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Review article

Progesterone signaling in uterine leiomyoma biology: Implications for potential targeted therapy

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ABSTRACT

Uterine leiomyomas (ULs) are the most common benign smooth muscle cell steroid-dependent tumors that occur in women of reproductive age. Progesterone (P4) is a major hormone that promotes the ULs development and growth. P4 action in ULs is mediated mainly by its nuclear progesterone receptors (PGRs), although rapid non-genomic responses have also been observed. Data on the membrane progesterone receptors (mPRs) regulated signaling pathways in ULs in the available literature is still very limited. One of the essential characteristics of ULs is the excessive production of extracellular matrix (ECM). P4 has been shown to stimulate ECM production and collagen synthesis in ULs. Recent research demonstrated that, despite their benign nature, ULs may present with abnormal vasculature. P4 has been shown to regulate angiogenesis in ULs through the upregulation of vascular endothelial growth factor (VEGF) and by controlling the secretion of permeability factors. This review summarizes the key findings regarding the role of PGRs and mPRs in ULs, especially highlighting the potential ECM and angiogenesis modulation by P4. An increased understanding of this mechanistic role of nuclear and specifically mPRs in the biology of P4-modulated ECM and angiogenesis in the growth of ULs could turn out to be fundamental for developing effective targeted therapies for ULs.

1. Introduction

Uterine leiomyomas (ULs) are monoclonal, heterogeneous, benign tumors derived from smooth muscle cells, occurring in approximately 60–70 % of reproductive-age women [1–3]. Clinical symptoms of ULs depend on their location and can manifest as excessive and prolonged menstrual bleeding leading to anemia, and painful menstruation. ULs may also lead to infertility [4,5]. The main risk factors for ULs development are race, age, genetic factors, age of first menstruation, metabolic factors, and parity. The early onset of menarche has been identified as a risk factor for the development of ULs, due to prolonged exposure to sex steroids [6]. Parity has been shown to reduce the risk of ULs development, while nulliparity has been associated with an increased risk [7]. Moreover, it has been observed that ULs present before pregnancy often decrease in volume after gestation [7]. However, the etiology of ULs is still poorly understood [8]. ULs exhibit a high frequency of somatic mutations. It has been demonstrated that alteration in the *MED12* gene plays a significant role in ULs development [9]. Approximately 70 % of patients with ULs are characterized by MED12 mutations within the tumors [9]. The overexpression of HMGA2 is another major mutation observed in approximately 10 % of ULs cases, however, its presence is typically restricted to ULs that do not have underlying MED12 mutations [10,11].

The main factors driving the growth of ULs are steroid hormones – estradiol (E2) and progesterone (P4), as well as growth and angiogenic factors [12,13]. E2, by activating estrogen receptors (ERs), induces the expression of nuclear progesterone receptors (PGRs), which are then responsible for tumor development [14]. Up-regulated expression of PGRs has been demonstrated in UL tissue compared to normal myometrium [15,16]. P4 has been shown to affect UL biology through pro-proliferative and anti-apoptotic effects and stimulation of extracellular matrix (ECM) production [17]. Moreover, during the

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neoangiogenesis process in ULs, an interaction between the endothelium and the ECM collagens type I and III has been demonstrated [18]. Clinical evidence has indicated that P4 may exert mitogenic effects in patients with ULs, as the growth of tumors is enhanced during the secretory phase, which is characterized by increased P4 secretion [19,20]. Furthermore, P4 may activate various receptors, kinases, transcription and growth factors, as well as numerous autocrine and paracrine factors [17,21,22]. So far, several mechanisms have been proposed to explain the role of P4 signaling in ULs, however, the exact mechanism underlying the action of P4 and the activation of all progesterone receptors (PRs) is yet to be described.

