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Hormonal regulation of endometriosis and clinical significance

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Worldwide almost 10% of reproductive-aged women are affected by endometriosis and suffer from dysmenorrhea, dyspareunia, chronic pelvic pain, and infertility. Endometriosis is a gynecological condition in which endometrial cells are deposited outside the uterine cavity and eventually develop into functional endometrial glands and stroma. It is an estrogen-dependent disease and is critically modulated by other hormones of the reproductive system. Estrogen promotes the cell survival and pro-inflammatory roles for both endometrial epithelial and stromal cells. Overexpression of ER-β promotes invasion of endometriotic lesions as well as epithelial-mesenchymal transition. Moreover, estrogen stimulates the production of prostaglandin E2 (PGE2), which supports angiogenesis in the ectopic lesions. Progesterone counteracts estrogen and inhibits the growth of the endometrial glandular cells. Progesterone resistant endometrial cells confer apoptotic-resistance and aggravate disease condition. Oxytocin stimulates the contraction of uterine muscles by upregulating PGF2α secretion *via* calcium-mediated pathways leading to dysmenorrhea in endometriosis. On the contrary, gonadotropin and its receptor produce amenorrhea by inducing mitochondrial apoptosis and reducing angiogenesis. Scientists are now exploring these hormone-dependent pathologies of endometriosis to develop anti-endometriotic drugs, which mostly include androgen-based drugs and/or potential estrogen inhibitors. This review highlights the role of some important hormones *e.g*. estrogen, progesterone, prostaglandin, oxytocin, gonadotropin and melatonin in endometriosis progression and their pharmaceutical potentials.

Keywords: Endometriosis, Estrogen, Growth factors, Hormone, Melatonin

Hormones are special messenger molecules secreted by the endocrine glands which are involved with the regulation of several physiological as well as pathological responses. Hormones are mostly classified into three categories: protein derivatives, steroids, and eicosanoids. Although endocrine glands are the major source of hormone secretion, the various other cells can also secrete hormones in response to different biochemical signals. Hormonal signaling encompasses its biosynthesis, storage and secretion, recognition by its receptor, relay, and amplification of its signal, and finally degradation. Hormones are mostly transported through the circulatory system to act on other distant organs (endocrine), or can also act in an autocrine/paracrine manner. It can be stimulated or inhibited by various growth factors[1,2].

Endometriosis is a hormone- dependent gynaecological disease characterised by the growth of endometrial glands outside the uterus. Endometriosis is associated with severe pelvic pain responses and infertility[3]. The etiology of endometriosis remains unknown; however, several plausible theories have been proposed. According to Sampson's retrograde menstruation theory, the endometrial lining is refluxed out of the fallopian tubes into the peritoneal cavity, leading to the development of ectopic lesions[4]. Another theory states that specialised cells of the normal mesothelial lining transform into ectopic lesion *via* metaplastic transition. Cyclical sex-steroid levels are mainly responsible for maintaining the endometrial lining by regulating the cell proliferation. During lack of hormone, mainly estrogen and progesterone, the endometrium becomes thin and inactive resulting in amenorrhea, whereas excess levels of estrogen lead to hyperplasia and often positively associated with the development of endometriosis[5,6]. Moreover, similar to the normal endometrium, endometriotic glands also undergo menstrual cycles of shedding, leading to iron deposition and formation of an inflammatory milieu, along with increased oxidative stress and cellular proliferation[7]. Aberrant progesterone signaling in the

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Abbreviation: ER, Estrogen receptor; GnRH, Gonadotropin releasing hormone; OTR, Oxytocin receptor; OXT, Oxytocin; PG, Prostaglandin; PR, Progesterone; TGF, Transforming growth factor; VEGF, Vascular endothelial growth factor

endometrium plays a significant role in the development of endometriosis[8]. In addition, endometriotic tissues contain 17β-HSD (hydroxysteroid dehydrogenase) type-1, instead of the 17β-HSD type-2, which is more potent in converting estrone to estradiol and thus locally support the proliferative microenvironment of endometriotic cells[9]. Hormones promote the production of several growth factors, including epidermal growth factor (EGF) and insulin-like growth factor (IGF) which modulates cellular proliferation in human endometrium and endometrial cells[10-12].

