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Review

The prolactin receptor: Diverse and emerging roles in pathophysiology

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ABSTRACT

Investigations over two decades have revised understanding of the prolactin hormone. Long thought to be merely a lactogenic hormone, its list of functions has been extended to include: reproduction, islet differentiation, adipocyte control and immune modulation. Prolactin functions by binding cell-surface expressed prolactin receptor, initiating signaling cascades, primarily utilizing Janus kinase-signal transducer and activator of transcription (JAK-STAT). Pathway disruption has been implicated in tumorigenesis, reproductive abnormalities, and diabetes. Prolactin can also be secreted from extrapituitary sources adding complexity to understanding of its physiological functions. This review aims to describe how prolactin exerts its pathophysiological roles by endocrine and autocrine means.

Introduction

The hormone prolactin has long been recognized for its role in lactation. However, evidence has emerged of its more promiscuous nature, with proposed functions as diverse as islet differentiation, immune modulation, adipocyte control and reproduction (Fig. 1). With such a variety of functions reputedly contributed to by prolactin it is perhaps unsurprising that its receptor, the prolactin receptor (PRLR), is expressed on diverse tissues [1–6]. The PRLR is a type-I cytokine receptor that signals predominantly via the JAK2-STAT5 signaling pathway, but is capable of initiating other signal cascades [7]. The structure and signaling pathways of prolactin and its receptor have been the focus of several excellent reviews [7,8] and therefore will not be the focus of this review. Instead, the pathophysiological roles of prolactin will be discussed, taking into consideration both its endocrine role, when produced by the pituitary, and its autocrine role, when produced locally by tissues.

Role of PRLR in lactation and reproduction

A role for prolactin in lactation has been established for decades, yet new insights continue to emerge. Prolactin plays a crucial role in two reproductive functions: mammary gland development during late gestation and the early post-partum period, and formation of the corpus luteum following blastocyst implantation [9,10].

During pregnancy the mammary gland undergoes extensive ductal side-branching and alveolar budding evolving to a milk-secreting gland [11]. Prolactin contributes to both proliferation and differentiation of mammary tissue [12]. *Prlr*$^{-/-}$ mice do not develop mammary gland terminal-end buds and are unable to lactate, similarly to *Jak2*-conditional and *Stat5a*-conventional knockout mice [13–17]. Impairment of mammary gland development is not as severe in *Stat5b*-null mice, but milk protein production is affected, demonstrating both STAT5 components are necessary for lactation [18,19]. Furthermore, these studies suggest that other PRLR-mediated signaling pathways, and PRLR-independent pathways, are unable to fully compensate for the JAK-STAT pathway in mammary gland function.

Both long and short forms of PRLR are required for milk protein expression and lactation [20]. Initial studies of *Prlr*$^{+/-}$ mice demonstrated impaired mammary gland alveolar differentiation and failure to lactate on first pregnancy, but recovery on subsequent pregnancies [15,16,21,22]. However, later investigations showed this recovery may be mouse strain dependent as breeding onto a pure C57BL/6 background could not rescue heterozygous lactation in most animals [23]. Mammary gland developmental defects observed in *Prl*$^{-/-}$ and *Prlr*$^{-/-}$ mice are largely mediated by loss of the progesterone surge in early pregnancy [16,24]. Treatment of mice with progesterone restores ductal side-branching defects [15].

The progesterone surge is produced by the corpus luteum, and is necessary for decidualization of endometrial tissue [10]. PRLR expression increases at decidualization [10,25] and prolactin stimulates progesterone secretion and progesterone receptor expression on uterine epithelium, providing favorable conditions for implantation

