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REVIEW

Oncostatin M: friend or foe in PCOS pathogenesis?

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Abstract

Polycystic ovary syndrome (PCOS) is a primary endocrinological disorder in women of reproductive age that is characterized by androgen excess and ovulatory irregularities. This syndrome is associated with adipose tissue dysfunction, an elevated risk of insulin resistance, hyperinsulinemia, obesity, and type 2 diabetes. Adipocyte dysfunction affects the secretion of adipokines and pro-inflammatory cytokines. Nevertheless, adipose tissue is not an exclusive source of adipokines as it can also be produced locally by reproductive tissues. Although adipokines have been recognized in the development of PCOS, the role of oncostatin M (OSM), a multifaceted adipokine, remains unclear. Current evidence suggests that this cytokine is associated with key aspects of the syndrome, including obesity, insulin resistance, hyperandrogenism, and inflammation. However, the data are often contradictory, likely due to variations in study designs, methodologies, and species differences. By investigating the link between OSM and PCOS-associated issues, this review identified the potential role of this adipokine in PCOS pathogenesis. This underscores the need for further research to clarify its predominant effects and assess its relevance as a therapeutic target.

Keywords: insulin resistance; obesity; oncostatin M; ovarian function; PCOS

Introduction

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder among women of reproductive age, impacting approximately 12–18% of women according to established diagnostic criteria (March *et al.* 2010). The key manifestations of PCOS include excessive androgen levels, irregular ovarian function, and polycystic ovaries. This syndrome can adversely affect both reproductive and metabolic processes, increasing the vulnerability to insulin resistance, diabetes mellitus, and dyslipidemia among affected individuals (Wild 2012). Although the exact underlying causes are not fully understood, available data indicate that adipokines play a significant

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role in the etiology of PCOS (Schüler-Toprak *et al.* 2022, Xu *et al.* 2022).

Oncostatin M (OSM) is a multifunctional cytokine involved in a broad spectrum of biological processes, including homeostasis, hematopoiesis, hepatogenesis, adipogenesis, inflammation, and extracellular matrix remodeling (Brounais *et al.* 2008, Hermanns 2015, Sanchez-Infantes & Stephens 2020, Sims & Lévesque 2024). Its role in inflammatory conditions is well documented, with altered OSM levels observed in various diseases such as rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, and fibrosis (Albasanz-Puig *et al.* 2011, Stawski & Trojanowska 2019, Garbers & Lokau 2024). Emerging evidence also highlights OSM production within reproductive tissues, suggesting its involvement in key stages of ovarian function, including folliculogenesis, ovulation, and the luteal phase (Martins *et al.* 2019, Nikanfar *et al.* 2022). These roles are explored in greater detail in subsequent sections.

Transcriptomic investigation of granulosa cells (GCs) from individuals with PCOS revealed the significance of OSM, along with several other genes, in the initiation of PCOS (Li *et al.* 2023). In contrast, another study showed a noteworthy reduction in the concentrations of OSM and its receptor (OSMR) in the follicular fluid of individuals diagnosed with PCOS (Nikanfar *et al.* 2022). This decline might represent a secondary response, as the study demonstrated a substantial upregulation in one of the inhibitory factors within the OSM signaling pathway, the suppressor of cytokine signaling-3 (SOCS3), which exhibited a significantly negative correlation with OSMR expression levels. Another possible explanation for this controversy could be the ovarian stimulation protocol given that these PCOS patients were undergoing infertility treatment. Additionally, a recent study by Camili *et al.* (2024) reported lower plasma concentrations of OSM in PCOS patients. Given the limited number of studies on OSM signaling in PCOS pathogenesis, this review aimed to explore the role of OSM in PCOS-related issues and its potential relevance in this syndrome.

Oncostatin M

The IL-6 or gp130 cytokine family comprises cytokines that share similar structures, including OSM, IL-6, IL-11, IL-27, IL-30, IL-31, leukemia inhibitory factor (LIF), cardiotrophin-1, ciliary neurotrophic factor (CNTF), neuropoietin, and a novel neurotrophin-1/B cell-stimulating factor-3 or cardiotrophin-like cytokine (CLC) (Rose-John 2018). OSM plays a regulatory role in diverse cellular and biological processes such as lipogenesis/adipogenesis, inflammation regulation, hematopoiesis, osteogenesis, immune responses, stem cell potency, reproduction, and cardiovascular function, depending on the specific target cells involved (Sanchez-Infantes & Stephens 2020, Xu *et al.* 2023, Sims & Lévesque 2024).

The primary origin of this cytokine is activated immune cells, namely T cells, macrophages, neutrophils, and eosinophils, as well as hematopoietic and mesenchymal cells (Sanchez-Infantes *et al.* 2014). Moreover, it has been documented that the presence of OSM in adipose tissue is linked to its synthesis by immune cells rather than adipocytes, whereas its receptor (OSMRβ) is found in both immune cells and adipocytes (Elks *et al.* 2016). All IL-6 family receptors, including those for OSM, involve a complex that contains the gp130 subunit. OSM exerts its effects through interactions with both the type I and type II receptor complexes. In the type I complex, heterodimerization occurs between the LIF receptor and gp130, whereas in the type II complex, the specific receptor for OSM, OSMRβ, forms a complex with gp130 (Stawski & Trojanowska 2019, West 2019). OSM first forms a low-affinity interaction with gp130, after which either the OSMR or LIFR subunit is recruited to complete the high-affinity receptor complex. The receptor composition of OSM varies among species. For example, murine OSM exhibits a pronounced affinity for the type II receptor complex, whereas OSM in rats and humans can bind to both receptor complexes (Juan *et al.* 2009, Drechsler *et al.* 2012). In addition to full-length OSMRβ, two additional forms of OSMR exist: a short form and a soluble variant known as sOSMRβ (Hermanns 2015). The latter is generated through alternative splicing and, in conjunction with sgp130, functions as an antagonist to impede the signaling initiated by the binding of OSM to OSMRβ (Diveu *et al.* 2006).