Estrogen receptor acts through mainly estrogen response element (ERE) and *via* protein–protein interactions with other transcription factors such as AP-1 and SP1[13]. ER-α and ER-β have been detected throughout the menstrual cycle in the eutopic endometrium of endometriosis patients, where the expression of ER-α is much higher than that of ER-β, while the expression of the ERs does not correlate with menstrual phases in ectopic endometrium[14,15]. Gonadotropin Releasing Hormone (GnRH) releases the follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Both FSH and LH act on the ovaries to produce estrogen and progesterone and on the testes to produce testosterone. GnRH, FSH, and LH have a critical role in endometriosis progression. Progesterone, on the other hand, counteracts with estrogen by decreasing the ER receptors in the endometrium and increases the rate of conversion of 17β-estradiol. It plays an anti-steroidogenic effect on the uterine myometrial cells by decreasing their sensitivity to oxytocin[16]. The feedback effect of progesterone is *via* inhibition of LH surge from the hypothalamic and pituitary axis. Furthermore, case-control cohort studies have found that promoter polymorphism of ER, PR and cytochrome P450 (CYP1A, 17A, 19A) influence the propensity for endometriosis development in women[17]. Oxytocin receptor (OTR) is expressed in normal endometrial and myometrial cells of the human uterus where its expression varies according to the phases of the menstrual cycle, suggesting its involvement in endometrial functions[18-20]. Oxytocin also stimulates PGF2α secretion by using both the extracellular and intracellular Ca^{2+} in bovine endometrial tissue[21,22]. Oxytocin receptor (OTR), estrogen receptor (ER), and progesterone receptor (PR) are up-regulated by estradiol stimulation and downregulated by progesterone in the uterine myometrial cells.

The treatment regime for endometriosis is limited to surgical procedures and steroidogenic treatments[23,24]. GnRH antagonists as well as anti-inflammatory drugs such as cyclooxygenase (COX) inhibitors are widely used. In this regard, the role of melatonin an endogenous antioxidant with multiple attributes is worth reporting. Melatonin acts as an anti-oxidant and anti-inflammatory molecule *via* both direct and melatonin receptor-mediated pathways, which are present in the uterus. It has potent analgesic and anti-estrogenic attributes as well. Moreover, it can modulate matrix metalloproteinase (MMP) levels modulating cellular invasiveness and pathological angiogenesis. Studies have shown that melatonin can suppress endometriosis development by decreasing the oxidative stress and inflammation as well as induces apoptosis in ectopic endometriotic lesions[25,26].

Role of different hormones in endometriosis

Estrogen

Estrogens are sex-steroid hormones, produced primarily from the ovary, corpus luteum, placenta, adrenal cortex, in smaller amounts from liver, pancreas, bone, adrenal glands, skin, brain, adipose tissue, and breasts. Estrogens are mainly responsible for maintaining the window of uterine receptivity along with progesterone. Estradiol, an aromatized C18 steroid, is the primary potent form of mammalian estrogenic steroid. Aromatase P450 is the key enzyme for ovarian estrogen biosynthesis, catalyzing the conversion of androstenedione and testosterone produced to estrone and estradiol (E2) (Fig. 1). Higher levels of E2 have been reported in menstrual blood of endometriosis patients, in comparison with healthy women[2]. Endometriotic lesions express aromatase and are able to synthesize their own E2[1,27]. Ectopic endometrium of patients with ovarian, peritoneal, and deep infiltrating endometriosis show increased aromatase expressions[28]. The successful treatment of several cases of endometriosis, using aromatase inhibitors, showed inhibition of local estrogen formation[27]. All the enzymes necessary for the local production of estrogens are expressed in the human endometrium including aromatase, oxidative 17βHSD, and sulfotransferases[29]. Ovarian, peritoneal and deep-infiltrative endometriosis expresses predominantly 17βHSD type 1 isoform, as compared to the 17βHSD type 2[9,30].

