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REVIEW

The role of the prolactin/vasoinhibin axis in rheumatoid arthritis: an integrative overview

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Abstract Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory disease destroying articular cartilage and bone. The female preponderance and the influence of reproductive states in RA have long linked this disease to sexually dimorphic, reproductive hormones such as prolactin (PRL). PRL has immune-enhancing properties and increases in the circulation of some patients with RA. However, PRL also suppresses the immune system, stimulates the formation and survival of joint tissues, acquires antiangiogenic properties upon its cleavage to vasoinhibins, and protects against joint destruction and inflammation in the adjuvant-induced model of RA. This review addresses risk factors for RA linked to PRL, the effects of PRL and vasoinhibins on joint tissues, blood vessels, and immune cells, and the clinical and experimental data associating PRL with RA. This information provides important insights into the pathophysiology of RA and highlights protective actions of the PRL/vasoinhibin axis that could lead to therapeutic benefits.

Keywords Gender · Stress · Reproduction · Angiogenesis · Joint tissues · Immune cells · Cartilage · Bone · Blood vessels

Abbreviations

RA	Rheumatoid arthritis
PRL	Prolactin
ACPA	Anti-citrullinated peptide antibodies
RF	Rheumatoid factor
TRAF1-C5	Tumor necrosis factor receptor-associated factor 1
STAT	Signal transducer and activator of transcription
NF-κβ	Nuclear factor κβ
Th1	T helper 1
Th2	T helper 2
IL	Interleukin
IFNγ	Interferon γ
TNF α	Tumor necrosis factor α
JAK	Janus kinase
PI3k	Phosphatidylinositol 3-kinase
MAPK	Mitogen-activated protein kinase
BMP-1	Bone morphogenetic protein-1
RANKL	Receptor activator of NF-κβ ligand
VEGF	Vascular endothelial growth factor
FGF-2	Fibroblast growth factor-2
HO-1	Heme oxigenase-1
BK	Bradykinin
ACh	Acetylcholine
PAI-1	Plasminogen activator inhibitor-1
uPA	Urokinase plasminogen activator
uPAR	Urokinase plasminogen activator receptor
eNOS	Endothelial nitric oxide synthase
PP2A	Protein phosphatase 2A

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TRPC5	Transient receptor potential channel 5
PRLR	Prolactin receptor
NK	Natural killer
iNOS	Inducible nitric oxide synthase
NO	Nitric oxide
TRH	Thyrotropin-releasing hormone
TIMP-1	Tissue inhibitor of MMP
CFA	Complete Freunds adjuvant
AP	Anterior pituitary gland

Introduction

Rheumatoid arthritis (RA) is a disabling disease affecting nearly 1 % of the adult population worldwide with a female:male ratio of 3:1. The causes of RA remain unknown but may involve a combination of genetic, environmental, and host factors that initiate the response to an unidentified trigger and result in the recruitment of immune cells into the joints. Production of autoantibodies, inflammatory interactions between activated immune cells and synoviocytes, and synovial angiogenesis sustain and amplify the inflammatory reaction. Chronic inflammation, invasion, cell death, and proteolytic matrix degradation destroy the adjacent cartilage and bone and lead to systemic complications and increased comorbidities.

Among host factors able to affect the pathophysiology of RA is the sexually dimorphic hormone, prolactin (PRL). PRL is a stress-related [1, 2] and reproductive hormone, essential for lactation, that regulates a wide diversity of processes [3–5] including events in joint tissues and immune cells. PRL regulates cartilage survival [6, 7], bone formation and resorption [6, 8], the growth of blood vessels [9], the proliferation, survival, and function of immune cells [10–12], and the progression of rheumatic diseases [6, 10, 11]. Some of these actions are affected by the proteolytic conversion of PRL to vasoinhibins, a family of PRL fragments with effects opposite to those of PRL on inflammation and angiogenesis [13]. The generation, secretion, and action of PRL and vasoinhibins are integrated at the hypothalamus, the pituitary, and the target tissue levels and this organization has been recently defined as the PRL/vasoinhibin axis [14]. In this review, we briefly summarize current knowledge of risk factors for RA that can be linked to PRL, the effects of PRL and vasoinhibins on joint tissues, blood vessels, and immune cells, and the experimental and clinical evidences associating PRL with RA. We propose that the ability of the PRL/vasoinhibin axis to exert opposing effects on inflammatory reactions and angiogenesis contributes to the controversial role of PRL on the pathophysiology of RA and offers opportunities for the development of new treatments.

RA essentials

RA is the most common form of inflammatory arthritis; it occurs at any age but its incidence is higher among those aged 40–70 years. Chronic synovitis underlies the primary manifestations of this disease, including pain, stiffness, and swelling, which are eventually followed by cartilage destruction, bone erosion, subsequent joint deformities, and systemic complications.

The detailed essentials of RA are beyond the scope of this article and can be found in several reviews [15–18]. A major challenge is that RA manifests in distinct disease subsets with different phenotype, fluctuating course, and uncertain progression. While some patients show a mild development that can be self-limiting, others acquire severe, erosive disease with systemic manifestations. Nonetheless, it is increasingly clear that the outcome of RA depends on the complex interaction of genetic, environmental, and host-related factors, which suggests the existence of parameters that can be evaluated to facilitate early diagnosis and prevention (Fig. 1).

Studies in monozygotic twins have estimated the relative contribution of genetic factors to be about 50 % for RA predisposition, leaving the remaining part to environmental and host issues [19]. The association between RA and major histocompatibility complex class II polymorphisms, specifically those having a conserved sequence of amino acids in a number of human leukocyte antigen DRBl alleles, called the RA-shared epitope, closely correlates with the presence of rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPA), or both [16]. This is consistent with T cell selection and antigen presentation playing a role in the induction of the autoimmune response in RA. However, the shared epitope has not been found in forms of RA negative for RF or ACPA, which may account for up to 20–30 % of patients [16, 20]. Other gene polymorphisms that differ among RA subsets include *PTPN22* (coding a tyrosine phosphatase that has a role in T-cell and B-cell signaling) [21] and genes implicated in nuclear factor κB (NF- κβ)-dependent signaling [Tumor necrosis factor receptor-associated factor 1(TRAF1-C5)] [22], interferon regulatory factors [interferon regulatory factor 5] [23], and T-cell stimulation, activation, or differentiation [signal transduction and activator of transcription 4 (STAT4)] [24].