The engagement of OSM with either receptor complex I or II initiates the activation of the Janus kinase/signal transducers and activators of the transcription (JAK/STAT) signaling pathway (Dey *et al.* 2013). This interaction triggers a series of intracellular events where the conserved region on the intracellular side of the OSM receptor recruits and activates JAK1 and JAK2 through the gp130 subunit. This activation leads to the phosphorylation and dimerization of STAT proteins, which then translocate to the nucleus to regulate the expression of target genes. Additionally, these receptors can induce the activation of the mitogen-activated protein kinase (MAPK) and PI3K/AKT signaling pathways (Arita *et al.* 2008). Nonetheless, alternative signaling pathways, such as extracellular signal-regulated kinase (ERK1/ERK2), c-Jun N-terminal kinase (JNK), p38, and protein kinase C delta (PKCσ), may be activated by diverse OSM concentrations across various cell types (Hermanns 2015). Human OSMRβ contains a specific tyrosine motif that serves as a recruitment site for STAT5 (Hintzen *et al.* 2008). Interestingly, STAT5 is activated by both mouse and human OSM. Similar to other cytokine receptors, JAK2 directly activates STAT5 upon receptor engagement. However, STAT1 and STAT3 activation involve distinct mechanisms. Although STAT3 activation relies on two conserved tyrosine motifs within the receptor, STAT1 functions in a tyrosine-independent manner, with JAK1 playing a crucial role in its activation (Hintzen *et al.* 2008, Hermanns 2015). These differences

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underscore the complexity of the signaling pathways triggered by OSM and its receptors (Fig. 1).

One of the controllers of OSM signaling is SOCS3, which exerts a negative regulatory influence on this pathway through JAKs, as opposed to direct binding to OSMRβ (Liu *et al.* 2014). OSM induces the expression of SOCS3 primarily through the activation of STAT3. In addition to STAT3, ERK1/2, and JNK also contribute to the induction of SOCS3 (Ehlting *et al.* 2015). Additionally, OSM can induce degradation of its associated receptors, including gp130, LIFRβ, and OSMRβ, thereby modulating their expression. Nevertheless, there is a subsequent elevation in OSMRβ levels due to increased synthesis over time (Blanchard *et al.* 2001).

Roles of OSM in reproductive function

OSM role in ovarian function

The ovaries of newborn mice show positive expression of the OSM protein (Hara *et al.* 1998), and its expression has been observed in both human oocytes and GCs of follicles from the primordial to subsequent stages. The expression of OSMR is limited to oocytes (Abir *et al.* 2005, Eddie *et al.* 2012). Evaluation of expression in primordial follicles and only in a single antral follicle may explain the observed results. However, our previous findings showed both gene and protein expression of OSMR, as well as gene expression of OSM, in GCs of mature human oocytes (Nikanfar *et al.* 2022). Recently, it has been reported that bovine luteal cells have positive mRNA expression of OSM and OSMR, whereas GCs show positive expression only for OSMR during follicle selection and ovulation (Martins *et al.* 2019). Within-species differences may account for some of these discrepancies in the expression of OSM and its receptor. Similar to other ligands of the IL-6 family, OSM is developmentally regulated during gestation in the human fetal ovary. gp130, a co-receptor of OSM, plays a key role in meiosis and ovulation, and its high expression has been reported at the beginning of meiosis in human primordial germ cells (Akdemir *et al.* 2022). OSM has a stimulatory effect on bFGF, which can regulate ovarian development by promoting primordial follicle formation (Zhang *et al.* 2015). Recent research has demonstrated that culturing immature oocytes in maturation media supplemented with OSM increases the maturation rate. The percentages of successfully rescued oocytes from GV to MII and MI to MII were 53.5% and 100%, respectively (Akdemir *et al.* 2022). Furthermore, the beneficial effects of OSM supplementation in IVM on the induction of cumulus-oocyte complex expansion have been previously demonstrated (Clark 2004).

Prior to ovulation, macrophages migrate toward the theca layer of pre-ovulatory follicles, potentially leading to local secretion of OSM and subsequent upregulation of its receptor (Rychli *et al.* 2010). The OSM signaling pathway is one of the most highly enriched pathways among the upregulated inflammatory genes associated with the ovulatory process in GCs (Poulsen *et al.* 2019). The high expression of OSMR in bovine GCs during ovulation may be related to its involvement in inflammatory-like processes (Martins *et al.* 2019). OSMR is among the genes upregulated in GCs following human chorionic gonadotropin (hCG) triggering, with two pathways associated with this gene: acute-phase response signaling and JAK family kinases (Wissing *et al.* 2014, Poulsen *et al.* 2019). OSMR expression in the corpus luteum supports the hypothesis of polymorphonuclear neutrophil migration and accumulation (Martins *et al.* 2019).

Research has demonstrated that treating GCs with OSM in conjunction with follicle-stimulating hormone (FSH) can increase apoptosis by enhancing the BAX/BCL2 ratio and decreasing XIAP mRNA expression. Furthermore, it has been suggested that OSM may influence follicular atresia by activating STAT3 signaling pathways (Martins *et al.* 2019). These findings emphasize the importance of understanding OSM and its receptor regulation at various stages of ovarian function, including oocyte maturation, ovulation, follicle atresia, and luteolysis (Fig. 2).