Estrogen exerts its actions through both nuclear estrogen receptors, namely ERα and ERβ, along with

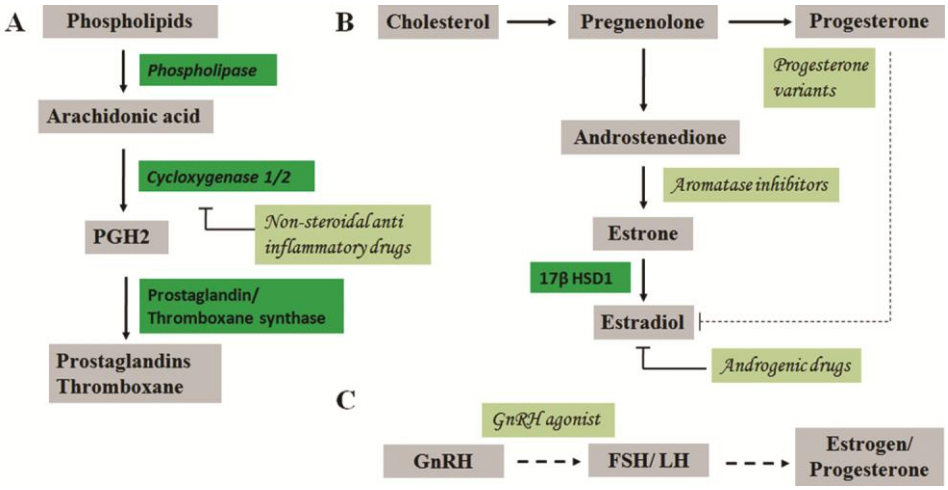

Fig. 1—Hormonal regulatory pathways for endometriosis and possible inhibitors for anti-endometriotic therapy. A. Prostaglandin synthesis *via* arachidonic acid metabolism. Generally, NSAIDs are used as COX/prostaglandin inhibitor. B. Estrogen and progesterone biosynthesis through the steroidogenic pathway. Aromatase inhibitors, progestins and several androgenic drugs are used for endometriosis therapy. C. GnRH regulates the release of FSH and LH *via* hypothalamus–pituitary axis .GnRH agonist is widely used for the treatment of endometriosis patient by inhibiting the LH/FSH function

G–protein coupled estrogen receptor 1 (GPER1). Studies with ER-α knockout mice revealed the necessity of ER for the normal functioning of the uterus. ER-β knock-out mice show enhanced responses to estrogen stimulation, indicating that ER-β is a modulator of ERα action[31,32]. ER-α predominates over ER-β in human endometrium and their expression differs between the menstrual phases. Aberrant expression of ERs has been reported in estrogen-dependent diseases like endometrial cancer and endometriosis[13-15]. A decreased ratio of ER-α/ER-β has been observed in the ectopic endometrium of patients with ovarian and peritoneal endometriosis. Highest ER-β/ER-α ratio has been reported in ovarian endometriomas, indicating ERβ mediated inflammation endometriotic lesions formation. Vivacqua *et al.* reported that 12-hE2 exposure reduced ERα expression, but did not affect the expression of ERβ, suggesting that down-regulation of ERα is a consequence of increased local E2 formation[30]. Overexpression of ER-β promotes invasion of endometriotic lesions through epithelial-mesenchymal transition. E2 exerts its proliferative effect *via* ERβ, the MAPK or AKT signaling pathways[34]. E2 is also known to induce human endometrial stromal cell invasion and angiogenesis by enhancing β-catenin expression associated with the LEF/TCF family along with VEGF-mediated angiogenesis in endometriosis[11].