Surgical interventions like myomectomy and hysterectomy are leading indications for ULs. These procedures may carry a risk of mortality, as well as exert an economic burden on the healthcare system [2]. Progestogens, selective progesterone receptor modulators (SPRMs), oral contraceptives, nonsteroidal anti-inflammatory drugs, letrozole, tranexamic acid, and gonadotropin-releasing hormone (GnRH) analogs are used in the pharmacological treatment of ULs [3]. These drugs reduce E2 and P4 production, regulate uterine contractility, and reduce bleeding. Unfortunately, symptoms tend to recur after termination of treatment [23]. Among all pharmacological therapies for ULs, SPRMs still seem to be the most effective drugs, although their exact mechanism of action and potential interactions with PRs are not yet known [24–26]. Moreover, the molecular mechanism of P4 action underlying the growth of ULs also remains unclear, limiting the development of an effective pharmacological treatment.

A PubMed search request for “progesterone and UL” provided 242 hits for “reviews”; whereas “membrane progesterone receptors and UL” only 22 hits, where most of them were of a non-focused generalized nature. These searches emphasized that the relevant recent publications are not adequate in the available literature focusing exclusively on the “membrane progesterone receptor” functional effects on ULs, which emphasized the novelty of our present minireview. The innovative idea behind this review was therefore a focus on the membrane progesterone receptors (mPRs) and ULs, which should fill up the data gap in the existing literature. This could further be an important addition to our current knowledge of UL biology for the successful potential development of new effective pharmacological therapies. Moreover, this review will summarize the most important findings of the role of all nuclear and mPRs in ULs, especially highlighting the potential ECM and angiogenesis modulation by P4, as well as containing expert comments in almost all subchapters.

2. Review

2.1. Progesterone and its receptors

P4 is a steroid hormone, synthesized and secreted by various organs, including the ovaries, testes, placenta, and adrenal glands [27–29]. It can also be produced from cholesterol or circulating pregnenolone in the nervous system [30]. P4 is a crucial hormone for female reproductive function, playing an important role in numerous processes such as ovulation, embryo implantation, pregnancy maintenance, development of mammary glands, and sexual differentiation [31]. In males, P4 also affects sperm development and function [32]. In addition, non-reproductive functions of P4, including neurogenesis and neuroprotection, regulation of the immune system, prolactin secretion, and lactotroph proliferation, as well as initiating role in breast, brain, and gynecological cancer growth and development have also been demonstrated [33–41]. Distinct characterization of these P4 effects is strongly needed as such information could then further be utilized in disease treatment/management.

P4 mechanism of action can be classified into two categories: classical (genomic) and non-classical (non-genomic), with the possibility of both occurring simultaneously in the cell [42,43]. The classical mechanism involves long-term effects regulated by the A and B PGR isoforms [44] that affect target genes [45]. PGR-B is a strong activator of P4 signaling, while PGR-A exhibits a weak ability to activate P4-dependent genes [45]. When both isoforms are activated, PGR-A may act as an inhibitor of PGR-B, blocking the effects of P4 on target cells [45]. PGR-A is also able to inhibit the actions of other members of the nuclear receptor superfamily, such as estrogen, glucocorticoid and mineralocorticoid receptors [46]. Inactivation of both isoforms in transgenic mice has been shown to lead to anovulation, uterus and decidualization dysfunctions, impaired sexual behavior, and defective mammary gland morphogenesis [47]. PGR-A knockout mice exhibited partial impairment of ovulation and inhibition of decidual transformation but well-developed mammary glands [48,49]. Mice with PGR-B knockout demonstrated unaffected ovulation but impaired mammary gland development [48–50]. From the discovery of two P4 binding isoforms of the PGR in the 1970s, there has been an ongoing debate on the distinct roles of PGR isoforms in P4-related reproductive functions. The mammary glands in virgin mice [51], as well as during pregnancy [52], express both isoforms of PGR. However, the levels of isoform A surpass those of isoform B by a ratio of a minimum of 2:1. PGR knockout mouse reproductive characteristics showed that PGR-A and PGR-B operate in a tissue-specific manner, therefore orchestrating distinct reproductive functions attributed to P4. Although these investigations have established the role of PGR-A in ovulatory and uterine responses to P4, it remains uncertain whether PGR-A alone is 100 % capable of mediating these responses [49].