In general, individual gene polymorphisms are of minor value for predicting disease risk unless they combine with environmental or host RA risk factors. For example, smoking is the best-defined environmental risk factor for RA, and the risk for RA increases 21-fold in smokers that are ACPA positive and homozygous for the RA shared epitope, compared to non-smokers without the shared

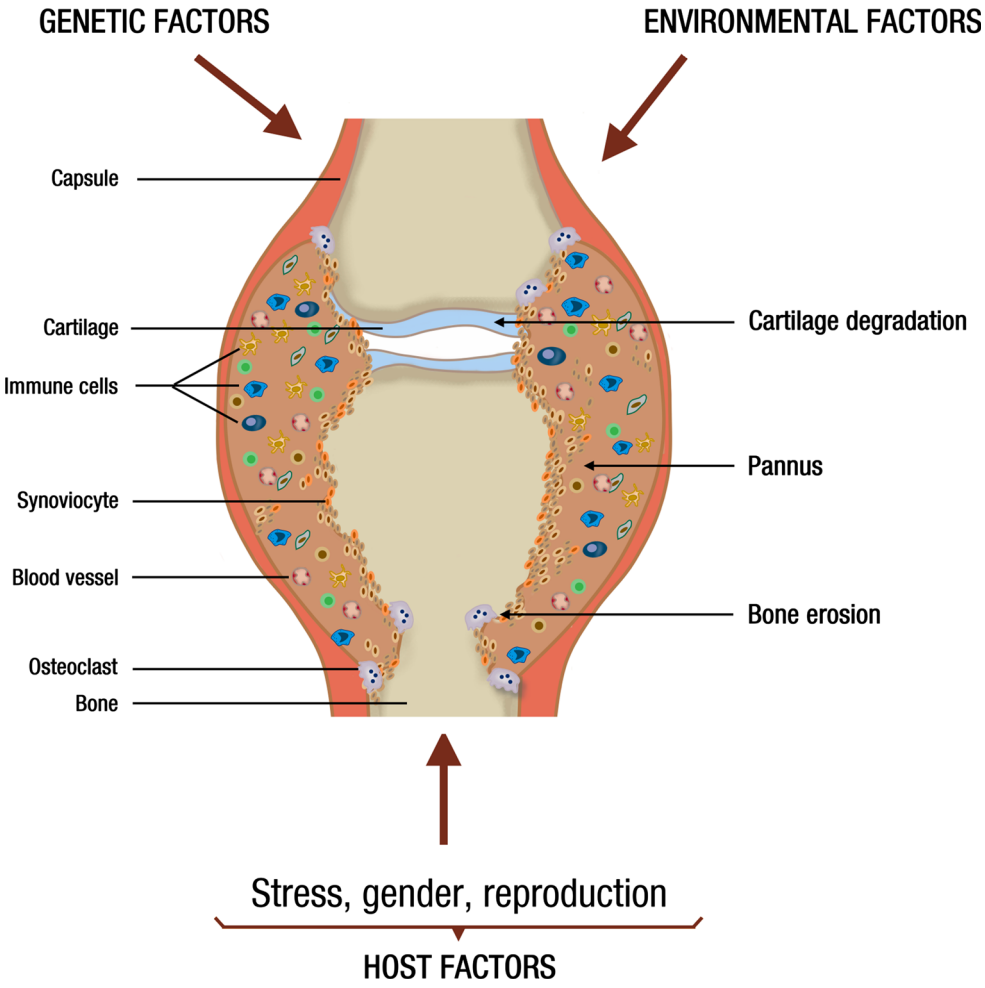

Fig. 1 Schematic view of a joint affected by RA indicating that a combination of genetic, environmental, and host factors (including stress, gender, and reproduction) influence the recruitment of immune cells and the proliferation of synovial cells, which together with the local formation of blood vessels (angiogenesis), sustain the proliferation of an inflamed, invasive pannus causing cartilage degradation and bone erosion

epitope gene [25]. Likewise, stress, gender, and reproduction are host factors influencing the susceptibility for RA in genetically restricted individuals (Fig. 1).

Stress

The long-held perception that psychological stress triggers and worsens RA has been the focus of much basic and clinical research [26–28]. Different forms of stress act in the brain (hypothalamus and brain stem) to activate efferent neuronal (i.e., norepinephrine) and hormonal (i.e., glucocorticoids, epinephrine, and PRL) pathways modifying the level of inflammation and pain [28–31]. The high prevalence of stressful events preceding the onset of RA supports the pathogenic role of stress [32], although this conclusion remains controversial [27]. Moreover, the influence of stress on RA appears to vary depending on the duration, intensity, and type of stressor, with short-lived, minor stress increasing [27, 28, 33, 34] and chronic, stronger stress ameliorating [27, 28, 35] disease activity. Similarly, exposure to different psychological or physical stressors can promote or reduce the onset and activity of experimental arthritis in rodents [36–38].

In general, stress has been considered as immunosuppressive. Exposure to stress mediators (glucocorticoids and catecholamines) counter-regulates increases in inflammatory activity by suppressing T helper 1 (Th1) cell responses and proinflammatory cytokine [interleukin-12 (IL-12), interferon γ (IFNγ), and tumor necrosis factor α (TNFα)] production and by boosting T helper 2 (Th2) responses and production of anti-inflammatory cytokines (IL-10, IL-4) [39–41]. However, glucocorticoids and catecholamines can also worsen inflammation by eliciting the expression of pro-inflammatory mediators (IL-12, IFN-γ, TNFα, IL-6, IL-23) and the down-regulation of IL-10 [28, 39, 42–44]. These opposing actions may relate to the concentration of stress hormones. There is evidence that lower cortisol, catecholamine, and PRL concentrations are immunostimulatory, whereas higher levels are immunosuppressive [26, 45–47]. Along this line, stressors can increase PRL levels in the hypothalamus by downregulating its proteolytic conversion to vasoinhibins [48], which have anxiogenic

[48] and proinflammatory effects [49]. Of note, stress axes are hyporesponsive in patients with RA [50–52] and in experimental models of RA [53], and it has been proposed that the inadequate secretion of stress hormones constitutes the basis for stress-induced aggravation of the disease [26, 28]. In this regard, elevating the levels of endogenous glucocorticoids, which appear insufficient to reduce inflammation, is the basis for their successful long-term therapeutic use in RA patients [54].

Gender and reproduction

Women are more susceptible to RA than men. Increased incidence is established before menopause, implying that hormonal and reproductive exposures are involved [55]. The sex hormones estrogens, androgens, and PRL influence susceptibility to RA. However, the metabolism of androgens to estrogens, hormone levels, age, reproductive state, and the fact that each hormone is able to exert opposing effects on immune responses have complicated the study of their role in gender- and reproduction-related RA susceptibility.

In general, androgens are anti-inflammatory and suppress both humoral and cellular immune responses, whereas estrogens reduce cellular and enhance humoral immunity [56]. Ovariectomy increases and estrogens reduce the severity of collagen-induced arthritis in female mice [57–60]. In castrated male and female arthritic rats, administration of androgens that can (testosterone) and cannot (dihydrotestosterone) be converted to estrogens alleviates the disease [61]. Because lower androgen levels occur in men [62] and in women [63] with RA, androgen deficiency could explain gender differences in RA [55, 64].

The protective role of ovarian steroids is further suggested by studies showing that contraceptive treatment decreases RA risk [65, 66] and ameliorates its severity [67], although a lack of effect has also been reported [68]. More importantly, RA often shows remission in pregnancy and exacerbation during the postpartum period in women [69] and in rodents subjected to the experimental disease [70–72]. In the context of RA being characterized by a Th1-driven immunity, the shift to a dominant Th2 phenotype occurring during pregnancy is beneficial [73], and the high gestational levels of estrogens and progesterone promote the Th2-mediated responses [74]. Therefore, protection against RA after delivery would be withdrawn by the decrease in steroid hormones and the re-establishment of a Th1 immune response [75]. Indeed, estradiol treatment immediately after parturition protects mice from a postpartum flare of the disease. Estradiol administration also increases systemic PRL, and lactating mice show a reduced postpartum exacerbation [70]. Nonetheless, breastfeeding, a stimulus that elevates circulating PRL levels, enhances the severity [76] but reduces the risk [77] of RA.