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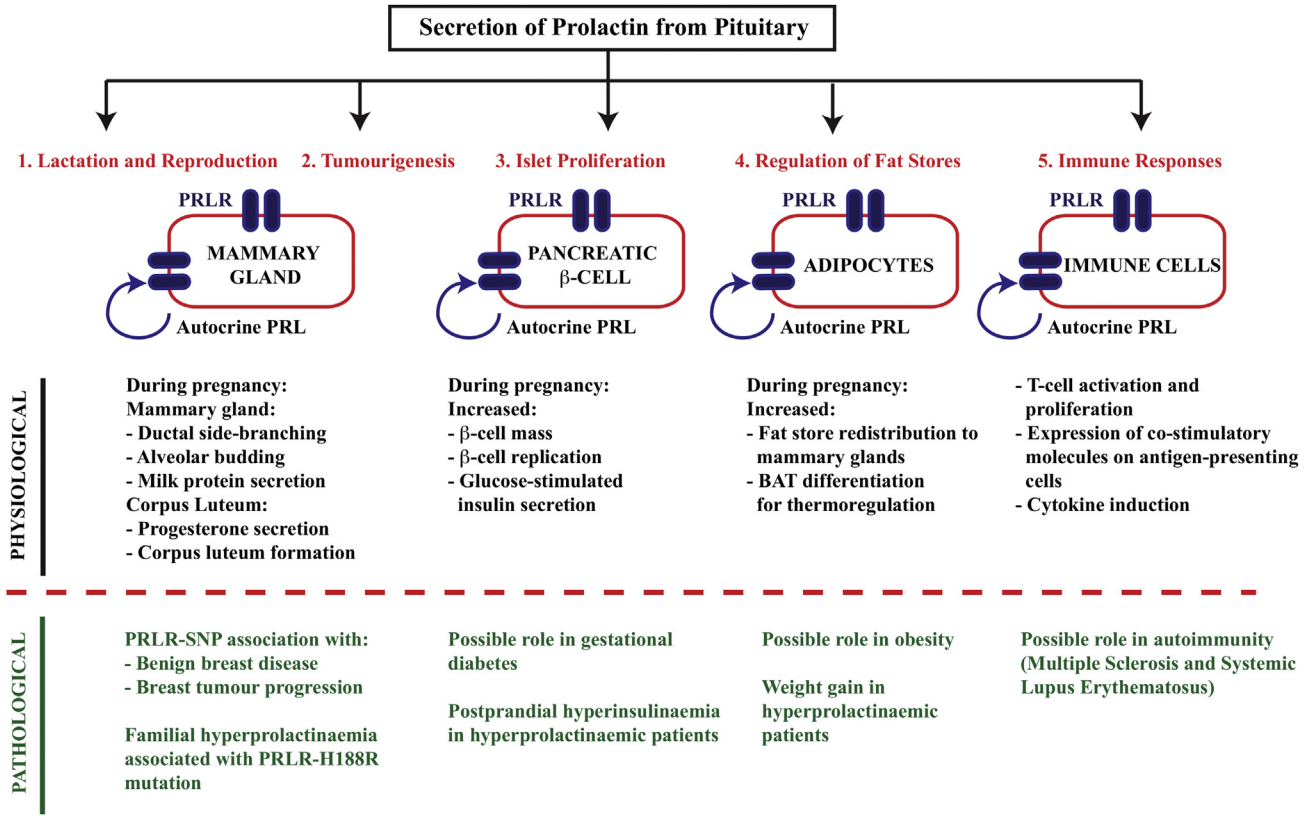

Fig. 1. Summary of the diverse functions of the PRLR. The PRLR is proposed to have a role in reproduction, islet differentiation, regulation of fat stores and immune responses. PRLR is expressed on mammary gland cells, pancreatic β-cells, adipocytes and immune cells. Prolactin secreted by the pituitary gland has a number of physiological effects on these tissues (black text). Prolactin can also be secreted by cells within these tissues, leading to autocrine effects. Impairments of these functions due to mutation of the receptor, or changes in expression, may lead to pathological states (green text).

[8,26]. Prolactin reduces the frequency and amplitude of luteinizing hormone pulses by direct actions on gonadotropin-releasing hormone neurons, and indirectly via γ-aminobutyric acid and kisspeptin neurons [27]. *Prlr*$^{-/-}$ female mice are hyperprolactinemic and infertile [16]. Egg development, ovulation and blastocyst implantation are reduced in *Prlr*-null mice [16,21,24,26]. In addition, corpus luteal formation is regressed in early pregnancy and progesterone production reduced [26]. As in the mammary gland, progesterone administration is able to rescue these phenotypes in *Prlr*$^{-/-}$ mice [28]. Full corpus luteal formation requires both STAT5a and STAT5b as double knockout mice are infertile, with no corpus luteum, while single knockouts retain some fertility [18,19,29]. Autocrine prolactin produced by uterine cells may also have a function in maintenance of the corpus luteum following initial formation [10].