OSM in pregnancy

Plasma levels of OSM are higher during pregnancy than during early postpartum or non-pregnancy (Bränn *et al.* 2019). It seems that higher levels during pregnancy produced by decidual and chorionic tissues play an important role in the endocrine function of the placenta, such as hCG production by chorionic tissue (Lee *et al.* 2009, Bränn *et al.* 2019). OSM shows an increasing trend of expression from week 8 to 20 of gestation in the human fetal ovary (Eddie *et al.* 2012). Previously, OSM mRNA expression has been observed in the gonadal region of mice during mid-pregnancy (Van den Hurk *et al.* 2000). OSM supports the survival of post-migratory primordial germ cells (PGCs), and increases their number and proliferation during the migratory phase in mice (Koshimizu *et al.* 1996, Hara *et al.* 1998).

OSM expression has been demonstrated at the implantation site and shows an increasing pattern of expression during days 1 to 4 of pregnancy in the uterine epithelium of mice (Fouladi-Nashta *et al.* 2005). In this regard, the stimulatory role of OSM in upregulating the implantation markers of either p-Stat3 or integrin β3 has been reported. In addition, prostaglandin E2-induced OSM participates in implantation and decidualization via the Stat3-early growth response protein 1 (Erg1) pathway and IL-33, respectively (Fu *et al.* 2019). Furthermore, OSM synthesis by trophoblast cells is a determinant factor in the survival of implanted blastocysts (Eddie *et al.* 2012, Chaiwangyen *et al.* 2016). OSM enhances the invasive properties of trophoblast cells throughout the first trimester by increasing the enzymatic activities of matrix metalloproteinase (MMP)-2 and -9 (Wie *et al.* 2018).

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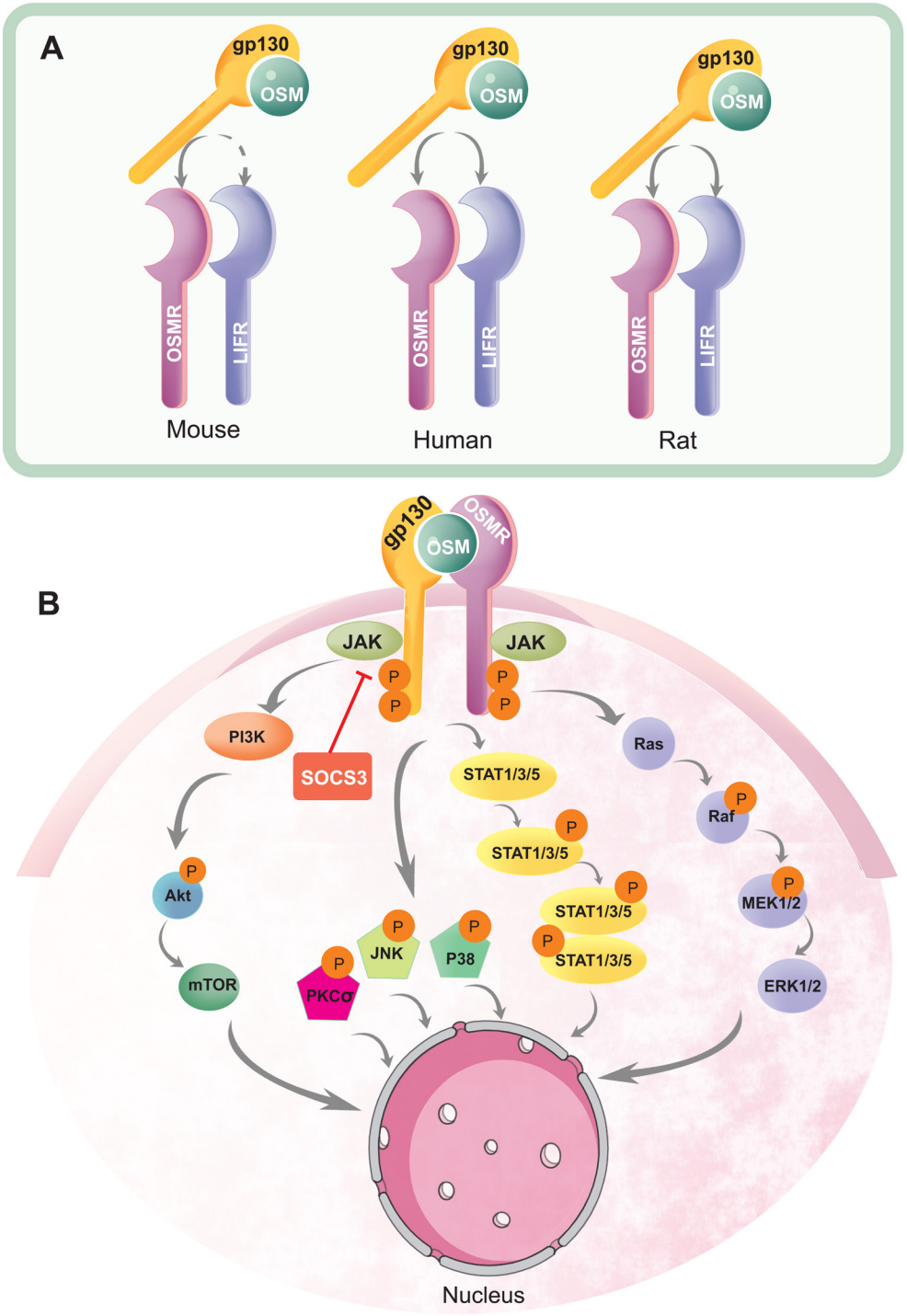