While it is evident that the influence of stress, gender, and reproduction on RA results from complex interactions between neuroendocrine and immunologic systems among persons genetically prone to RA, optimal management of such interactions could help to prevent and control the disease. More in-depth studies are needed to address the role of hormonal mediators upregulated during conditions affecting the course of RA. One such influence is the activation of the PRL/vasoinhibin axis.

PRL and vasoinhibins

PRL is a multifaceted anterior pituitary hormone discovered by its stimulatory effect on milk production; it is known to regulate a strikingly diverse array of physiological functions, which include events in reproduction, osmoregulation, growth, brain function, metabolism, immune response, and angiogenesis [3, 5, 9, 10, 13, 78]. PRL synthesis has been demonstrated in numerous extrapituitary tissues [79, 80] which, together with the ubiquitous expression of its receptors [3, 79], has led to the concept of PRL acting both as a circulating hormone and as a local regulator or cytokine. The tenet of PRL as a classical cytokine is further established by the fact that PRL is a member of the hematopoietic family of cytokines. Like other members of this family, PRL has a three-dimensional structure consisting of four long α-helices arranged in antiparallel fashion and linked by flexible loops [81]. PRL receptors also share structural and functional characteristics with the hematopoietin receptor superfamily [81], and they signal by activating various kinases including its canonical Janus kinase 2 (JAK2)-signal transducer and activator of transcription (STAT) pathway, the phosphatidylinositol 3-kinase (PI3K)/AKT pathway, and the mitogen-activated protein kinase (MAPK) pathway [82].

Adding complexity to PRL actions is the structural polymorphism of the hormone [83]. PRL is proteolytically cleaved to vasoinhibins, a family of PRL fragments with molecular masses ranging from 11 to 18 kDa, that signal through receptor complexes distinct from the PRL receptor [84, 85] to exert effects opposite to those of the full-length hormone (23 kDa) on blood vessels. PRL stimulates blood vessel growth (angiogenesis), whereas vasoinhibins inhibit angiogenesis, vasodilation, and vasopermeability [9, 13]. Beside vascular actions, vasoinhibins have other effects opposite to PRL. Vasoinhibins promote anxiety [48] whereas PRL is anxiolytic [86]; and vasoinhibins [49] and PRL [87] stimulate and inhibit inflammatory reactions in lung tissues, respectively. The structural diversity of vasoinhibins derives from the fact that different proteases,

including cathepsin D, matrix metalloproteases (MMP) and bone morphogenetic protein-1 (BMP-1), generate the various fragments by cleaving near or within various sites of the large disulfide loop linking α-helixes 3 and 4 of the PRL molecule (for reviews [13, 14, 88]). Of relevance to RA, joint tissues are targets of the PRL/vasoinhibin axis. PRL is present in synovial fluid [89], and both PRL and vasoinhibins are produced in joint tissues, including cartilage [90], vascular endothelium [91], synoviocytes [92], fibroblasts [49], and immune cells [10, 79, 92], where they can act in local- and hormonal-related fashion.

Effects of PRL and vasoinhibins on joint tissues

A summary of PRL and vasoinhibin effects on joint tissues is illustrated in Fig. 2.

Bone and cartilage

Bone loss occurs in association with hyperprolactinemia during lactation, in patients with prolactinomas, and in patients treated with antipsychotic drugs [93–96]. Although increased bone loss involves PRL-induced hypogonadism [93, 97] and the interaction of PRL with other hormones (parathyroid hormone related peptide [98]), clinical [96] and experimental evidence support direct effects of PRL on bone metabolism. PRL receptor null mice are osteopenic and display a reduced rate of bone formation [8], indicating that PRL promotes the maintenance of bone mass. However, PRL has opposite effects on bone depending on the age and physiological state of the animals. Prolonged treatment with PRL increases bone formation and bone calcium content in growing rats [99], whereas it stimulates bone resorption and calcium turnover in sexually mature rats [100] and in pregnant and lactating rats [101]. In the latter, bromocriptine-induced inhibition of PRL secretion results in higher bone volume, lower mineral apposition rates, and reduced bone resorption [102]. It has been proposed that PRL stimulates maternal bone turnover during pregnancy and lactation as a means to satisfy the demands of calcium and phosphate needed for fetal growth and milk production [102].

Of note, PRL can act directly on bone. PRL receptors have been found in bone tissues of humans, mice, and rats [103, 104] and in osteoblasts from neonatal rodents [8, 105] and human fetuses [106]. Also, high levels of PRL stimulate bone resorption over bone formation in cultured osteoblasts derived from adult tissues. In these cells, PRL reduces the expression of Runx2 and osteocalcin, lowers alkaline phosphatase activity, and increases the ratio of receptor activator of nuclear factor κB ligand (RANKL) to osteoprotegerin [106, 107]. In contrast to these findings and consistent with the net bone gain effect of PRL observed in