Hyperprolactinemic patients have variable reproductive abnormalities. 40% of hyperprolactinemic women have amenorrhea [27], other patients have galactorrhea, infertility or hypogonadism [30]. The variability in reproductive abnormalities in humans is reflected in the recently reported hyperprolactinemic family, which harbor a heterozygous PRLR-H188R loss-of-function mutation [31]. The three sisters reported in this study had a shared phenotype of oligomenorrhea, with galactorrhea and infertility also reported [31]. This infertility was not accompanied by abnormal ovulation, and luteal phase progesterone levels were normal [31]. Differences in reproductive abnormalities in patients could stem from different causes of hyperprolactinemia, utilization of different PRLR isoforms, or in the case of this family, from the heterozygous nature of the mutation. Discovery of further families with PRLR mutations could yield further insights into these differences.

Prolactin is less abundant in males than females, consistent with the hormone's primary role in lactation. However, male-specific roles may exist. Hyperprolactinemic patients experience erectile dysfunction (16%) and oligospermia (10%) [27]. *Prl*-null mice have reduced ventral prostate weight compared to wild-type littermates, and mice overexpressing prolactin have prostate hyperplasia [32,33]. Similarly, rats with chronic hyperprolactinemia have prostate enlargement [34]. However, *Prlr*$^{-/-}$ mice have normal plasma testosterone levels and testicular weights [35] and despite a reduced ability to produce a first pregnancy in *Prlr*$^{-/-}$ male mice, subsequent matings were successful [36].

Role of PRLR in tumourigenesis

Elevated PRLR expression and high circulating levels of prolactin have been associated with increased risk of tumor progression and invasion [37–39]. Prospective studies demonstrate up to 95% of female mammary tumors, and 60% of male breast carcinomas express prolactin and/or PRLR [40–42]. This association is replicated in animal models including transgenic mice overexpressing prolactin that develop mammary carcinoma [43,44]. In humans, a direct correlation between single nucleotide polymorphisms (SNPs) in *PRL* and/or *PRLR* and tumor incidence has been sought. Many of these studies failed to identify associations [45–48], however two SNPs, PRLR-I70V and I146L, demonstrate constitutive receptor activity, with one correlating with the occurrence of benign breast disease in a patient cohort [49]. However, these patients did not have elevated serum prolactin, nor did they have differences in other clinical parameters investigated [49,50]. Furthermore, other studies in which

these variants were identified failed to correlate their appearance with cancer prognosis, casting doubt on their importance in neoplasia, not least because of their high prevalence in the normal population [31,46,48]. Other non-coding SNPs in *PRL* or *PRLR* have been associated with breast cancer, however their functional effects are unknown [47,51]. Larger cohorts of cancer patients and a better understanding of PRLR variants across normal populations are required to better understand its role in pathogenesis.

The molecular mechanisms by which prolactin exerts mitogenic actions are being explored, and it is likely multiple complex pathways are involved. This is complicated further by emerging hypotheses that prolactin may alter its signal transduction pathways in breast carcinogenesis. Thus many breast tumors are characterized by reduced STAT5 despite high levels of PRLR expression [52,53]. Often these tumor subtypes: exhibit high levels of mitogen-activated protein kinase (MAPK) signal components including activator protein-1 (AP-1) and pro-invasive matrix metalloproteinases (MMPs); are highly invasive; are associated with resistance to chemotherapy and anti-estrogen treatments; and have a poor prognosis [54]. The tumor microenvironment may be responsible for favoring one signal pathway over another [55]. Stiff collagen matrices are associated with invasive breast cancer [55] and shift prolactin signaling profiles from STAT5-mediated pathways to focal-adhesion kinase and MAPK pathways, favoring proliferation [55]. Furthermore, prolactin signals in high-density matrices, increased MMP expression and favored a disorganized structure allowing for cellular motility [55]. Blocking JAK2 had a similar effect, elevating extracellular signal-regulated kinase 1/2 (ERK1/2) and transforming growth factor-β favoring epithelial-mesenchymal-transition and tumor metastasis [56].