Figure 1

(A) Illustration of Type I and Type II receptor complexes in humans, mice, and rats. The Type I complex consists of the leukemia inhibitory factor (LIF) receptor and gp130, while the Type II complex comprises the oncostatin M receptor (OSMRβ) and gp130. Notably, mouse OSM exclusively utilizes the Type II receptor complex, a heterodimer of mouse gp130 and OSMRβ. (B) OSM signaling pathways. Formation of type II receptor complex leads to JAK-mediated phosphorylation of STATs. Phosphorylated STATs dimerize and translocate to the nucleus to regulate gene expression. OSM also activates other pathways, including Ras/MAPK, PI3K/AKT, ERK1/ERK2, JNK, p38, and PKCσ pathways. Inhibitory effect of suppressor of cytokine signaling-3 (SOCS3) on OSM signaling has been demonstrated. ERK, extracellular signal-regulated kinase; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3 kinase; PKCσ, protein kinase C delta; STAT, signal transducer and activator of transcription. A full colour version of this figure is available at https://doi.org/10.1530/JOE-24-0140.

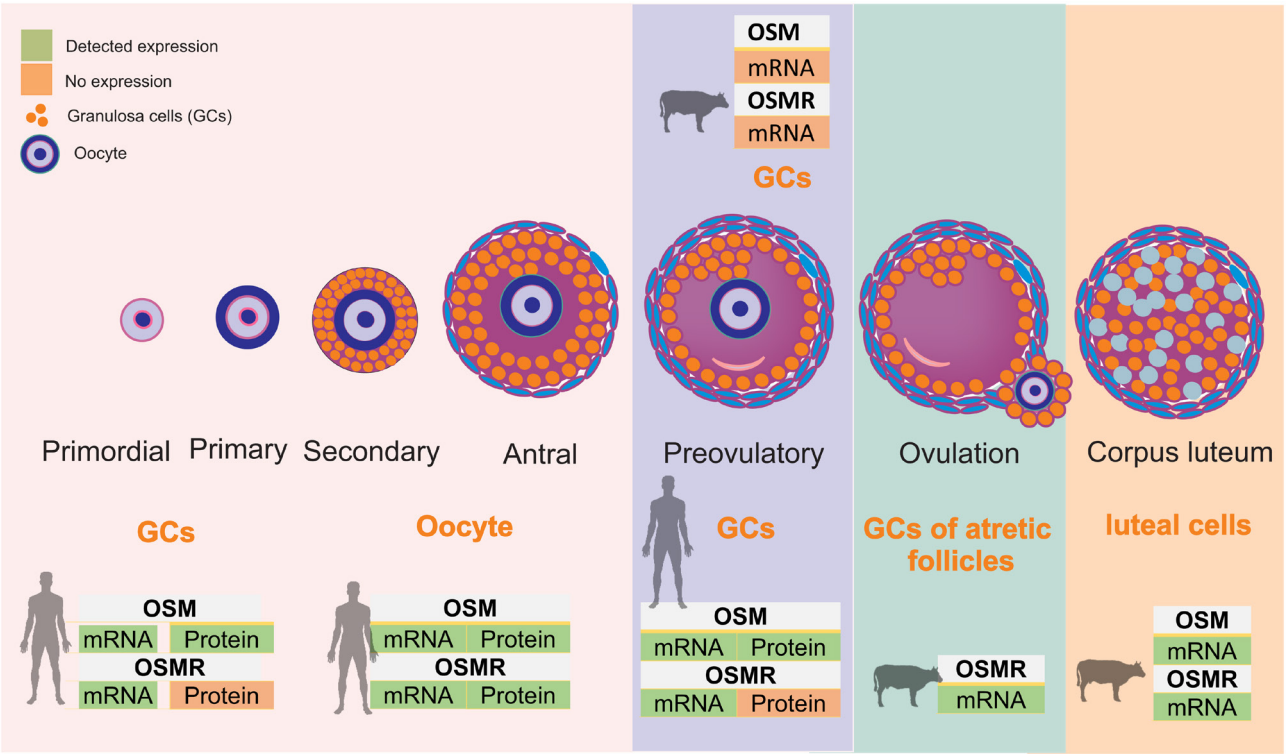

Figure 2

Expression of oncostatin M (OSM) and its receptor (OSMR) in various follicular compartments, including granulosa cells (GCs) and oocytes, throughout folliculogenesis. A full colour version of this figure is available at https://doi.org/10.1530/JOE-24-0140.

Extrathymic differentiation of T cells, which is activated during natural pregnancy, can be induced by OSM (Samstein *et al.* 2012). Shirshev *et al.* (2019) reported that OSM, in combination with hCG and estriol, stimulates the production of induced regulatory T cells (iTreg) and T-cell receptor revision by upregulating the recombination activating gene (RAG-1), thereby enhancing tolerance to fetal antigens. This evidence supports the beneficial role of OSM in pregnancy. However, its precise role remains unclear.

The role of OSM in PCOS-associated issues

Obesity

Evidence suggests that individuals with PCOS often experience accumulation of abdominal fat and weight gain prior to the onset of anovulatory cycles and associated consequences (Dumesic *et al.* 2015). Additionally, a meta-analysis indicated that obese or overweight individuals with PCOS exhibited more severe metabolic and reproductive complications than those with a normal weight (Tokmak *et al.* 2017, Kite *et al.* 2019). The association between adiposity, elevated free testosterone levels, and insulin resistance has been previously demonstrated (Tosi *et al.* 2015).