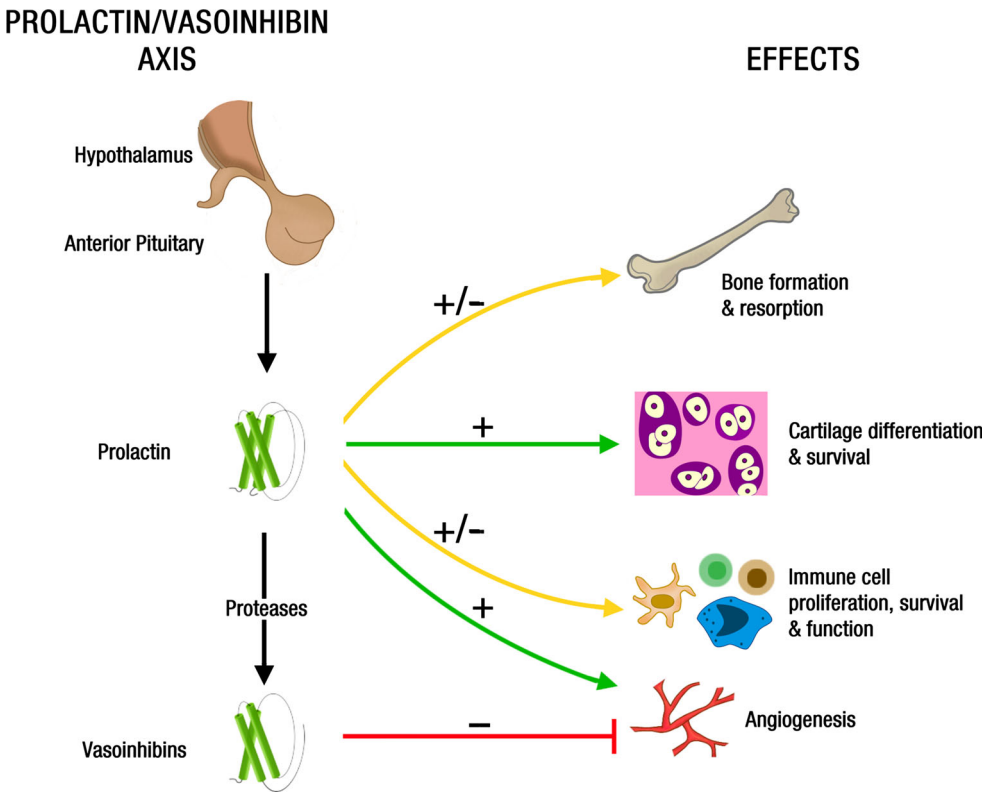

Fig. 2 Schematic representation of PRL and vasoinhibin effects on joint tissues. The anterior pituitary gland secretes PRL and vasoinhibins into the systemic circulation. Also, PRL produced locally by joint tissues can be proteolytically converted to Vi. By virtue of mechanisms poorly understood, PRL stimulates and inhibits (±) bone formation and resorption, promotes (+) cartilage differentiation and survival, and stimulates and inhibits (±) immune cell proliferation, survival, and function. In addition, PRL is proangiogenic (+) and, upon proteolytic cleavage to vasoinhibins, acquires antiangiogenic (−) properties. The effects of Vi on bone, cartilage, and immune cells are unknown

young animals, studies on PRL-exposed osteoblasts from fetal bone showed enhanced Runx2 and osteocalcin expression and a decreased RANKL/osteoprotegerin ratio, suggesting stimulation of bone formation and suppression of bone resorption, respectively [106, 108].

Bone tissues affected by PRL include cartilage. Chondrocytes in both reserve and proliferating regions of the developing long bone express PRL receptors [105], but cartilage formation and growth do not seem to be adversely affected in the PRL receptor null mice [8] or after elevating PRL levels during early life [105]. Nonetheless, PRL may contribute to the chondrogenic process by regulating cartilage formation and maintenance in the adult. Human adult bone marrow pluripotential mesenchymal stem cells express PRL receptors and PRL stimulates their proliferation and differentiation into chondrocytes (type II collagen and proteoglycan synthesis) in culture [89]. Also, PRL activates their receptors in articular chondrocytes from rat postpubescent and adult cartilage to inhibit apoptosis [7]. Because cartilage lacks blood vessels, the sparse distribution of chondrocytes encased within the extracellular matrix suggests that autocrine/paracrine anti-apoptotic factors are an efficient mechanism for maintaining cartilage survival. Along this line, PRL is a component of synovial fluid [89] and is generated by articular chondrocytes [90] and bone-marrow mesenchymal cells undergoing chondrogenic differentiation [89]. Therefore, PRL may help preserve the generation and functional integrity of cartilage. Moreover, chondrocytes produce several MMP that generate vasoinhibins from circulating and locally produced PRL and release vasoinhibins into their conditioned medium [90], suggesting that the PRL/vasoinhibin axis contributes to the local maintenance of cartilage avascularity.

Blood vessels

The regulation of blood vessel growth and function underlies the physiology of joint tissues. Fenestrated capillaries close to the synovial surface are a main source of synovial fluid, a plasma ultra-filtrate transporting lubricants, nutrients, waste products, hormones, growth factors, and cytokines within the joint, particularly to the avascular cartilage. Avascularity is essential for the biomechanical properties of cartilage and, although the subchondral vasculature contributes to the metabolic support of normal articular cartilage [109], vascular invasion from bone into cartilage leads to chondrocyte apoptosis and is a mechanism mediating cartilage substitution by bone during growth [110]. While blood vessels are known targets of PRL and vasoinhibins, and chondrocytes produce these peptides [90], no study has addressed the actions of the PRL/vasoinhibin axis on the joint vasculature.

The effects and signaling mechanisms of PRL and vasoinhibins on blood vessels have been well documented and reviewed [9, 13, 88]. The following summarizes some of the relevant findings. PRL promotes in vivo angiogenesis in the corpus luteum [111], the testis [112], the heart [113], the pancreas [114], and the liver [115]. This action involves a direct effect on endothelial cells [116–118], through both long and short isoforms of the PRL receptor [119–121], but also through the PRL receptor on other cell types (epithelial, immune, and stromal cells) where PRL induces the expression of proangiogenic factors, such as vascular endothelial growth factor (VEGF) [122, 123] and fibroblast growth factor-2 (FGF-2) [124, 125]. PRL signals to promote endothelial cell proliferation, migration, and tube formation through the JAK2/MAPK/early growth response gene-1 pathway [122], the heme oxygenase-1 (HO-1) [116], and the JAK2/STAT5 pathways [118]. However, controversial findings (for a review see [9, 13, 126]) have shown that PRL is unable to stimulate angiogenesis in the cornea and the in vitro proliferation of some endothelial cell types. Also, lack of PRL expression increases angiogenesis in the retina [127] and associates with highly vascularized pituitary tumors [128]. Moreover, PRL has opposing effects on vascular resistance, blood flow, and vasopermeability that depend on experimental conditions (for a review see [126]). These inconsistencies may result from a variable rate of proteolytic conversion of PRL to vasoinhibins.

Vasoinhibins inhibit vasoproliferation, vasodilation, and vasopermeability and promote vascular regression in the cornea [129], retina [127, 130], heart [113], and xenografted tumors [85]. They act directly on endothelial cells to inhibit the action of several vasoactive substances, including VEGF, FGF-2, interleukin 1β, bradykinin, and acetylcholine [130–135]. Binding sites for vasoinhibins were reported in endothelial cell membranes, but their chemical nature was not resolved [84]. Recently, vasoinhibins were shown to bind to a multicomponent complex conformed by plasminogen activator inhibitor-1 (PAI-1), urokinase plasminogen activator (uPA), and the urokinase plasminogen activator receptor (uPAR) on endothelial cells and that such binding was required for some antiangiogenic properties of vasoinhibins [85]. Vasoinhibins signal by blocking the activation of the Ras–Raf–MAPK pathway [136, 137], the Ras–Tiam1–Rac1–Pak1 pathway [133], and the Ca^{2+}/calmodulin-mediated activation of endothelial nitric oxide synthase (eNOS) [134]. They also promote protein phosphatase 2A-induced dephosphorylation and inactivation of eNOS [130], downregulate transient receptor potential channel 5 expression [138], stimulate the activation of proapototic proteins of the Bcl-2 family, and the NFκB-mediated activation of caspases [139] and upregulation of microRNA-146a expression [140].

Therefore, PRL and vasoinhibins act through the activation of distinct receptors and target cells to stimulate and inhibit blood vessels, respectively. Vasoinhibins bind to a multi-component complex involving PAI-1, uPA, and uPAR on endothelial cells, while PRL signals through the PRL receptor not only on endothelial cells, but also on other cells in the capillary microenvironment, including immune cells (Fig. 2).