The tumor microenvironment potentially holds the key to deciphering the complex interplay between PRLR and estrogen receptor (ERα). Whilst expression of ERα or PRLR alone had no effect on tumor progression, co-expression of PRLR and ERα within a non-compliant, stiff matrix is associated with increased invasiveness in tumor cell models and reduced responsiveness to estrogen antagonists [57]. Furthermore, co-operativity between the two pathways exists with each hormone inducing expression of the reciprocal receptors in cellular studies [58–60].

Other molecular markers of breast cancer exist within the PRLR pathway. PRLR turnover mediated by phosphorylation of S349 is critical in preventing long-term stabilization of the receptor that favors tumor progression [41]. Receptors resistant to degradation had higher levels of MMP9 and exhibited invasive behaviors [41,61]. A novel protein partner of the PRLR, calcium-modulating cyclophilin ligand (CAML), is highly expressed in breast cancer [62]. CAML acts as a scaffold protein, prolonging PRLR interaction with signal transduction components, and increasing proliferation [62]. Studies have also revealed an intrinsic component of the PRLR pathway may contribute to understanding of prolactin's role in tumorigenesis. The STAT5 proteins, STAT5a and STAT5b, though highly related, have distinct expression patterns in breast tumors where nuclear STAT5a is reduced, while STAT5b remains unchanged [63]. This low level of STAT5a was associated with poor prognosis [63], indicating it could act as a novel biomarker to predict tumor outcomes. This finding may explain some of the conflicting reports regarding STAT5 expression in breast cancer, as commonly used antibodies often cannot distinguish between STAT5a and STAT5b proteins [63].

Investigation of the neoplastic role of prolactin has been further hampered by the indiscriminate study of global prolactin, without consideration of prolactin produced by the mammary gland [64]. Autocrine prolactin production has been shown in human breast tissue [65,66], and in mouse models (following hypophysectomy [65], and in the transgenic NRL-PRL mouse model that enriches prolactin within the mammary environment, while retaining normal global prolactin levels) [59,67]. In NRL-PRL female mice estrogen treatment, although not necessary for tumor development, enhances prolactin-induced tumorigenesis [68]. However, one study examining breast cancer tumors and cell-lines was unable to detect elevated prolactin [44], concluding that autocrine prolactin may not be important in all patients.

The prolactin autocrine-paracrine loop may play a role in male breast carcinoma [40] and other reproductive cancers including cervical [69] and prostate cancer [34,40]. Evidence for this autocrine role is provided by transgenic mice overexpressing *Prl* under a prostate-specific promoter (Pb-PRL) that developed prostate hyperplasia in the absence of elevated serum androgen levels [70].

There is still much to be learned about the role of prolactin and its receptor in tumorigenesis. It is likely further investigation of the tumor microenvironment and the effects of autocrine–paracrine signaling will yield new avenues of investigation. Further, a greater understanding of the molecular signatures of breast tumors could highlight new therapeutic targets, yielding fresh hope for drugs targeting PRLR pathways that have thus far produced poor results [67].

Role of PRLR in islet proliferation

The PRLR is highly expressed at the pancreatic β-cell, and may play a fundamental role in the β-cell expansion that occurs to meet increased metabolic demands required during pregnancy [5,71]. Correlations between the rise in β-cell mass and the mid-pregnancy lactogenic surge led to the hypothesis that prolactin and placental lactogen drives this β-cell differentiation [5,71]. In support of this hypothesis cellular studies show the lactogenic hormones increase PRLR expression on β-cells, induce β-cell replication and increase glucose-stimulated insulin secretion (GSIS) [5,72] *In vivo* studies provide further evidence. *Prlr*$^{-/-}$ mice had reduced β-cell mass, reduced islet density, impaired glucose tolerance, reduced insulin secretion, and islets contain 20–35% less insulin [5]. Heterozygous mice similarly had impaired glucose tolerance, which was affected by maternal genotype, with more pronounced impairments in those with heterozygous mothers [5]. This is reminiscent of human gestational diabetes in which it has been observed that prenatal exposure to gestational diabetes increases its risk in the next generation [73].