Higher expression of G protein-coupled estrogen receptor (GPER) mRNA was reported in primary human endometriotic cells as compared to normal endometrium[13]. GPER activation in endometriotic and endometrial cancer cells promotes the activation of PI3K and MEK/ERK MAPK pathways, leading to cell proliferation and invasion. Estrogen exerts anti-inflammatory actions by repressing pro-inflammation genes, such as IL-6, IL-8, TNF-α through of the NF-κB pathway, or by recruiting steroid receptor co-activator (SRC)-2, which acts as a transcriptional repressor[35]. Endometrioma induces inflammation within the peritoneal cavity, which results in the production of IL-1β and VEGF and increased levels of PGE2 [36,11]. Moreover, COX-2 induction also indirectly increases the local concentration of E2, which further up-regulates COX-2 and aromatase and establishes a positive-feedback loop during endometriosis progression[37,38].

Progesterone

Progesterone is a C_{21} steroid mainly secreted by corpus luteum. The hormone is mainly responsible for the pro-gestational changes in the endometrium, cervix, and vagina. There are two isoforms of the progesterone receptor PR-A and PR-B; the former serving as a trans-repressor of the latter[39]. Progesterone counteracts with estrogen by decreasing the ER receptors in the endometrium and increases the rate of conversion of 17β-estradiol[16] (Fig. 1B). Aberrant progesterone signaling in the endometrium plays a significant role in the development of endometriosis through progesterone resistance and impaired decidualization of effluxed endometrium[40,41]. The exact mechanism of

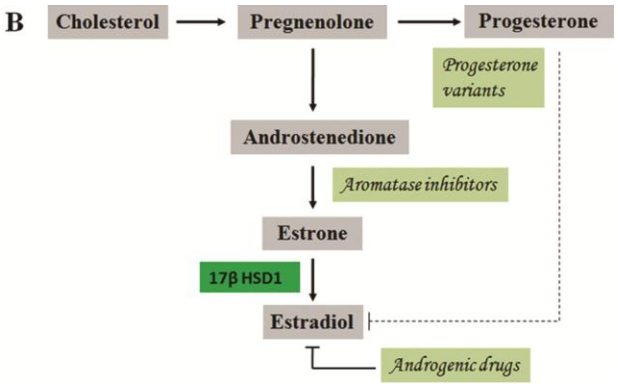

Fig. 1B—Estrogen and progesterone biosynthesis through the steroidogenic pathway. Aromatase inhibitors, progestins and several androgenic drugs are used for endometriosis therapy

progesterone resistance is yet to be elucidated; however, aberrations in the genetic and epigenetic regulation of PRs and their targets have been demonstrated[42]. Several studies have reported that the PR-B levels were significantly reduced in endometriosis lesions, whereas PR-A isoforms were generally increased[39,43]. The anti-inflammatory properties of progesterone in uterine cells have been well-established. Progesterone suppresses NF-κβ signalling pathway in endometrial cells[44]. Other cytokines also play a vital role in progesterone resistance through alteration of PRs. Epigenetic modifications of PR isoforms directly control the inflammatory cytokine levels. For example, TNF-α exposure leads to promoter hypermethylation of the PR-B isoform in endometriotic cells, causing a decrease in expression and increase in PR-A/PR-B ratio[45]. Alterations in steroid receptor chaperone proteins, such as the FKBP5, and receptor coactivators such as hydrogen HIC-5/ARA55 cytokines may also disrupt receptor function[46]. Other mechanisms by which pro-inflammatory cytokines disrupt PR function are through competitive inhibition of the receptors and other transcription factors, such as FOXO1[47]. Modulation of post-translational modifications, including serine phosphorylation, ubiquitination and sumoylation can affect PR stability, half-life, and trafficking[39]. Epigenetic modifications to the transcriptional machinery within endometriotic cells may also contribute to the regulation of progesterone resistance[47,48]. Progesterone receptor modulators (PRM) are hormonally active drugs effective in the management of endometriosis. PRMs are synthetic compounds that interact with the progesterone receptor to inhibit or stimulate a downstream hormonal response[49]. Synthetic progestins, such as dienogest, are used as anti-endometriotic drugs, increase progesterone receptor expression and decrease pro-inflammatory cytokines levels[50].