Immune cells

The action of PRL on immunocytes has been known for more than three decades, when PRL effects [141] and PRL receptors [142] on immune cells were first discovered. PRL operates not only by systemic but also by paracrine/autocrine mechanisms to regulate immune responses [10–12, 29, 80, 143–145]. PRL and the PRL receptor (PRLR) are expressed on T cells, B cells, natural killer (NK) cells, macrophages, neutrophils, and antigen-presenting dendritic cells; and PRL regulates various immune cell responses, including T-cell proliferation and survival, B-cell antibody production, NK-cell proliferation and mediated cytotoxicity, and macrophage effector functions. Notably, PRL exhibits both inmunoenhancing and immunosuppressive properties depending on its concentration (with lower levels augmenting and higher levels inhibiting immune responses) [12, 143, 145].

The first observation linking high PRL levels with immunosuppression was made more than 40 years ago, when lactation [146], as well as PRL treatment [147], was shown to increase susceptibility to worm-infection resulting from impaired differentiation of lymphocytes to mature effector cells. The opposite actions of different PRL concentrations was initially suggested by showing that a lower dose of PRL (100 μg/rat) stimulated antibody production and T cell proliferation, whereas a higher dose (400 μg/rat) was inhibitory [148]. Also, the number and function of circulating NK cells and mature T cells were reduced in patients with hyperprolactinemia (32–394 ng/ml) [149–151], and in vitro studies showed that higher (100–200 ng/ml) and lower (12–25 ng/ml) PRL levels inhibit and stimulate, respectively, the proliferation of blood NK cells and T cells [47]. Likewise, lower concentrations of PRL (<20 ng/ml) were more effective than higher PRL levels (100 ng/ml) in stimulating antibody production by circulating lymphocytes from patients with systemic lupus erythematosus [152]; while high doses of PRL enhanced the in vitro release of proinflammatory mediators by peritoneal macrophages and peripheral blood mononuclear cells, a much higher dose induced the release of anti-inflammatory IL-10 [153, 154].

Nevertheless, it has been widely assumed that PRL functions as an immuno-enhancing hormone. This notion is largely based on the use of experimental models of PRL deficit, including dwarf mice [155], hypophysectomized rats [144], and treatment with bromocriptine (a dopamine D2 receptor agonist that inhibits pituitary PRL release) in rodents and humans [11, 144]. These experimental approaches result in deficient B- and T-cell-mediated immune responses that can be restored by PRL treatment. However, it should be noted that multiple endocrine pathways are being altered in these experimental models, PRL is also produced by extrapituitary sources [79, 80], and bromocriptine can affect immune function independently of PRL [156, 157]. A more direct evaluation of loss of PRL function on the immune system has been done using PRL [158] and PRLR [159] null mice. Both mice exhibit normal numbers of lymphocytes and myeloid cells and mount effective innate and adaptive immune responses when subjected to immune challenges, thus implying that PRL is not essential for normal immune system development and function. Nonetheless, compensatory actions by other cytokines have not been examined, and experiments using these mice have not ruled out a contribution of PRL to immune-system homeostasis under conditions characterized by the up-regulation of PRL levels, such as under stress [29], reproductive adaptations, and pathologic hyperprolactinemia [160].

Indeed, renewed interest has focused on the possibility that elevated circulating PRL levels following stress [1, 2] represent an adaptation to help adjust the frequently observed stress-related immunosuppression [29]. PRL improves macrophage and splenocyte functions following trauma-hemorrhage and infections [161, 162], stimulates lymph node cellularity and antigen-specific proliferative responses under stressful housing conditions [155, 163], and it can help counteract glucocorticoid-induced lymphocyte apoptosis and signaling [164, 165]. However, PRL can also inhibit immune responses during stress. Bone marrow myelopoiesis and splenic lymphocyte proliferation induced by a burn injury are enhanced in PRL null mice [166], PRLR knockout mice show increased mortality and elevated IL-6 after partial hepatectomy [115], and PRL administration associates with decreased survival and an inhibition of cellular immune functions in septic mice [167]. The reason for the opposite effects of PRL on immune function during stress is unclear, but may relate to differences in PRL levels and in immune processes occurring in response to specific stressors. A possible explanation also involves the generation of vasoinhibins from PRL. Exposure to physical restraint increased PRL levels in the hypothalamus partly by reducing its rate of cleavage to

vasoinhibins [48]. Because vasoinhibins are anxiogenic, this change would favor the anxiolytic effect of PRL, thereby reducing the emotional response to stress [48]. Similarly, such reciprocal interplay during stress could favor PRL-induced suppression of inflammatory responses. Vasoinhibins act as potent proinflammatory cytokines, via the activation of NFκB signaling pathways, to stimulate inducible nitric oxide synthase (iNOS) expression and nitric oxide (NO) production in fibroblasts and type II epithelial cells of the lung [49, 168], which are important cells for inflammatory reactions in the airways. Conversely, PRL has anti-inflammatory effects on the same cells [87].

Pregnancy and lactation constitute other important contexts for understanding the role of PRL in the immune system. Elevated PRL levels in pregnancy and early stages of lactation may help suppress immune responses required for successful maternal-fetal and maternal-nursing young interactions. Excessive production of IL-6 in the decidua can trigger an inflammatory response that leads to the termination of pregnancy, and estradiol and PRL inhibit IL-6 expression and signaling by decidual cells [169]. Moreover, PRL produced by the decidua [170] and PRL-like proteins produced by the placenta [171] interact with maternal immune cells (NK cells and megakaryocytes) to ensure successful fetal development [172, 173], and PRL regulation of humoral immunity can influence the levels of immunoglobulins in milk [174–176].

PRL and RA

The association of RA with stress, gender, and reproduction prompted the investigation of PRL as a biological explanation, but the significance of PRL to RA pathogenesis remains unclear. Several reviews have addressed this topic under the general assumption that PRL is a negative (proinflammatory) influence aggravating the disease [10, 177–186]. This conclusion contrasts with the lack of agreement between circulating PRL levels and disease severity, the inconsistent action of dopamine agonists and antagonists, the protective and worsening influence of physiological hyperprolactinemia (pregnancy and lactation), and the ability of PRL to exert both stimulatory and inhibitory effects on immune cells and joint tissues. Our work reviews this controversial field with the idea that its solution requires understanding the mechanisms mediating the dichotomous actions of PRL. Because PRL and vasoinhibins have opposite effects on immune reactions and angiogenesis, we propose that explanatory mechanisms lie within the PRL/vasoinhibin axis, an integrative framework influencing not only the levels of systemic and local PRL, but also the proteolytic conversion of PRL to vasoinhibins.

Clinical data

Several [182, 187–189], albeit not all [189–191], epidemiological studies have claimed that nulliparity and, paradoxically, the postpartum period increase the risk for developing RA. Nulliparity could be linked to hyperprolactinemia-induced infertility [97] and, of course, breastfeeding in the postpartum period elicits hyperprolactinemia. Originally, the connection between breastfeeding and RA generated controversial findings. Exposure to breastfeeding associated with increased risk [192, 193], had no effect [189] or was protective [194] against RA development. However, large cohort studies have now shown that breastfeeding for more than 12 months is inversely related to the development of RA and suggested that the protective effect of parity could be attributed to confounding breastfeeding in previous lactations among parous women [77, 191, 195].