OSM as a risk factor for obesity

Research has shown that the upregulation of OSM and OSMR in adipose tissue is linked to obesity in both mice and humans (Sanchez-Infantes *et al.* 2014). This upregulation correlates with markers of metabolic disease, such as decreased expression of Glut4, increased insulin resistance indices, and hyperglycemia in obese individuals, underscoring the involvement of OSM in obesity-related pathways. However, this study involved only eight human subjects, which calls for a cautious interpretation of the findings due to the small sample size. In murine models, it has been shown that OSM treatment (12 ng/g of body weight per day for 1 week using micro-osmotic pumps implanted subcutaneously adjacent to adipose tissue) could hinder adipogenesis in brown adipose tissue and the transformation of white adipose tissue into a brown-like state *in vitro* and *in vivo* (Sánchez-Infantes *et al.* 2017). Nevertheless, the administration of an anti-OSM neutralizing antibody in high-fat diet-fed mice did not affect weight or adipose tissue mass. This outcome might stem from either the short duration of treatment or dosage used (Piquer-Garcia *et al.* 2020). However, it is important to note that most studies on OSM have been conducted using mouse models, in which OSM exhibits a different affinity and binds exclusively to type II OSMR. In studies involving OSMR deletion in mice, the observed physiological responses may differ considerably from those in

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humans, in which OSM can interact with both LIFR and OSMR (Han *et al.* 2023).

Role of OSM in improving obesity

In contrast to the aforementioned findings, OSM treatment (1.25, 3.75, and12.5 ng/g of body weight, twice a day for one week, intraperitoneally) in obese mice resulted in improvements in body weight, insulin sensitivity, and reduction in systemic levels of free fatty acids and glycerol (Komori *et al.* 2014, Komori *et al.* 2015). Moreover, the mouse liver exhibits repression of lipogenesis and induction of lipolysis following intraportal infusion of OSM (Komori *et al.* 2014).

Previous research has demonstrated that mice with a targeted deletion of OSMR from adipocytes (OSMR FKO) exhibited increased local inflammation in these cells when subjected to a high-fat diet (Elks *et al.* 2016). A negative correlation has also been reported between serum OSM levels and metabolic markers, including total and non-HDL cholesterol, in PCOS patients (Camili *et al.* 2024). This suggests that OSM may play a role in the metabolic dysregulation observed in PCOS, potentially linking it to the lipid metabolism and cardiovascular risk factors in this population. Further research is required to conclusively determine the precise effect of OSM on lipid metabolism and its relationship with obesity.

Insulin resistance

Women with PCOS often exhibit an inherent form of insulin resistance that is closely associated with their condition (Stepto *et al.* 2013, Cassar *et al.* 2016). This type of insulin resistance is believed to be a key contributing factor to reproductive and metabolic issues commonly observed in individuals with PCOS. A growing body of research has investigated the effects of OSM on insulin response. Although most studies on the association between OSM and insulin resistance have focused on mice, few clinical trials have been conducted in humans. A close association has been observed between serum OSM levels and insulin resistance indices in humans (Sanchez-Infantes *et al.* 2014, Akarsu *et al.* 2019). Moreover, OSM was positively correlated with body weight and negatively correlated with glucose disposal rate (Sanchez-Infantes *et al.* 2014). The implications of these findings and their relevance to metabolic disorders are discussed in detail in the following sections.

OSM role in adipose tissue

Higher levels of OSM expression have been reported in the adipose tissue of diabetic and obese mice and humans (Sanchez-Infantes *et al.* 2014). The M1/M2 ratio of adipose tissue macrophages (ATMs) and the subsequent pro-/anti-inflammatory cytokine ratio can be altered in the adipose tissue of obese mice. The OSM produced by M1 ATMs induces insulin resistance by inhibiting insulin-activated transportation of glucose to the tissues (Yamauchi *et al.* 2001). Furthermore, treatment of murine 3T3-L1 preadipocytes with 1 nM OSM increased the expression of IR-related pro-inflammatory adipokines, including Mcp1, Pai1, Timp1, Spp1, and Igfbpc3 (Elks *et al.* 2016). Similarly, the administration of an anti-OSM neutralizing antibody in high-fat diet mice led to a reduction in blood glucose levels and an increase in insulin levels (Piquer-Garcia *et al.* 2020).

In contrast, OSMRβ−/− mice exhibited adipose tissue inflammation and insulin resistance (Komori *et al.* 2014). In line with these findings, metabolic disorders were improved after intraperitoneal injection of OSM (12.5 ng/g of body weight; twice a day for one week) in a mouse metabolic syndrome model (Komori *et al.* 2014, Komori *et al.* 2015). One suggested mechanism involves the conversion of ATMs phenotypes to anti-inflammatory M2 phenotypes (Komori *et al.* 2013, Komori & Morikawa 2018). The lack of data on body weight and food intake for assessing the health status of mice during injections may be one of the limitations of this study, because the supraphysiological doses of OSM may negatively affect appetite and body weight.

Discrepancies in the role of OSM in insulin resistance in adipose tissue may be partly explained by the differences in OSM expression between the adipose stromal vascular fraction (SVF) and adipocyte fractions of adipose tissue. Sanchez-Infantes *et al.* (Sanchez-Infantes *et al.* 2014) found that most OSM protein was present in murine SVF rather than in adipocytes. Additionally, variations in the effects of global versus tissue-specific knockout of OSMR (Komori *et al.* 2013) could influence outcomes, as OSMR is critical for various biological functions, including hematopoiesis (Sims & Lévesque 2024). Consequently, systemic alterations observed in global knockout models may reflect broader disruptions beyond local tissue effects.