The non-classical (non-genomic) mechanism generates rapid effects in the cell membrane and cytoplasm, such as activation of ion channels and kinases [43]. These effects are usually mediated by the interaction with PGRs, ion channels, neurotransmitters and growth factors receptors, and specific membrane and membrane-associated receptors [53–55]. Recent advancements have greatly enhanced our understanding of the topology and structural characteristics of membrane PR alpha (mPRα). This progress was achieved through techniques including homology modeling based on the structure of adiponectin receptor 2, mutational analyses, and ligand specificity studies [56]. The close association between progesterone receptor membrane component 1 (PGRMC1) and mPRα, along with the observation that PGRMC1 may act as an adaptor protein, suggests that they may function as a complex [57]. There is still a lack of comprehensive research on the effects of mPRs knockout in mammals. By far only preliminary results on the mPRα knockout mice have been published [58]. mPRs are widely expressed in various organs, including the brain, and reproductive, immune, and respiratory systems [59]. Among the mPR subtypes, mPRα is found primarily in the reproductive system, mPRβ in neuronal tissues, and mPRγ in the kidneys, colon, and lungs [59]. The binding of P4 to mPRs leads to an increase in cyclic adenosine monophosphate (cAMP)-dependent mitogen-activated protein (MAP) kinase activity [59–61]. It has been shown that a decrease in cAMP level may inhibit steroid hormone production in luteal cells, while activation of MAP kinase may contribute to apoptosis in the ovary [60]. Additionally, when bound to P4, mPRs can activate phospholipase C to elicit calcium ($Ca2+$) release from intracellular reserves [62]. The PGRMC family plays an important role in numerous physiological processes, such as regulation of the estrous cycle, pregnancy, and cell cycle progression in granulosa cells [63,64]. It has been demonstrated that PGRMC1 binds to the polypeptide serpin mRNA-binding protein 1 (SERBP1), forming a P4 membrane receptor complex that activates protein kinase G and regulates intracellular $Ca2+$ levels, mediating the anti-apoptotic effect of P4 [60,65,66]. Additionally, PGRMC1 can interact with cytochrome P450 [67] or translocate to the nucleus to directly regulate target gene expression [68]. Much less is known about PGRMC2, a highly homologous receptor to PGRMC1. Differences in their transmembrane and N-terminal domains suggest that both receptors may interact with different proteins [69]. The abundant expression of PGRMC2 during the secretory phase may indicate an important role of PGRMC2 in uterine decidualization [70]. Moreover, altered expression of mPRs and PGRMCs has been demonstrated in reproductive, neuronal and immune systems [71]. mPRs and PGRMCs have also been linked to key

processes in cancer regulation, such as proliferation, apoptosis, and formation of metastases [68,72–75].

Despite extensive research showing the importance of all PRs in reproductive tissues, understanding of the distinct functions of the mPR and MAPR family members is still limited. All receptors have been found to interact with a variety of ligands and proteins, opening the way to study their regulation and find appropriate pharmacological modulation for novel therapeutic strategies development. There still exists a need to find novel co-activators and co-inhibitors that may act on PRs, mPRs and MAPR family members during the P4-mediated growth of ULs.

2.2. Progesterone and progesterone receptors in ULs

The pathogenesis of ULs remains poorly understood, however, the involvement of various mediators and proteins, i.e. hormones, cytokines, growth factors, and metalloproteinases has been suggested [76]. Despite comprehensive clinical evidence regarding the hormonal influence on the development of ULs, the functional role of sex steroids in this process still requires further thorough investigations [77].