The associations above encouraged an investigation of PRL levels in the circulation of patients with RA (Table 1). Several reports found that PRL levels were higher, albeit usually within the normal range ($\leq$20 ng/ml), in patients with RA compared to healthy or osteoarthritic subjects [196–204]. Nonetheless, no differences [51, 52, 205–209], as well as lower than normal levels of the systemic hormone [210], have also been reported in RA. Because PRL levels vary according to the time of day and stress exposure [1, 2, 211], studies attempting to control for these variations showed that the RA group had significantly higher PRL levels at the diurnal hormonal peak, before and after stress (surgery), and following thyrotrophin releasing hormone (TRH) stimulation [197, 202]. However, no difference in PRL levels after TRH or even a decreased PRL release in response to other forms of stress (hypoglycemia), were also found [51, 205, 209]. Moreover, lowering circulating levels of PRL with dopamine D2 receptor agonists (bromocriptine, quinagolide, cabergoline) proved to be effective [177, 212–214], or ineffective [215–217] for reducing RA. In one report, RA improved after treatment with cabergoline in a hyperprolactinemic patient (76.5 ng/ml) with a microprolactinoma [214]. However, cases of PRL excess due to prolactinomas appear to be extremely rare in autoimmune diseases and are not consistent with their severity [218]. Also, PRL levels above normal have been detected in only 1 or 6 % of patients with RA and have either no correlation with disease activity [219] or a low disease activity score [220]. Along this line, human pathological hyperprolactinemia has been associated with immunosuppression (decreased number and function of NK cells and T cells) [149–151].

The major endpoint of these studies is the concentration of systemic PRL. However, it is now clear that local PRL produced and metabolized in the tissues can be influential.

Table 1 Circulating PRL levels in RA

PRL levels	RA (*n*)	Control (*n*)	Serum PRL (ng/ml)		*p* value	Special features	References
			RA	Control			
Higher	99	68 (OA)	11.7 ± 7.6[a]	8.9 ± 4.0	<0.01	PRL levels correlate with RA duration and severity	[196]
	10	10 (OA)	21.2–26.9[a]	4.7–20.3	<0.005	Higher PRL diurnal levels and after surgery in RA	[197]
	39	22	16.0 ± 11.2[a]	10.4 ± 6.9	<0.05	PRL levels correlate with chemokine MIP-1α serum levels	[198]
	29	30 (OA)	13.1 ± 1.7[b]	7.5 ± 0.5	<0.01	PRL levels correlate with RA duration	[199]
	10	10	20.6 ± 5.1	12.1 ± 4.3	<0.005	Higher PRL levels in RA only at 0200 h	[200]
	29	26 (OA)	14.1 ± 1.3[a]	10.9 ± 0.8	<0.04	PRL levels correlate with RA severity	[201]
	23	8	27.3 ± 3.8[b]	8.8 ± 2.2	<0.01	Higher PRL levels in response to TRH	[202]
	60	31 (OA)	10.6 ± 4.9[a]	8.3 ± 3.2	<0.04	Both total and *free PRL were measured	[203]
	20	20	40.2 ± 5.6[a]	16.2 ± 3.1	<0.001	PRL levels correlate with ESR and C-reactive protein	[204]
Not different	38	23	10	8	n.s.	Higher and lower PRL levels in response to hypoglycemia and TRH, respectively	[205]
	27	12 (OA)	6.05 ± 1.1[b]	8.49 ± 2.4	n.s.	PRL levels in plasma and synovial fluid correlate positively	[206]
	20	28	11.5 ± 7.4[a]	12.5 ± 6.5	n.s.	No association with thyroid autoantibodies in RA	[207]
	10	10	10.1 ± 1.4[b]	13.7 ± 2.4	0.32	Similar PRL levels in response to TRH between RA and control	[208]
	10	9	10	12.5	n.s.	Similar PRL levels in response to TRH between RA and control	[209]
	20	20	13.0 ± 7.5[a]	15.0 ± 8.0	0.2	Reduced PRL levels in response to hypoglycemia in RA	[51]
	7	10	10.6	10.3	n.s.	Lower increase in PRL levels in response to exercise in RA vs control	[52]
Lower	48	23	7.9 ± 0.3[b]	9.5 ± 0.5	<0.05	Association between RA and PRL deficiency	[210]

In some studies PRL data were converted from units to mass (ng/mL × 21.2 = mIU/L). OA indicates osteoarthritic patients as control group *MIP-1α* macrophage inflammatory protein-1α, *TRH* thyrotropin releasing hormone, *ESR* erythrocyte sedimentation rate, *ns* non-significant

PRL values are [a] means ± SD, [b] mean ± SEM, or means

* Free PRL refers to monomeric, unbound PRL

In RA, synovium infiltrating T lymphocytes and fibroblast-like synovial cells produce PRL able to promote inflammation at the local level [92]. PRL stimulates proliferation and the production of proinflammatory cytokines and MMP, and it inhibits the synthesis of tissue inhibitor of MMP (TIMP-I) by RA synovial cells in culture [92]. Moreover, bromocriptine inhibits the expression of PRL mRNA by primary cultures of RA synovial cells [92] and can suppress their activity in a PRL-dependent and PRL-independent manner [92, 156, 157]. Also, the presence of a PRL-1149 T polymorphism in the promoter region controlling the production of extrapituitary PRL associates with reduced PRL production by lymphocytes [221], but not with the systemic levels of the hormone, and correlates with a decreased risk of developing RA [222, 223]. Therefore, local PRL levels may correlate better than systemic PRL levels with the ongoing inflammation.

An additional complexity is added by the paradox that activation of dopamine D2 receptors may also protect against RA. Haloperidol, a D2-receptor antagonist leading to hyperprolactinemia [224], alleviates inflammation in RA [225] by mechanisms that may include PRL-induced immunosuppression [6] and the direct blockage of D2 receptors on immune cells able to reduce proinflammatory cytokine release and action [226, 227].

The fact that both dopamine agonists and antagonists ameliorate RA may be due to the negative and positive effects of PRL on immune cells and joint tissues. To understand these opposite actions, it is important to study how PRL levels in the circulation and within the tissue microenvironment are being regulated to affect the function of the various targets. Experimental studies exploring the role of PRL in inflammatory arthritis mirror these conflicting observations but have also contributed to their clarification.

Experimental data

The causative link between PRL and RA is supported by studies using complete Freund's adjuvant (CFA)-induced arthritis in rats, a well-documented model for the induction of inflammation within joint tissues and for having cartilage and bone destruction similar to that in RA [228, 229]. Early studies claimed that the development of adjuvant arthritis was at least partially dependent on PRL. Hypophysectomized rats did not develop CFA arthritis

unless treated with PRL, and the CFA-induced joint swelling in intact rats was reduced by treatment with bromocriptine [230]. Moreover, hypophysectomized rats made hyperprolactinemic by placing anterior pituitary glands (AP) under the kidney capsule developed a more severe arthritis than sham-operated controls [230, 231]. It was reasoned that adrenocortical deficiency due to hypophysectomy favored the manifestation of PRL proinflammatory effects [231]. However, hypophysectomy could be a confounding factor. AP grafts and high PRL levels in the intact organism stimulate glucocorticoid release [232], and APs grafted into sham-operated rats result in a delay in the onset and a reduction in the severity of CFA-induced arthritis and higher corticosterone circulating levels [231]. Therefore, adrenocortical dysfunction due to hypophysectomy could also be counterbalancing the beneficial effects of PRL.