Oxytocin

Oxytocin (OXT) is a nine amino acid neuropeptide produced by the paraventricular nucleus of the hypothalamus and released by the posterior pituitary gland. OXT plays a key role in both female and male reproduction, but it is best known for its crucial role in the childbirth and breastfeeding. It stimulates the uterine muscle contraction during parturition. It also stimulates the production of prostaglandins that promote the uterine contractions. The oxytocin receptor (OTR) belongs to the rhodopsin-type (Class 1) of the G-protein-coupled receptor family that requires magnesium and cholesterol and regulated by local changes in oxytocin concentration. Estrogen has been found to increase circulating OXT concentration and OTR in the brain and in uterine tissues[51]. The maintenance of high receptor levels is done through the continuous *de novo* synthesis of the receptors. OTR activation triggers a number of signalling events primarily by elevating intracellular calcium, involving multiple mechanisms like sarcoplasmic reticulum Ca^{2+} release and sensitization of the contractile apparatus to Ca^{2+}, inositol-tris-phosphate-mediated stored calcium release, store-operated Ca(2+) entry and voltage-operated Ca(2+) entry[18-22].

Genomic regulation of the OTR is mediated by progesterone in the endometrium *via* suppression of ER signalling[52]. Upon OXT binding to its receptor on endometrial cells, both COX-2 and $PGF_{2\alpha}$ are released and transported to the ovary, which leads to luteal regression *via* a positive feedback loop, and also cause an increase in PGE [53-55]. In primary cultures of human decidua, IL-1β increases OXT production *via* COX-PGE signaling pathway, which may down-regulate the OTR and subsequent signalling cascade[56-58].

Smooth muscle cells, which mediate the contractile responses, are frequently found in peritoneal, deep, and ovarian, endometriotic lesions[59]. Smooth muscle cells express a high amount of OTR. Therefore, differential OTR expressions can distinguish uterine smooth muscle tumors from endometrial stromal sarcomas[60-62]. In addition, the oxytocin-OTR system may also be involved in the process of contractility regulation of non-pregnant uterus. The OTR concentrations are higher during the proliferative

phase as compared to the secretory phase[63]. Moreover, excessive estrogen alters the OTR distribution in endometriosis uteri, therefore prominently increasing the uterine contraction as compared to the women without endometriosis[18-20]. Studies suggest that atosiban, an OTR antagonist, can improve the clinical pregnancy and implantation rates in endometriosis-associated infertility [64,65]. However, blockage of the OTR may not be the suitable strategy for treating endometriosis, since oxytocin treatment showed decreased the ectopic endometrial implant size in an experimental endometriosis rat model. Treatment with OXT significantly decreases the peritoneal and plasma levels of VEGF, MCP-1, and TNF-alpha in an experimental murine model of endometriosis[66]. Szeto *et al*. reported that vascular oxidative stress and inflammation can be attenuated by OXT[67]. The protective effect of OXT involves the maintenance of anti-oxidant capacity in protecting the tissues against oxidative stress[68]. In addition, OXT also induces a release of nitric oxide (NO). In human endometrial carcinoma cell line, OXT treatment showed anti-proliferative responses, through intracellular cAMP and protein kinase A, a signal transduction system that is different from the classical calcium-inositol system involved in the contraction in myometrial and myoepithelial cells[69,70].