The biology of normal myometrium and ULs is strongly influenced by P4 and its receptors [16,78]. E2 through ERs induces PGRs expression, which regulates the responsiveness of ULs to P4 [78]. The effect of P4 on ULs has been linked to the activation of PGR-A or PGR-B. Both isoforms have been identified in ULs tissue [15,16,79,80]. P4 may regulate ULs growth by increasing proliferation and suppressing apoptosis [81]. Increased cellularity in ULs histology has been observed in patients treated with P4 daily for 30–128 days [82]. Moreover, higher mitotic activity in UL tissues of women treated with medroxyprogesterone acetate as well as in the luteal phase has also been found [19,83]. However, decreased proliferative activity has been shown in postmenopausal women ULs, in women without hormone replacement therapy (HRT) or with estrogen-only HRT [20]. ULs from postmenopausal women receiving both E2 and P4 as HRT had a similar proliferation index as women before menopause [20]. After menopause, ULs often decrease in size, however, some of them may continue to grow and still require surgical intervention [78,84]. In postmenopausal ULs compared to premenopausal ones, down-regulation of the PGR-A expression has been observed [85]. More detailed studies are required to show the functional implication of potential co-activators/co-inhibitors involved in the downregulation of PGR-A expression in postmenopausal ULs.

P4 may regulate ULs growth by interacting with various growth factors [86]. Studies have shown that P4 can up-regulate the expression of epidermal growth factor (EGF) and transforming growth factor-β3 (TGF-β3) [87,88], while down-regulate the expression of insulin-like growth factor 1 (IGF-1) [89] in ULs. P4 may also promote the survival of UL cells by up-regulating the expression of B-cell lymphoma 2 (BCL-2) protein and down-regulating the expression of tumor necrosis factor α (TNF-α) [90,91]. A direct interaction of P4 with the BCL-2 promoter has been shown [17]. Moreover, activation of the rapid AKT signaling pathway and its downstream effector, glycogen synthase kinase-3b and forkhead box O (FOXO)-1 by P4 suggests that a non-classical mechanism may also modulate the proliferation and survival of ULs [21]. The crosstalk between the P4 and the growth factors signaling pathways requires more attention and needs to be studied more extensively, as information on the mechanisms underlying the impairment of such signaling could be pivotal for future treatment strategies.

In recent years, several new concepts linking P4 to the process of ULs formation have been proposed. One of them suggests that P4 activity is related to progenitor stem cells [92]. These cells retain responsiveness to E2 and P4, contributing to tumor growth, and, according to this theory, mutations in these cells appear to play a significant role in ULs development [92]. It has also been found that P4 through the *receptor activator for nuclear factor kappa-B ligand* (*RANKL*) gene induction may promote ULs stem cell proliferation by activation of cyclin D1 [93]. Further functional mechanistic studies are needed to analyze P4-mediated RANKL/Cyclin D1 activation that promotes ULs stem cell proliferation for ULs growth.

Although PGR plays a critical role in mediating the actions of P4, studies with PGR null mutant mice have demonstrated that not all P4 effects are mediated by this receptor [94,95]. Numerous non-classical effects of P4 in the uterus have been reported [96,97] and disrupted P4 signaling has been implicated not only in the pathogenesis of ULs, but also in many other reproductive disorders, such as breast and endometrial cancers and endometriosis [98]. Moreover, there exists a major data gap on the expression and role of mPRs in ULs. The complex biology of these tumors and the multiple autocrine and paracrine signaling pathways that are involved in their regulation emphasize the potentially important role of all membrane receptors, as rapid actions of P4 have also been demonstrated in ULs. Summing up this mini-section, all potential P4 signaling pathways in ULs need to be examined thoroughly, which would be important for identifying novel targets for effective therapy or even for improving current treatments.

2.3. Progesterone and extracellular matrix regulation in ULs

The ECM is a complex system composed of various macromolecules organized in a cell- and tissue-specific manner [99]. These macromolecules provide further structural support to cells and tissues [99]. The components of the ECM are linked together to form a structurally stable compound that contributes to the mechanical attributes of the tissue [99]. Disproportionate accumulation and abnormal remodeling of the ECM are critical factors in the development and progression of fibrotic diseases [100]. Excessive production of ECM is one of the major characteristics of ULs [100]. Compared to the normal myometrium, ULs typically contain up to 50 % more ECM [101], which may act as a reservoir for various growth factors, cytokines and chemokines, mediators, and proteinases produced by the tumor cells [76,102].