Recent findings support the protective and regenerative effects of hyperprolactinemia in CFA-induced arthritis [6]. Increasing prolactinemia, either by PRL infusion or treatment with haloperidol, before or after inducing arthritis with CFA, ameliorated inflammation and joint destruction as revealed by lower proinflammatory cytokine (TNFα, IL-1β, IFNγ, IL-6) and iNOS expression in joint tissues, and reduced chondrocyte apoptosis, pannus formation, bone erosion, joint swelling, and pain. Proinflammatory cytokines are crucial for initiating the inflammatory process leading to joint destruction in RA [233, 234]. The concentration and expression of proinflammatory cytokines are significantly elevated in serum [228] and joint tissues [6] of CFA-injected rats, respectively, and IL-1 antagonists and TNFα-neutralizing antibodies reduce the severity of arthritis in these animals [229, 235]. Accordingly, PRL could be protecting against CFA-induced arthritis not only by reducing the levels of proinflammatory cytokines, but also by counteracting their proapoptotic and inflammatory effects. PRL inhibited the apoptosis of cultured chondrocytes in response to a combination of TNFα, IL-1β, and IFNγ by blocking the induction of p53 and decreasing the BAX/BCL-2 ratio through a NO-independent, JAK2/STAT3-dependent pathway [6]. Local treatment with PRL or increasing PRL circulating levels also prevented chondrocyte apoptosis evoked by injecting the cytokines into the knee joints of rats, whereas the proapoptotic effect of cytokines was enhanced in PRL receptor null mice [6]. Similar findings were also reported in pulmonary fibroblasts, where the induction of iNOS expression and NO production in response to TNFα, IL-1β, and IFNγ was reduced by PRL [87].

However, other studies have argued against the anti-inflammatory effect of PRL in arthritis. PRL treatment enhances disease progression of collagen-induced arthritis only when delivered during the immunization phase [236], although the same report revealed that treatment with bromocriptine caused exacerbation at a later stage of the disease. In addition, PRL enhances the proliferation and release of IL-6, IL-8, and MMP-3 by RA synovial cells in culture and lowers their production of TIMP-1 [92]. While variations in experimental conditions may contribute to these discrepancies, it cannot be disregarded that PRL can have both protective and exacerbating effects on arthritis and that addressing this paradox is challenging.

Opposing effects may relate to PRL levels since, as previously described, low doses can be proinflammatory and higher doses anti-inflammatory [47, 148, 152]. PRL levels are affected by exposure to a variety of active substances and hormones in the inflammatory milieu. There are reports showing that CFA-induced arthritis lowers [237, 238], enhances [239], or has no effect [6, 240] on PRL circulating levels. Proinflammatory cytokines, such as TNFα and IL-6, stimulate the release of PRL by AP cells [241, 242], and IL-1β, IL-2, and IL-4 downregulate PRL expression in immune cells [243].

Importantly, the inflammatory milieu could influence the conversion of PRL to vasoinhibins. MMP are upregulated in the joints of patients with RA [244] and proinflammatory cytokines [233] and PRL [92] stimulate MMP production by RA synovial cells. MMP cleave PRL to vasoinhibins [90] which, by being antiangiogenic, are able to suppress the neovascularization required for pannus formation [245]. Angiogenesis occurs from the early stage of RA and supports the invasive pannus by enabling the continued accumulation of immune cells, the proliferation of the inflamed tissue, and the swelling of the joints [246, 247]. The upregulation of MMP in the arthritic joint (in response to cytokines including PRL) and the fact that hyperprolactinemia reduces pannus formation [6] raise the possibility that, under a sustained administration of PRL, there is an enhanced generation of vasoinhibins which, by virtue of their antiangiogenic properties, contribute to the protective and regenerative effects of PRL.

The above proposal is challenged by the fact that increased collagenase activity leads to joint destruction and is the basis for the use of MMP inhibitors in RA clinical trials [248]. There is also evidence that vasoinhibins act as potent proinflammatory cytokines in lung tissues [49, 168], where PRL is anti-inflammatory [87, 249]. Much work is needed to characterize the proinflammatory effects of vasoinhibins, and nothing is known regarding the actions of these peptides in joint tissues. However, the notion that full-length PRL has anti-inflammatory and proangiogenic effects and acquires pro-inflammatory and antiangiogenic properties after undergoing proteolytic cleavage to vasoinhibins provides an efficient mechanism for balancing these two processes and a new avenue that may clarify the controversial role of this hormone in pathologies such as

RA that are characterized by inflammation and exacerbated angiogenesis.

Enhanced RA risk and severity correlate with pregnancy complications affecting the functionality of the PRL/vasoinhibin axis, which may help illustrate the considerations above. Such adverse pregnancy outcomes include preterm and small-for-gestational-age delivery [250], delivery of infants with very low and extremely low birth weight [251], low birth weight in general [252], and preeclampsia [253]. The levels of vasoinhibins are elevated in the serum, urine, and amniotic fluid of patients with preeclampsia, and vasoinhibin values in amniotic fluid are inversely correlated with birth weight [254–256]. Excessive inflammation and dysregulation of angiogenesis inhibitors are key factors in the etiology of preeclampsia [257] that may be influenced by an imbalance of the PRL/vasoinhibin axis [254, 258] and lead to the increased risk and severity of RA.

Evolutionary implications

RA belongs to a large family of acute and chronic arthritic diseases defined as inflammatory arthropathies that, in humans, also include spondyloarthritis (comprising ankylosing spondylitis, reactive arthritis, psoriatic arthritis, arthritis conditions associated with inflammatory bowel disease), septic arthritis, gout, and osteoarthritis. These are ancient diseases with cases identified in fossil records from millions of years ago in Triassic dinosaurs and Pleistocene mammals, and from thousands of years ago in Neolithic man (reviewed by [259]). In spite of evolutionary pressures, inflammatory arthropathies stand as prevalent disorders across contemporary terrestrial vertebrates. To explain such prevalence, it is proposed that the painful and limiting characteristics of arthritis could have represented an adaptation selected to restrain animals from physically demanding activities and energy expenditure when facing adverse conditions such as starvation, stress, pregnancy, lactation, and aging [260]. The strong association between inflammatory arthropathies and age, gender, and reproduction suggests that factors upregulated under these conditions helped to maintain these diseases throughout evolution. One such factor is PRL, a stress-related, sexually dimorphic, reproductive hormone with an ancient origin. The reader is directed to a recent overview addressing this idea [259].

PRL is thought to have evolved 400 millions years ago [261] to regulate osmoregulation and dispersion of skin pigments in fish and amphibians, ancestral activities that continue to be present in the PRLs of higher vertebrates [262]. Likewise, providing nutrients to the young and stimulating parental behavior, the best-known effects of PRL, also emerged in fish and have been retained in fish, birds, and mammals [259, 262].