Prostaglandins

Prostaglandins are potent bioactive lipid molecules which play important roles in uterine physiology as well as pathological responses such as endometriosis. The changes of concentrations of PGs are cyclic in the uterine tissues and contribute to steroid ovarian hormones. PGF2α vasoconstricts the endometrial vessels during menstruation and contracts the smooth muscle of the myometrium. PGE2 vasodilates the vessels of the endometrium, and PGI2 relaxes smooth muscle, vasodilates the vessels of the myometrium and inhibits thrombocyte aggregation[71]. Prostaglandins and thromboxane A_2 (TXA_2), collectively termed prostanoids, are formed from arachidonic acid (AA), a 20-carbon unsaturated fatty acid precursor that is released from the plasma membrane upon cleavage by phospholipases (PLAs) and metabolized by the sequential actions of cyclooxygenase (COX)[72]. Four principal bioactive prostaglandins namely prostaglandin E_2 (PGE_2), prostacyclin (PGI_2), prostaglandin D_2 (PGD_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) are ubiquitously produced. Usually, each cell type generates one or two dominant products and acts as autocrine and paracrine lipid mediators to maintain local homeostasis in the body. Both COX1 and COX2 enzymes contribute to the generation of autoregulatory and homeostatic prostanoids, and both can contribute to prostanoid release[73] (Fig. 1A). COX2 is over expressed in ectopic endometrial cells and might be linked to the overproduction of PGE2 and PGF2α[74].

High levels of prostaglandins, such as PGE2 and PGF2α are present in uterine tissues of women suffering from menorrhagia, dysmenorrhoea, and endometriosis[75-77]. PGE2 and PGF2α act in a temporal and cell-specific manner *via* its different receptors around the time of implantation and are important for blastocyst spacing, implantation, and decidualization in the mouse endometrium. According to Sharma *et al.*, the peritoneal fluid in women with early-stage endometriosis has higher PGF2α levels, but lower levels of PGE2 and PGE2:PGF2α ratio[78].

PGs exert their effects by activating rhodopsin-like seventransmembrane spanning G protein-coupled receptors, followed by activation of phospholipase C (PLC) and release of inositol trisphosphate (IP3) and diacylglycerol. The prostanoid receptor subfamily is comprised of eight members: EP1, EP2, EP3, and EP4 subtypes of the PGE receptor, PGD receptor (DP1), PGF receptor (FP), PGI receptor (IP), and TX receptor (TP)[79]. FP receptor is indispensable in female reproduction and that its ablation results in loss of parturition. Estradiol E2 and progesterone P4 regulate the expression of endometrial EPs and FP, and that these receptors have specific functions in the respective reproductive phase. The expression of the PGF2α receptor was increased in both ectopic and eutopic endometrium of endometriosis patients, while expression of EP3 and EP4 was increased in ectopic

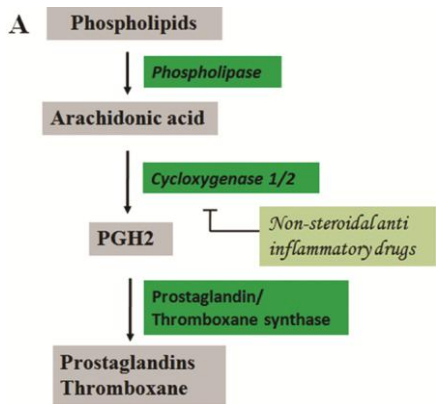

Fig. 1A—Prostaglandin synthesis *via* arachidonic acid metabolism. Generally, NSAIDs are used as COX/prostaglandin inhibitor