Several growth factors, such as TGF-β, activin A, and platelet-derived growth factor (PDGF), have been found to induce abnormal deposition of ECM in ULs [103–105]. Studies have shown that P4 enhances the production of TGF-β3, thereby promoting ECM accumulation in these tumors [104]. TGF-β3 may stimulate abundant secretion of the ECM macromolecules, collagens and fibronectin and modify the expression of matrix metalloproteinases (MMPs) [105,106], which together with tissue inhibitors such as MMPs (TIMPs) are the major regulators of ECM remodeling [107]. Differential expression of MMP-1, MMP-2, MMP-3 and MMP-9 as well as TIMP-1, and TIMP-2 has been found in ULs [108–110], and P4 signaling has been shown to regulate their expression [111]. Collagens are the primary components of the ECM that cooperate to stabilize and maintain the morphological integrity of the tissue [112]. In ULs, an abnormal structure and arrangement of the collagen fibers and overexpression of collagen types I, III, and V have been found [113–115]. Up-regulated expression of several collagen subtypes has also been reported in ULs, including COL1A1, 4A2, 6A1, 6A2, 7A1, and 16A1 [102]. It has recently been demonstrated that collagen synthesis in ULs may be stimulated by P4 [116]. Moreover, P4 may also down-regulate the small collagen-associated proteoglycan, decorin expression levels, which acts as a TGF-β3 inhibitor [117].

Taken together, excessive ECM production and its abnormal deposition is one of the major characteristics of ULs and P4 has been shown to regulate several ECM-related factors. Therefore, a call for further studies underscores the importance of expanding our knowledge of PRs and their impact on ECM, providing a scope of identifying potential therapeutic targets for conditions associated with impaired ECM deposition.

2.4. Progesterone and angiogenesis regulation in ULs

Angiogenesis is the process of sprouting new blood vessels, occurring sporadically in physiological adult tissue [118]. Angiogenesis occurs in the cyclical changes in the female reproductive system, like during folliculogenesis, ovulation, corpus luteum development, endometrial growth, and in the placenta [119]. Additionally, certain pathological

conditions like chronic inflammation, wound healing, and tumor growth may trigger angiogenesis [118].

While ULs are benign tumors and are typically considered to have a low rate of vascularization, recent studies have shown that their vasculature is structurally and functionally abnormal [120,121]. These findings may suggest that angiogenesis could potentially play a role in ULs growth and survival [122]. Although ULs are not highly vascularized, angiogenesis may have a role in their development and maintenance, suggested after the size reduction, vascular concentration decrease, or down-regulation of the expression of angiogenic factors, following uterine artery embolization or hormonal therapies, such as SPRMs [123–125]. Differential expression of numerous growth factors involved in angiogenesis has been shown in ULs tissue [126–128]. The levels of vascular endothelial growth factor (*VEGF*), a crucial promotor of angiogenesis, have been described as similar or increased in ULs compared to normal myometrium [129,130]. During pregnancy, P4 regulates angiogenesis by up-regulating *VEGF* and controlling the secretion of permeability factors [131]. Another important angiogenic factor cysteine-rich protein 61 (*CYR61*) is down-regulated, while basic fibroblast growth factor (*bFGF*) is up-regulated in ULs [127,132]. Elevated *EGF* expression in ULs in comparison with myometrium has been found [133]. It has also been shown that P4 may up-regulate EGF expression, while SPRM asoprisnil may down-regulate its expression in ULs [87,134]. However, more research is needed to examine which PRs may be responsible for the regulation of angiogenesis in ULs.

ULs, like many other tumors, have been shown to exhibit significant hypoxia [135,136]. It is known that hypoxia can stimulate angiogenesis by activating the signaling pathway involving hypoxia-inducible transcription factor (*HIF)-1α* and *VEGF* [137]. However, despite the severe hypoxic environment, studies have revealed that ULs did not express hypoxia-related genes, including *HIF-1α*, and *HIF-2α* [135,136]. The abnormal hypoxic and angiogenic response of ULs may sensitize them therefore to therapies targeting their blood supply.