The high-energy demands associated with feeding and tending the young make wild organisms particularly susceptible to adverse stressful conditions. Stress downregulates PRL levels in birds, thereby interfering with parental behavior [263]. In mammals, there is an attenuation of physiological and behavioral stress responses during pregnancy and lactation [264] that is counteracted by inhibiting the expression of PRL receptors in the brain [86]. Reduced reaction to stress not only ensures maternal care under aversive conditions, but can also be detrimental for parent survival. PRL inhibits anxiety [86] but acquires anxiogenic properties upon conversion to vasoinhibins [48]; thus, the PRL/vasoinhibin axis [14] may represent an efficient mechanism for adjusting stress responses and maximizing reproduction and survival under challenging conditions such as arthritis.

While ample evidence exists in rodents and humans, there have been remarkably few or no studies in non-mammalian vertebrates regarding effects of PRL on joint tissues and immune cells. However, the facts that reproductive effects of PRL and PRL stress-related interactions are phylogenetically conserved and that PRL receptors are present in immune, bone, and muscle cells of fish [265, 266] and birds [267, 268] prompt the speculation that the PRL functions in non-mammalian vertebrates, similar to its role in mammals, as an epigenetic, adaptive regulator of arthritis development, influencing its prevalence throughout evolution.

As for the PRL/vasoinhibin axis, a PRL sequence comparison between species of several taxons indicates the possibility that vasoinhibins first emerged in tetrapods as no vasoinhibin-generating cleavage site was identified in Teleost fish (Zebrafish), Ray-finned-fish (Spotted gar), and Lobe-finned fish (Coelacanth). Amphibians, reptiles and birds, however, possess cleavage sites required for the generation of vasoinhibins, indicating the possible existence of a PRL/vasoinhibin axis in these vertebrates [14]. The emergence of the PRL/vasoinhibin axis in tetrapods correlates well with the effects of this axis on joint physiology and disease, as arthritis essentially occurs in terrestrial vertebrates [259].

Concluding remarks

The influence of stress, gender, and reproduction on the pathogenesis of RA points to a possible contribution of PRL, a stress-related, sexually dimorphic, reproductive hormone with effects on joint tissues and immune cells. The female preponderance of RA, the increased levels of PRL in the circulation of patients with RA, and the ability

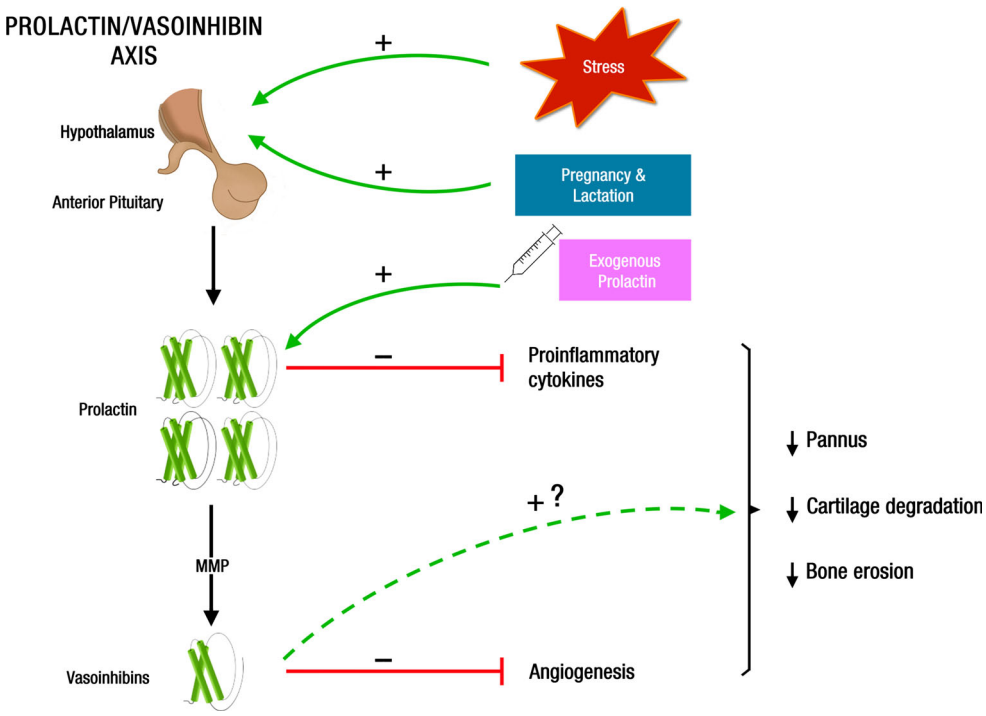

Fig. 3 Mechanisms that contribute to PRL-mediated protection against RA. Hyperprolactinemia induced by stress, reproduction (pregnancy and lactation), and PRL administration acts on joint tissues to reduce proinflammatory cytokine expression and action and to upregulate PRL cleaving proteases (MMP) leading to vasoinhibin-mediated antiangiogenesis; these effects, in turn, lead to reduced pannus formation, cartilage degradation, and bone erosion. Vasoinhibins may act as proinflammatory factors able to counteract PRL anti-inflammatory effects in arthritis, a possibility that needs to be investigated

of PRL to promote inflammation have been the basis for the long-held notion that this hormone is a negative factor aggravating RA. However, the risk and severity of RA are downregulated in reproductive states characterized by hyperprolactinemia (pregnancy and lactation); the circulating levels of PRL only increase in a small proportion of RA patients, and this hormone is also immunosuppressive. The paradox of PRL having both protective and exacerbating effects in RA is better explained when considering the PRL/vasoinhibin axis. This organizational principle takes into account that PRL actions are regulated at the hypothalamus, pituitary gland, and target-tissue levels not only by altering the synthesis and release of systemic and local PRL, but also by regulating the proteolytic conversion of PRL to vasoinhibins as PRL and vasoinhibins activate distinct receptor complexes and cell types to exert their opposite effects on blood vessels and inflammatory reactions. The PRL/vasoinhibin axis is exposed to a variety of active substances that vary according to stress-related and reproductive events preceding and modifying the progression of RA. Some of these agents (catecholamines, glucocorticoids, sex steroids, proinflammatory cytokines, anti-inflammatory cytokines) alter the systemic and local concentrations of PRL and vasoinhibins. Variations in the levels of PRL and vasoinhibins influence the direction of their action in RA. Lower and higher levels of PRL are immunostimulatory and immunosuppressive, respectively, and vasoinhibins counteract the anti-inflammatory and proangiogenic effects of PRL. Of much interest are observations in which hyperprolactinemic states (stress, pregnancy, and lactation) and PRL treatment protect against inflammation and joint destruction in arthritis by mechanisms that may include reduced proinflammatory cytokine expression and action and the upregulation of cleaving proteases (MMP) leading to vasoinhibin-mediated antiangiogenesis, actions that lead to reduced pannus formation, cartilage degradation, and bone erosion (Fig. 3). A therapy based on elevating PRL serum levels may be comparable to the well-established use of glucocorticoids in patients with RA, whose levels of the endogenous hormones appear insufficient to control the disease [269].

There is much to learn about the mechanisms mediating the opposite effects of PRL on joint tissues and immune cells and about how such mechanisms interact with those activated by vasoinhibins to result in specific outcomes in RA. Unraveling interactions at the level of the PRL/vasoinhibin axis will very likely help to understand the pathogenesis of RA and offer new treatment approaches to control this complex disease.

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