endometrium only[80]. Recent studies have demonstrated that selective blockade of EP4 signaling inhibits proliferation and adhesion of human endometriotic epithelial and stromal cells through suppression of integrin-mediated pathway[81-83]. In addition, inhibition of EP2 and EP4 signaling decreases the migration of human endometriotic epithelial and stromal cells *via* multiple mechanisms, including MMP-mediated responses. PGE2 promotes MMP2-mediated angiogenesis in endometriosis and inhibition of MMP-2 or COX-2 pathway can deteriorate the disease[84,85]. PGF2α can also induce angiogenesis in endometrial adenocarcinoma cells by transactivation of the EGFR and induction of VEGF mRNA expression[86]. EGFR activation promotes cellular transition through MMP dependent pathway in endometriosis[87]. PGE2 also promotes cell growth, survival and invasion of endometriotic epithelial cells and stromal cells through the EP2 and EP4 pathway. Selective inhibition of EP2 and EP4 decrease the expression of β1 and β3 subunits of integrin receptors, which is important for adhesion turnover, cell migration, and integrin receptor cross-talk with the MAPK[88]. Selective inhibition of EP2 and EP4 also reduce MMP levels and block endometriosis[81-83].

Gonadotropin releasing hormone

Gonadotropin Releasing Hormone (GnRH), a decapeptide, is secreted by the anterior hypothalamus and acts through its receptors. GnRHR, a seven-transmembrane G-protein-coupled receptor that is known to stimulates the synthesis and secretion of LH and FSH. In addition to ovulation induction, GnRH analogs are considerably useful in a variety of clinical indications including management of endometriosis, uterine leiomyomas, hirsutism, dysfunctional uterine bleeding, premenstrual syndrome, assisted reproduction, and some hormone-dependent tumours[23,24]. Several clinical trials support the use of GnRH agonists for endometriosis management and GnRH agonist treatments are done based on women's condition on amenorrhea and anovulation[89] (Fig. 1C).

GnRH analogues are found to directly act on endometrial cells and inhibit their growth and proliferation by regulating apoptosis and angiogenesis. Leuprolide acetate, an analog of GnRH, widely used to treat endometriosis because it modulates the expression of several miRNAs associated with the disease. Leuprorelin inhibits cell

Fig. 1C — GnRH regulates the release of FSH and LH *via* hypothalamus–pituitary axis .GnRH agonist is widely used for the treatment of endometriosis patient by inhibiting the LH/FSH function

proliferation and induces apoptosis in eutopic endometrial cells by elevating pro-apoptotic proteins Bax and FasL while decreasing the expression of Bcl-2. Leuprorelin also inhibits endometriosis progression by reducing the production of VEGF-A and IL-1β in eutopic endometrial cell cultures[90]. Leuprorelin is also reported to modulate miRNA levels in endometriosis[91]. Aromatase inhibitors (AIs) are generally used in treating endometriosis-related pain but they cause significant adverse effects that limit their long-term use[92]. Endometriosis can be treated by estrogen withdrawal which is effectively provided by the use of a GnRH agonist. However, complete estrogen withdrawal results in unacceptable side-effects, including accelerated bone density loss. On the contrary, upon sequential administration of the GnRH antagonist (Cetrotide), the regression of endometriotic lesion occurred in 60% of cases and the degree of endometriosis declined to stage II with symptomatic endometriosis from stage III. Recent clinical trials on GnRH antagonist showed the most promising results for the treatment of endometriosis[23].

Melatonin

Melatonin is a naturally occurring indoleamine, majorly controls circadian rhythm. In mammals, it is produced mostly from the pineal gland, although several other organs (*e.g*., retina, extra-orbital lacrimal gland, gastrointestinal tract, bone marrow cells, blood platelets *etc*.) also synthesize the hormone[93]. The initial precursor of melatonin biosynthesis is an amino acid, tryptophan. N-acetyl-5-methoxytryptamine (melatonin) is synthesized sequentially through several enzymatic steps including tryptophan 5-hydroxylation, decarboxylation, N-acetylation, and O-methylation[94]. Unlike other antioxidants, melatonin does not undergo redox cycling; therefore, it acts as terminal antioxidant[95]. Melatonin has also been shown to regulate NO synthesis, which in turn reduces production of pro-inflammatory cytokines and chemokines[96,97]. Melatonin is highly protective against several diseases, including cardiac toxicity, cerebral ischemia, gastric ulcer, endometriosis[98,99].