So far, multiple mechanisms have been studied to explain the role of P4 signaling in ULs, showing interactions with various receptors, kinases, transcription/growth factors, as well as numerous autocrine and paracrine factors, however, none of them fully explained its function (summarized schematically in Fig. 1).

2.5. Selective progesterone receptor modulators in the treatment of ULs

SPRMs are a family of synthetic substances that are known to exhibit either agonist or antagonist effects on PRs, depending on their interaction with receptors or specific co-activators and co-inhibitors in various cell types [24,25]. Given the critical role of P4 in the growth and development of ULs, it has been suggested that SPRMs represent a promising therapeutic option for the treatment of these tumors [24,25]. Several SPRMs have been evaluated in clinical trials for the treatment of ULs, including mifepristone, asoprisnil, ulipristal acetate (UA), and telapristone acetate [138]. All of them have demonstrated the ability to reduce ULs volume and alleviate associated symptoms [138]. Moreover, SPRMs have been shown to reduce collagen synthesis and resorption of ECM through the stimulation of MMPs and TIMPs [87,139,140]. It has been demonstrated that the effects of SPRM activity may depend on different factors, including the level of PR expression in the tissue, further influenced by various ligands [141]. However, data regarding the precise mechanism of action and the effects of SPRMs on sex steroid receptor activity in ULs cells is still limited [141] and this aspect should be further studied extensively.

UA, a relatively new SPRM, has been investigated for its efficacy in the treatment of ULs [142]. A significant size reduction of ULs has been observed in approximately 80 % of patients after UA treatment [142]. It has been shown, that UA may decrease fibrosis, down-regulate the expression of ERs, PRs, proliferating cell nuclear antigen (PCNA), and antigen Kiel 67 (Ki67), and increase cell apoptosis [143]. The inhibitory effect of UA on the proliferation of ULs may also be activated by an up-regulation of p21 and p27 expression, and a down-regulation of cyclin E and cyclin-dependent kinase 2 (CDK2) [144]. UA has been shown to inhibit ECM accumulation through stimulation of MMP-2 expression and induction of F-actin stress fibers, leading to the reduction of ULs size