In vitro and *in vivo* studies have provided a wealth of data on prolactin's effect on pancreatic islets allowing rudimentary pathway insights. Prolactin largely regulates its functions on the pancreatic β-cell via the JAK2-STAT5 pathway [74]. Cells infected with Ad-shSTAT5b that silences STAT5b, displayed reduced insulin signaling [75]. Furthermore, mice injected with Ad-shSTAT5b had reduced glucose tolerance, glucose clearance and insulin signaling in the liver [75]. Mice in which pancreatic β-cell *Stat5a/b* has been deleted exhibit no discernible defects in β-cell development, but aged and pregnant mice are mildly glucose intolerant [76]. This phenotype was milder than that observed in *Prlr*-null mice indicating STAT5 alone is not responsible for all prolactin-mediated effects on β-cells.

The activated PRLR acts as a hub to nucleate proteins from diverse signaling pathways. The insulin-related substrate proteins (IRS1-3) are one such protein family that act as signal adapters allowing recruitment of Akt and phosphoinositide-3 kinase (PI3K), that activate further signal cascades (e.g. MAPK) and gene transcription. Prolactin induces phosphorylation of all three IRS proteins, most likely via JAK2 [77]. Anti-sense PRLR blocks this prolactin-induced increase in IRS1/2, Akt and ERK1/2 phosphorylation [78].

Downstream targets of these prolactin-induced pathways include glucokinase [79] and cell-cycle proteins (e.g. cyclin-D2) [71,80] and transcription factors (e.g. forkhead-box protein D3 (FOXD3)) [81]. Glucokinase regulates the rate-limiting step in glucose metabolism [79]. Its expression is increased in

prolactin-treated cells, even in the absence of glucose [79]. This mechanism is STAT5-dependent and leads to increased insulin secretion [79]. *PRLR*-siRNA treatment reduces cyclin-D2 expression in INS-1 cells [71,80] and cyclin-D2 knockout mice are glucose-intolerant [82]. However, $Prlr^{+/-}$ mice had normal *CCND2* expression levels [83]. Pancreas-specific deletion of *FoxD3* leads to gestational diabetes in mice characterized by impaired glucose tolerance, reduced β-cell mass and reduced β-cell proliferation [81]. The wild-type offspring of $Prlr^{+/-}$ mice have reduced *FoxD3* and decreased Akt phosphorylation [73], indicating FOXD3 is a major driver of Akt-mediated β-cell proliferation [73].

PRLR may mediate its effect on islets in part by regulating the tumor suppressor protein menin. In the normal state, menin regulates expression of the cyclin-dependent kinase p27 and p18, whose function is to inhibit islet proliferation [84]. However, in the pregnant state, menin, p27 and p18 are reduced, which coincides with the increased proliferation observed in pancreatic β-cells [83]. $Prlr^{+/-}$ mice also have elevated p18 and fail to increase IRS2 and Akt expression [83]. These findings, when considered in light of previous findings that prolactin increases BCL6-mediated repression of MEN1 transcription via STAT5 activation [84], indicate that the reduced β-cell mass observed in $Prlr^{+/-}$ mice may be mediated by prolactin's action on menin, via Akt and JAK-STAT pathways within pancreatic β-cells.

