF- κ B in human keratinocytes.

These *in vitro* results indicate that PRL may act on epidermal keratinocytes in psoriatic lesions and enhance the production of CXCL9/10/11 or CCL20 in concert with IFN- γ or IL-17A, respectively. The infiltrated Th1 or Th17 cells may further produce IFN- γ or IL-17A, respectively, which further act on keratinocytes in paracrine manners, and amplify the production of these chemokines in concert with PRL and sustain the inflammation (Figure 2). The enhancement of chemokine production by PRL may be related to the stress-induced acceleration of psoriasis.

In vivo Effects of PRL on Imiquimod (IMQ)-induced Psoriatic Skin in Mice [59]

It is known that topical application of a toll-like receptor 7/8 ligand, IMQ, to the shaved back skin of mice induces psoriasis-like phenotypes such as acanthosis, scaling, and erythema [60-63]. Thus we have investigated whether intraperitoneal injection of PRL in mice exacerbates IMQ-induced psoriasis-like skin inflammation. Topical IMQ treatment increases erythema, scaling, and thickening of the back skin, and intraperitoneal treatment with PRL appears to exacerbate these features while PRL alone does not alter the skin characteristics (Figure 3). Intraperitoneal PRL increases the mRNA levels of IL-17A/F, IL-22, IFN- γ , IL-23p19, IL-12p40, IL-12p35, CCL20, CXCL2, STAT3, and TNF- α in IMQ-treated skin. Intraperitoneal PRL increases the numbers of T cells and neutrophils in the dermis of IMQ-treated skin [59]. These results suggest that intraperitoneal PRL enhances the expression of Th17/Th22/Th1 cytokines/chemokines, and accelerates T cell and neutrophil-mediated inflammation in IMQ-treated skin. Prolactin may act on keratinocytes and induce their proliferation and production of chemokines, CCL20 and CXCL2, attracting Th17 cells and neutrophils, respectively (Figure 4). Especially the induced CCL20 may result in the increased production of IL-17A/F and IL-22 by Th17 cells infiltrating the lesional skin. It is also indicated that PRL may act on TIP-DCs and induce their production of proinflammatory cytokine TNF- α or Th1/17/22-differentiating cytokines, IL-12 or IL-23. It is also indicated that PRL may directly act on T cells and up-regulate their production of IFN- γ , IL-17A/F, or IL-22 in the lesional skin. These possibilities should further be investigated.

Possible PRL-targeting Therapy for Psoriasis

Since PRL may trigger or accelerate psoriasis, it can be a therapeutic

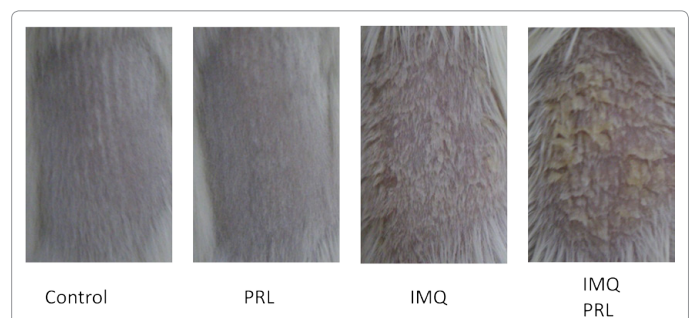


Figure 3: The exacerbation of IMQ-induced psoriasis-like eruption by PRL. Shown are the clinical pictures of the shaved back skin in BALB/c mice 24 h after six consecutive days of treatment with topical Vaseline plus intraperitoneal PBS (control), topical Vaseline plus intraperitoneal PRL (PRL), topical IMQ plus intraperitoneal PBS (IMQ), or topical IMQ plus intraperitoneal PRL (IMQ PRL). The results represent three separate experiments.

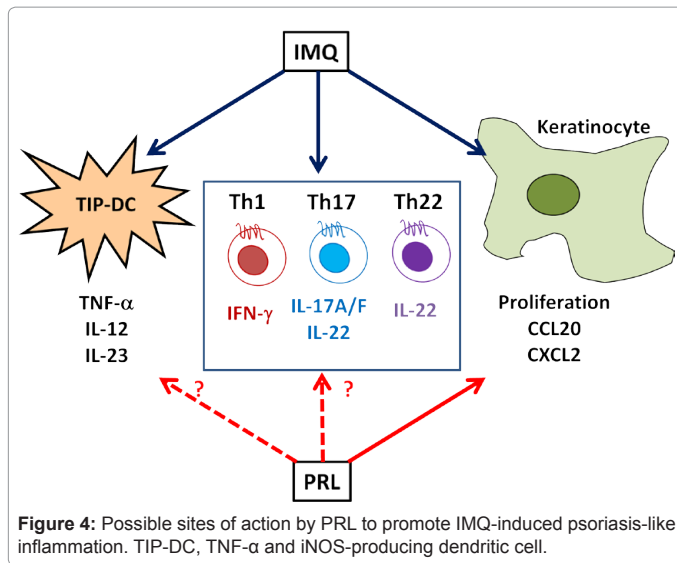


Figure 4: Possible sites of action by PRL to promote IMQ-induced psoriasis-like inflammation. TIP-DC, TNF- α and iNOS-producing dendritic cell.

target for psoriasis. Antibodies against PRL or PRL receptor may suppress the PRL-induced expression of Th17/Th22/Th1 cytokines/chemokines and T cell and neutrophil-mediated inflammation, and thus may be therapeutically effective for psoriasis patients especially with hyperprolactinemia. For those patients, the combined use of bromocriptine suppressing PRL release with cyclosporine A suppressing PRL binding to its receptors may synergistically improve the symptoms of psoriasis and decrease the cyclosporine A requirement, reducing side effects of this drug [64].

Conclusions

The abundant clinical and experimental data support that PRL may promote the development of psoriasis. To control the stimulatory effects of PRL can be a therapeutic target for psoriasis.

Ethics

The mouse experiments were approved by the Animal Research Committee of the University of Tokyo.

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