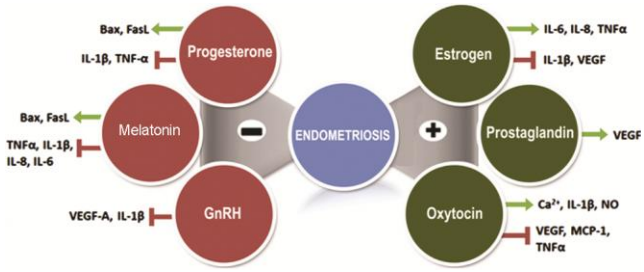

Fig. 2 — Positive and negative regulators of endometriosis. Endometriosis progression is controlled by different hormones either positively or negatively *via* inducing some cytokines and growth factors while inhibiting some others in disease stages

Studies from our lab found that melatonin can suppress the endometriosis development in a murine model of endometriosis[25]. Melatonin treatment has been found to decrease oxidative stress in the endometriotic lesions and decreased levels of acute inflammatory cytokines such as IL-1β, IL-6, and TNF-α. We identified the expression ratio of proMMP-9 versus TIMP-1 as a novel biomarker for assessing the severity and progression of endometriosis, which can be reversed with melatonin treatments by inhibiting MMP-9 activities[25]. Melatonin also inhibits the disease progression by down regulating MMP-3 and c-fos overexpression *via* inhibiting AP-1 activity. Melatonin induces apoptosis in ectopic endometriotic lesions by promoting Bax expression and caspase-9 activation along with the reduction of Bcl-2 expression[26]. Moreover, clinical phase II trial of melatonin with endometriosis affected women reports better pain management and improved life quality with melatonin treatments[100].

Conclusion

The pathogenesis of endometriosis relies on the ectopic hormonal milieu that includes estrogen, progesterone, oxytocin, gonadotropins, prostaglandins *etc*. Estrogen promotes the cell survival and pro-inflammatory roles for both endometrial epithelial and stromal cells, whereas progesterone counteracts estrogen and inhibits the growth of the endometrium (Fig. 2). Thus, progesterone therapy can reduce or eliminate endometrial growth in a controlled fashion. However, endometrial cells with progesterone resistance exhibit apoptotic resistance. The synthetic form of natural progesterone, like progestins, are used for endometriosis treatment as well as proved to be effective for pain management. GnRH agonists are also used for endometriosis treatment because it can repress the hypothalamic-pituitary-ovary axis. Because of the remarkably longer half-life of GnRH agonists (than natural GnRHs), the pituitary is exposed to continuous GnRH stimulation resulting negative feedback loop and down-regulation of LH and FSH secretion. Consequently, secretion of ovarian steroids like estradiol is blocked; resulting in postmenopausal E2 levels and pain relief is achieved in most cases. However, the side effects include unpleasant menopausal symptoms, and might leads to osteoporosis. To counteract the side effects, some estrogens may be needed through add-back therapy. Androgenic drugs, such as danocrine is also used as anti-endometriotic drugs, which inhibits the enzymes in the steroidogenic pathway and increases free testosterone concentrations. Apart from the conventional medicine, studies have reported other molecules which are effective in regressing endometriosis in animal models, which includes NSAIDs like COX-2/prostaglandin inhibitors. Moreover, recently usage of aromatase inhibitors, peroxisome proliferator-activated receptor (PPAR) agonists, and immunomodulatory drugs are gaining interests for treatment of endometriosis. Endogenous antioxidants such as melatonin are gaining special interests in endometriosis treatments. Therapies which blocks angiogenesis in endometriosis are also showing promising results in animal models of endometriosis. Combinatorial therapies with conventional hormonal treatment and new small molecular inhibitors or antioxidants might prevail as better management for endometriosis.

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