OSM role in the liver

Hepatic OSM plays a key role in the pathogenesis of steatohepatitis, cirrhosis, and insulin resistance. Higher levels of OSMRβ have been reported in the hepatocytes of a hepatic steatosis mouse model (Komori *et al.* 2014, Luo *et al.* 2016). Inhibitory effects of prostaglandin E2-induced OSM (10 ng/mL) released from rat Kupffer cells on glucose and lipid metabolism have been reported. These effects have been associated with the induction of STAT3 phosphorylation and SOCS3, suggesting a defective glucose metabolism. Another proposed mechanism involves the attenuation of insulin-stimulated Akt phosphorylation and stimulation of glucokinase (Henkel *et al.* 2011). These findings support the role of the OSM-OSMRβ signaling pathway in hepatic insulin resistance by promoting lipid accumulation and reducing glucose metabolism. Furthermore, although OSM treatment inhibits fatty acid oxidation in rat hepatocytes (Henkel *et al.* 2011), intraportal OSM injection

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in obese mice has been shown to improve fatty acid oxidation (Komori *et al.* 2015). Other protective effects of OSM have also been observed, such as a reduction in triglyceride accumulation and an increase in fatty acid oxidation, following the stimulation of HepG2 cells or administration of OSM in hamsters (Zhou *et al.* 2007). As mentioned previously, the pattern of OSM receptor usage differs between mice and rats, which may contribute to their contrasting outcomes. Additionally, the study by Henkel *et al.* (Henkel *et al.* 2011) was conducted *in vitro*, limiting its ability to fully reflect the complexities of the *in vivo* environment, where multiple factors interact to influence the metabolic processes.

It has been shown that global or hepatic-specific knockout of OSMRβ resulted in exacerbated diet-induced insulin resistance and inflammation in obese mice. On the other hand, liver-specific OSMRβ overexpression improves insulin sensitivity in mouse models. These findings support the protective role of OSMRβ against obesity-induced hepatic insulin resistance and inflammation via activation of the JAK2/STAT3 pathway in the liver (Luo *et al.* 2016). However, it is noteworthy that suppressing OSMR may affect co-receptors other than gp130, such as IL-31 receptor α, and their signaling pathways (Furue *et al.* 2018). Therefore, tissue-specific manipulation of this cytokine and its receptor, along with measuring the levels of other factors in related signaling pathways (such as IL-31) is essential to elucidate their role in insulin metabolism.

Hyperandrogenism

The relationship between OSM and androgens remains poorly understood due to the limited available information. OSM treatment inhibits testosterone production in immature Leydig cells isolated from rats (Tian *et al.* 2022). Similarly, intratesticular OSM injection in another study resulted in reduced testosterone levels, hindering Leydig cell regeneration without affecting serum LH and FSH levels (Wang *et al.* 2019). Camili *et al.* (2024) did not find a significant association between serum levels of OSM and total testosterone in patients with PCOS. In contrast, Hatziagelaki *et al.* (2020) showed a statistically significant positive correlation between the serum concentrations of OSM and androstenedione levels in PCOS patients. Notably, they observed this positive correlation only after adjusting for age and BMI, highlighting the importance of accounting for confounding factors in such analyses. Hence, further investigation is warranted to elucidate this relationship.

Inflammation

Inflammatory factors may show different expression patterns at various locations within the tissues. For example, it has been documented that the expression of genes associated with inflammation is decreased in the ovarian stroma of individuals with PCOS, whereas in granulosa cells, these genes exhibit an upregulated pattern. The diminished gene expression in the stromal tissue of PCOS patients may have been influenced by the lower presence of leukocytes, as indicated by the quantification of CD45 mRNA levels (Schmidt *et al.* 2014). Owing to the intriguing association of low-grade inflammation with PCOS, we will review the evidence regarding the possible involvement of OSM in this disease. Inflammation is one of the biological functions regulated by OSM (Akarsu *et al.* 2020). Upregulation of OSM has been reported in various inflammatory conditions including rheumatoid arthritis, atherosclerosis (Albasanz-Puig *et al.* 2011), systemic lupus erythematosus, and systemic sclerosis (Pradeep *et al.* 2010, Liang *et al.* 2012) However, its role in ovary-related diseases remains unknown.

Inflammatory role of OSM

OSM is produced by different inflammatory cells, including eosinophils, activated T cells, neutrophils, and macrophages, which are the main sources of OSM in adipose tissue (Ma *et al.* 2019). Furthermore, OSM may influence responses to other cytokines and activate cell adhesion molecules, which subsequently promote leukocyte recruitment. In addition, OSM can regulate the intensity and duration of inflammatory responses by affecting non-hematopoietic cells (West 2019). Immune cell-produced OSM in adipose tissue acts on adipocytes through paracrine mechanisms to induce inflammation.

Inflammation can be associated with cardiovascular risk factors and insulin resistance as other features of PCOS (Abraham Gnanadass *et al.* 2021). In this regard, the role of OSM-regulated pro-inflammatory adipokines (PAI-1, Timp1, Spp1, and Igfbp3) in insulin resistance has been observed in adipose tissue (Elks *et al.* 2016). Moreover, a strong positive correlation was observed between OSM and C-reactive protein (CRP), a marker of inflammation and a significant cardiovascular risk factor (Akarsu *et al.* 2020). However, in the study by Akarsu *et al.*, the correlation was examined in the entire population, including both healthy individuals and those with insulin resistance. This approach could be affected by various factors such as differing levels of chronic inflammation and metabolic profiles between the groups. This could potentially mask important subgroup-specific dynamics, making it challenging to draw precise conclusions about the underlying biology of different populations.