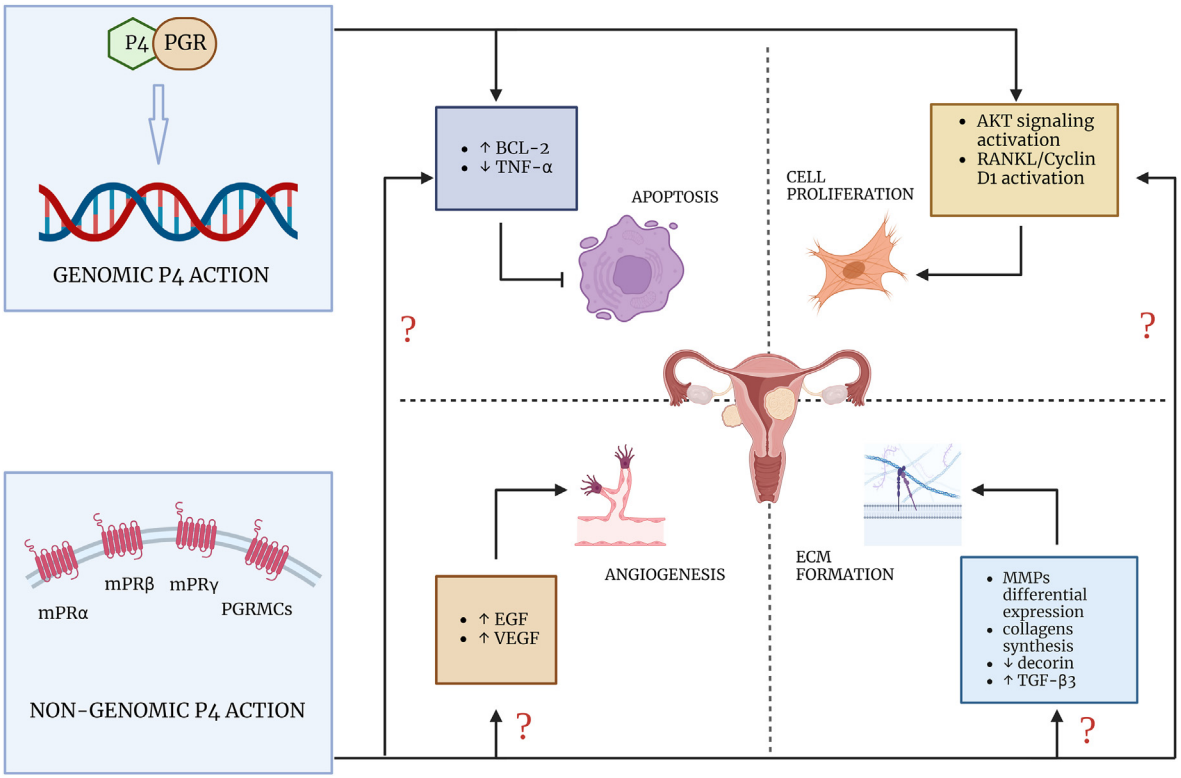

Fig. 1. A schematic overview of the potential progesterone (P4) receptors action in leiomyoma tissue.

[144]. Moreover, UA treatment has been associated with the deregulation of the TGF-β3 signaling pathway by inhibiting collagen, fibronectin, and versican proteins, and increased fibrillin levels, which binds inactive TGF-β complexes [145]. UA has also led to the down-regulation of the integrin subunit beta 4, tenascin-C, and surviving expression in UA-responsive tumors, but up-regulation of catenin delta 2 expression in non-responsive tumors [146]. Differential responses to treatment with UA have also been demonstrated between ULs with MED12 or HMGA2 mutations [147]. MED12-mutant tumors showed a greater reduction in tumor size after UA treatment suggesting that molecular subclassification may serve as a predictive factor for treatment response [147]. Despite many studies showing the deregulation of individual factors after UA treatment, there is still a lack of detailed characterization of the effect of SPRMs on all types of PRs and signaling pathways regulated by them in ULs.

A better understanding of the molecular mechanism underlying UA action is necessary for the development of novel and safe therapeutic strategies for ULs. A few cases of severe liver injury have been reported during the treatment with UA. Of the 765,000 women, 5 women had very rare idiosyncratic acute liver failure, and 4 of them required liver transplantation [148,149]. These incidents prompted the European Medicines Agency to limit the use of UA, i.e. in the case of surgery failure in premenopausal women [148,149]. Recently, a gonadotropin-releasing hormone antagonist (relugolix) has been tested in combination with add-back therapy (estradiol and norethindrone acetate) as an alternative treatment option for ULs [150]. Once-daily combination therapy with relugolix significantly reduced menstrual bleeding, pain, pelvic discomfort, anemia, and uterine volume, but not ULs volume [150]. It seems, therefore, that this therapy may only bring relief from symptoms and reduction of burdensome side effects, which might not affect the ULs. The advantage of PR-targeted therapies is the effect on the size of the ULs, not only the reduction of symptomatic effects.

3. Conclusion

ULs are still the most frequent indication for surgical treatments like myomectomy or hysterectomy. Therefore, there is an urgent need for an effective novel pharmacological therapeutic approach for ULs, which will not affect patients' fertility. It would be still important to know the mechanism how P4 proliferates ULs growth and proliferation, how it interacts with growth factors, and co-activators/-inhibitors and affects the signaling pathways. Modulation of P4 action on ULs holds promises for UL treatment. SPRMs, therefore, may represent a valuable treatment option, as targeting PRs appears to be most effective in reducing the size of these tumors. Further research is needed to reveal the interactions between P4, all PRs, downstream regulators and their effects on ULs biology, especially essential processes including ECM and angiogenesis regulation.

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