Other regulators of the prolactin-induced effects during pregnancy have emerged recently, though their precise roles remain controversial. These include the enzyme tryptophan hydroxylase (Tph1) that regulates the rate-limiting step in serotonin synthesis that was reported to be increased during pregnancy [85]. Mice fed a low-tryptophan diet had mild gestational glucose intolerance [85]. Furthermore, prolactin treatment was shown to increase *Tph1* expression and serotonin synthesis during pregnancy [85], whilst *PRLR* knockdown in insulinoma cells reduced *Tph1* expression [71]. This led to the proposed model in which lactogenic hormones drive the expression of Tph1 and its receptor on target cells leading to $G\alpha_q$-mediated activation of β-cell proliferation during pregnancy, followed by $G\alpha_i$-mediated inhibition of β-cell proliferation in the post-partum period [85]. Although, Schraenen et al. [86], were able to demonstrate a similar increase in Tph1 induction by PRLR-JAK2-STAT5 in a subset of islets, they observed no differences in β-cell proliferation in *Tph1*-null mice compared to control mice [86]. Such discrepancies may lie in the mouse strains used to study these effects as proposed recently by Goyvaerts et al. [87]. Alternatively, the serotonin-induced effects may be mediated via a different mechanism, such as the β-cell expressed serotonin-gated cation channel that has been shown to depolarize the β-cell membrane, thus lowering the threshold for glucose-stimulated insulin secretion required during pregnancy [88]. Such findings have highlighted the requirement for further investigation of the function of serotonin in human islets, and the role PRLR plays.

In spite of growing evidence that prolactin plays a critical role in regulating β-cell changes observed in pregnancy, a convincing role in man has yet to be identified. Studies of chronic hyperprolactinemia demonstrate patients have postprandial hyperinsulinaemia and an exaggerated insulin secretory response to glucose [89]. Furthermore, significant associations between two PRLR SNPs and gestational diabetes mellitus have been shown [90]. However, other studies could not demonstrate similar effects, possibly due to the complex cross-talk between PRLR and insulin receptor. Further research is required to determine the role, if any, that prolactin plays in human pancreatic adaptation to pregnancy.

Role of PRLR in adipose tissue

In a situation analogous to that of the pancreatic islet, the adipocytes must undergo extensive changes during pregnancy and lactation, comprising neuronal changes that permit increased food intake, and fat store redistribution to satisfy energy demands [91]. During these periods fat store distribution shifts from abdominal tissues to mammary glands [91]. Coincident with this fat redistribution is the lactogenic surge at mid-to-late pregnancy, implicating a role for prolactin in this process. $Prlr^{-/-}$ mice have reduced weight gain after 16 weeks which is more obvious in females [92]. Consequently abdominal fat stores are reduced and fasting plasma levels of the adipocyte hormone leptin are reduced in $Prlr^{-/-}$ female mice [92].

The role of prolactin in adipocyte differentiation in brown adipose tissue (BAT) has been investigated [93]. BAT mediates adaptive thermogenesis, a process required for thermoregulation in neonates. The protein UCP1 plays a critical role in this process by shifting proton gradients generated at the inner mitochondrial membrane from energy production to generate heat [94]. BAT mass in neonate PRLR-null mice was significantly reduced compared to wild-type littermates, and brown adipocytes had decreased triglyceride content [93]. Furthermore, these mice were more sensitive to a cold challenge, and had reduced expression of uncoupling protein-1 (UCP1), known to be involved in the thermogenesis process, as well as genes involved in adipocyte differentiation (e.g. peroxisome proliferator-activated receptor-γ (PPARγ)) [93]. $Prlr^{-/-}$ neonates had smaller mitochondria in BAT. PRLR overexpression rescued BAT differentiation in immortalized preadipocytes and restored PRLR, UCP1 and PPARγ protein expression illustrating the critical role for PRLR in regulation of BAT differentiation. Furthermore, the authors demonstrated that IGF2 may mediate the growth of adipocytes downstream of PRLR-STAT5 [93].

Modulation of food intake is partially controlled by the hormone leptin whose receptor shares signaling pathways with PRLR. During lactation, plasma leptin levels reduce by 40% [92]. Furthermore, rats and mice have gestational leptin-resistance attributed to the lactogenic surge that occurs at this period [95]. The prolactin receptor and leptin receptor share expression sites within the hypothalamus and brainstem, thus crosstalk may exist between the receptors [96]. It has been suggested that PRLR activation induces increased expression of suppressor-of-cytokine signaling (SOCS) proteins which directly inhibit STAT3-mediated pathways downstream of the leptin receptor [96]. However, other studies suggest no interaction between PRLR and the leptin receptor, as demonstrated by normal responses exhibited by the $Prlr^{-/-}$ mice exposed to a leptin antagonist [91]. Such discrepancies may have arisen because prolactin-mediated effects require insulin coexpression [25,28].