Anti-inflammatory role of OSM

On the other hand, some studies have introduced OSM as an anti-inflammatory cytokine owing to its suppressive effects on inflammation in animal models of diseases, including antibody-induced arthritis, inflammatory bowel disease, multiple sclerosis, and experimental autoimmune encephalomyelitis (Guihard *et al.* 2015, Garbers & Lokau 2024). Increased adipose tissue inflammation has been observed in both global

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(Komori *et al.* 2013) and adipose-specific (Stephens *et al.* 2018) OSMR knockout mouse models. However, in the adipocyte-specific knockout of OSMR, changes in body mass and blood glucose levels were not significant, and insulin responsiveness showed only a modest reduction. These findings suggest that systemic loss of OSMR, likely due to its involvement in hematopoiesis and developmental functions, has broader metabolic consequences (Komori *et al.* 2013, Sims & Lévesque 2024). This highlights the complex tissue-specific roles of OSMR in the regulation of metabolic and inflammatory processes.

Moreover, it has been demonstrated that treatment of both genetically and diet-induced obese mice with OSM improved adipose tissue inflammation, possibly through steering the phenotype of macrophages toward anti-inflammatory M2 and shifting the cytokine synthesis profiles to anti-inflammatory (IL-10 and -13) (Komori *et al.* 2013, Komori *et al.* 2014). Treatment of obese mice with OSM leads to a reduction in both the expression and serum levels of TNF-α (Komori *et al.* 2015). This suggests that OSM may have anti-inflammatory effects in obesity, potentially contributing to the reduction of systemic and local inflammation in the adipose tissue.

Treatment of mouse adipose tissue macrophages with OSM significantly increased the mRNA expression of anti-inflammatory markers such as IL-10 (Komori *et al.* 2015). Furthermore, the injection of wild-type mice with OSM decreased adipose tissue macrophages and upregulated anti-inflammatory genes including, IL-13, IL-10, adiponectin, macrophage galactose-type lectin (Mgl1), and Mgl2 (Komori *et al.* 2013, Komori *et al.* 2015). The anti-inflammatory effects of OSM on mouse T-helper cells are mediated by the inhibition of Th17 differentiation via regulation of SOCS3, STAT-3, and -5 (Son *et al.* 2017). A more recent study demonstrated a negative correlation between OSM and CRP levels in PCOS patients (Camili *et al.* 2024).

The discrepancies in the pro- and anti-inflammatory effects of OSM may depend on the target cell type, disease context, doses used, and source and purity of the recombinant OSM (Komori & Morikawa 2018). It has been shown that both excessive signaling and complete abolition of OSM signaling in adipose tissue may lead to inflammation (Elks *et al.* 2016). On the other hand, insulin resistance and obesity can stimulate chronic inflammation by releasing pro-inflammatory cytokines (Stephens *et al.* 2018).

Follicle development and ovulation

Ovulatory disorders are among the factors that can contribute to infertility in one-fourth of couples, and PCOS is observed in 85% of patients with anovulatory infertility (Lindsay & Vitrikas 2015). Aberrant growth of early preantral follicles in polycystic ovaries results from defects in folliculogenesis, in which follicles begin their journey of development but are unable to complete it (Woodruff & Shea 2011). An increased density of preantral follicles has been reported in polycystic ovaries using cortical biopsy analysis (Franks & Hardy 2010). This finding is in agreement with the findings of Du *et al.* (2021), which previously demonstrated an elevated density of primary follicles in the ovaries. In anovulatory PCO, the rate of GC proliferation was found to be higher relative to oocyte growth when compared to both normal and ovulatory PCO (Stubbs *et al.* 2007).

In addition to aberrant growth, atresia in the culture of preantral follicles from polycystic ovaries was decreased compared with that in normal ovaries (Webber *et al.* 2007). In contrast, GCs of PCOS patients showed an elevated occurrence of early and late apoptosis compared to controls (Mikaeili *et al.* 2016). However, it is important to note that the women in their study underwent ovarian stimulation, which could have influenced the results and limited the generalizability of these findings to all PCOS patients. Transcriptomic analyses of cumulus cells from human oocytes at different maturation stages showed decreased apoptosis in the MII stage compared to the GV stage, which coincided with the upregulation of OSMR, a known activator of Akt-mediated proliferation (Wyse *et al.* 2020).

Martins *et al.* (2019) suggested that secreted OSM from other cells may impact gene expression related to cell viability in bovine granulosa cells due to their lack of OSM expression. Moreover, they demonstrated that treatment of GCs with OSM (10 ng/mL) in the presence of FSH elevated the BAX/BCL2 mRNA ratio, and its high concentrations (100 ng/mL) increased OSMR and decreased XIAP mRNA levels. The expression of OSM and OSMR was upregulated during PGF-induced luteolysis in bovine GCs, suggesting an important role for OSM signaling in the apoptosis process (Martins *et al.* 2019). However, OSM was predicted to be inhibited in GCs from the most recently recruited follicles compared with the pre-recruitment follicles in chicken (Ghanem & Johnson 2021). Variations in gene expression within the GCs may be attributed to species-specific differences. To the best of our knowledge, no previous study has directly investigated the effect of OSM on proliferation and apoptosis in individuals diagnosed with PCOS. Therefore, there is a pressing need for further research in this domain.