In humans, sustained hyperprolactinemia caused by antipsychotic drugs or prolactinoma is associated with weight gain and insulin resistance [97]. This can be corrected by administration of dopamine agonists such as bromocryptine [98]. Furthermore, two SNPs located close to the *PRL* gene have been associated with increased risk of obesity [99,100]. Examination of larger cohorts with detailed phenotyping may provide fresh insight into PRLR's role in adipocytes.

Role of PRLR in immune responses

PRLR is expressed on all leukocytes of the immune system, and highly expressed in the spleen and thymus [101]. Although numerous *in vitro* studies have demonstrated prolactin can activate immune system cells, this remains controversial, with evidence indicating these findings may have no relevance in physiological settings, not least because mouse models fail to replicate these responses.

Studies demonstrate that prolactin enhances T-cell activation by several means including: 1) activation of the earliest known T-cell surface antigen, CD69, that is necessary for prolonged T-cell

activation and proliferation [102,103]; 2) activation of CD25, the α-chain of the interleukin (Il)-2-receptor, that regulates proliferation and expansion of T-cell subsets [103]; 3) phosphorylation and activation of the T-cell receptor component CD3, and second messenger kinases Fyn and ZAP70 [64,104,105]; 4) enhanced expression of CD40, CD80 and CD86 co-stimulatory molecules on antigen presenting cells [106]; 5) induction of cytokines involved in enhancing T-cell responses including Il-1, Il-12 Il-16 and interferon-γ [106,107]; and 6) sensitivity of immune responses to dopamine agonists [106]. It is largely accepted that prolactin is unable to initiate these responses in isolation, and more likely acts as an adjuvant to existing immune responses, evidence of which is provided by enhanced activation of T-cell pathways in response to concanavalin-A, lipopolysaccharide and phytohaemaglutinin (PHA) stimuli [107–109].

Autoimmune states provide a model to investigate prolactin's role in immunity. Multiple sclerosis (MS) is one such state, which is more prevalent in females, indicating a possible hormone-driven effect. Pregnant MS patients have increased relapse rates within the first three months post-partum, correlating with increased prolactin levels [110]. Similarly in systemic lupus erythematosus (SLE), elevated prolactin levels in patients correlate with disease severity [110] and treatment with bromocryptine relieved symptoms [106]. However, SLE mouse models were unable to demonstrate an enhancement of the condition in the presence of prolactin [110].

The controversies in this field not only lie in these autoimmune discrepancies. Much of the evidence for prolactin-mediated immune responses are derived from *in vitro* studies using peripheral blood mononuclear cells (PMBCs) or immortalized cells such as Jurkat T-cells, which may not reflect the physiological state. *In vivo* studies using $Prl^{-/-}$ and $Prlr^{-/-}$ mouse models have cast doubt on prolactin-mediated immune modulatory functions. $Prl^{-/-}$ mice have comparable levels of CD4+ and CD8+ cells to wild-type littermates [111]. Furthermore, PHA-stimulated T-cell and B-cell responses were only impaired in $Prl^{-/-}$ mice following thermal stress [108], indicating PRL may not have a role in physiological states. $Prlr^{-/-}$ mice have no differences in either pro- or pre-B-cells, mature circulating B-cells, early T-cell precursors, immunoglobulin subclasses or NK-cells compared to wild-type littermates [112]. In addition, combination treatments of PRL and concanavalin-A or *Listeria monocytogenes* were unable to enhance immune responses above that seen with pathogen alone [112].

Finally, studies of immune responses in affected members of the hyperprolactinemic family with the PRLR-H188R mutation indicated no changes in immune cell subsets [31]. Furthermore, prolactin did not enhance T-cell responses to PHA in PMBCs isolated from affected family members [31]. These studies indicate that the role of prolactin in immune responses may be more complicated than originally proposed, with the possibility that prolactin responses are mediated by another receptor.

Summary

Research within the last two decades has identified new and unexpected roles for prolactin and its receptor, governed by multiple signaling pathways. Potential pathogenic roles in infertility, cancer, diabetes and obesity raise the possibility that PRLR and/or its downstream pathways will likely lead to novel therapies in these vital and highly prevalent disease states.

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