Conclusion

In summary, existing evidence on the role of OSM in PCOS remains limited and somewhat contradictory. Our review sought to establish a connection between OSM levels and PCOS-related issues, as summarized in Fig. 3. However, even in this scenario, considerable debate persists among the findings, which can be attributed to several factors, such as the systemic versus localized effects of OSM, potential variations in its impact at

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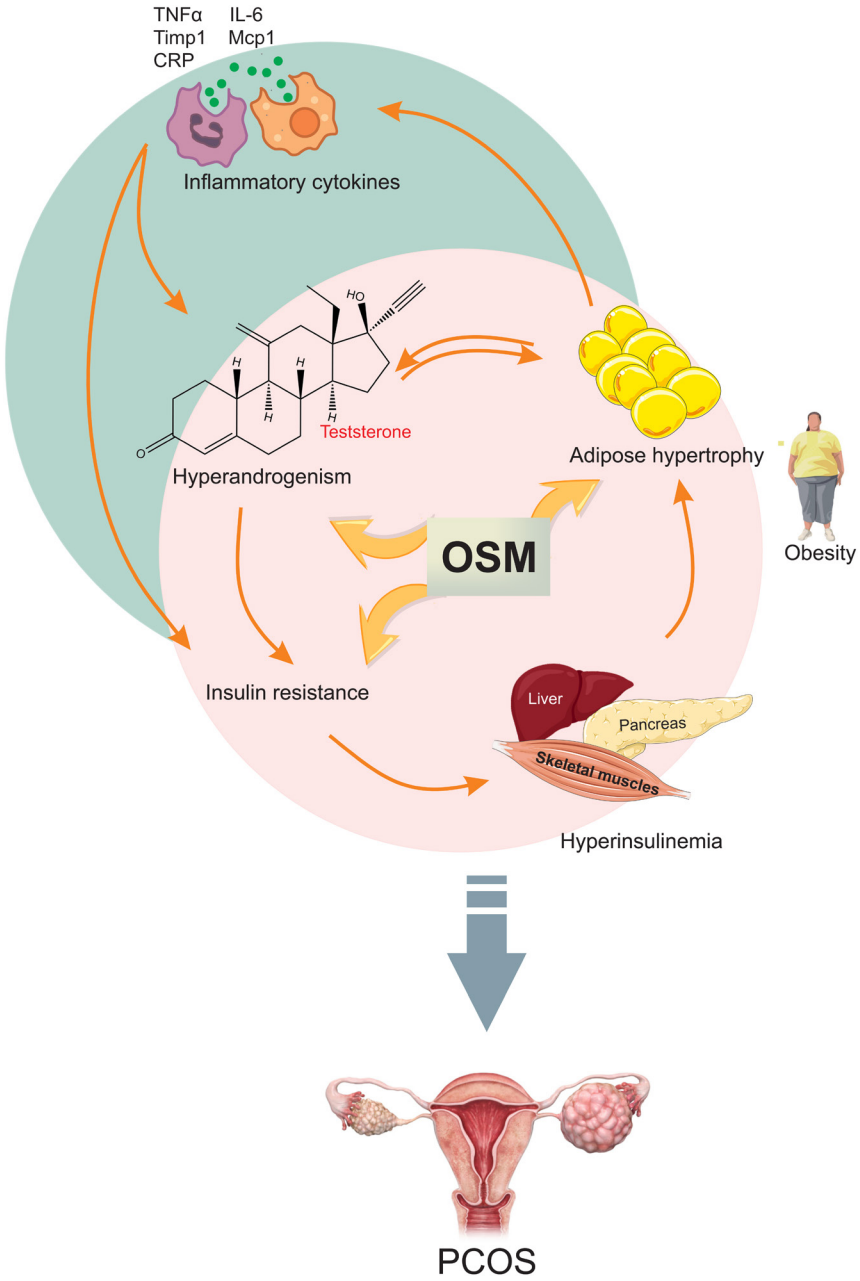

Figure 3

The diagram illustrates the sequence of events involved in the pathogenesis of polycystic ovary syndrome (PCOS). Excessive levels of androgens contribute to increased fat mass, particularly observed in obese individuals with PCOS. In turn, adiposity may trigger hyperandrogenism originating from sources such as the ovaries or adrenal glands, and can also induce insulin resistance and inflammation. The involvement of oncostatin M (OSM) has been illustrated in various stages of PCOS complications. A full colour version of this figure is available at https://doi.org/10.1530/JOE-24-0140.

supraphysiological concentrations, species-specific differences in receptor patterns, and differences in global vs. tissue-specific knockout of OSMR.

Currently, there is no comprehensive understanding of the expression patterns of OSM and its receptors across various compartments of reproductive tissues, particularly the ovary. Most studies have relied on mouse models that exhibit different OSM receptor expression patterns than humans. Additionally, research on PCOS often involves individuals undergoing ovarian stimulation or fails to clearly define the phenotypes of these patients. To address these gaps, future studies should focus on a comprehensive analysis of OSM and its receptor expression patterns across different ovarian cell types. To ensure relevance to human conditions, it is essential to conduct OSMR knockout or overexpression studies, specifically in animal models with receptor patterns similar to those in humans. Additionally, research on patients with PCOS should differentiate among PCOS phenotypes, as the presence of hyperandrogenism may impact outcomes. Addressing these issues will improve our understanding of OSM's role in PCOS pathogenesis and may pave the way for utilizing this pleiotropic cytokine as a therapeutic target for ovarian-related disorders.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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SN: Conceptualization, Funding acquisition, Writing - original draft; FO: Investigation**,** Visualization, review and editing; HRN: Writing - review and editing; RZ: Writing - review and editing; ZL: Investigation; SHL: Conceptualization; lK: Writing - review and editing; RK: Writing - review and editing; CA: Writing - review and editing; AF: Project administration, Writing - review and editing.

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