Biological Roles of Estrogen and Progesterone in Human Endometrial Carcinoma — New developments in potential endocrine therapy for endometrial cancer —

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Abstract. Endometrial carcinoma is one of the most common female pelvic malignancies. It is well known that uterine endometrial cell proliferation is under the control of both estrogen and progesterone. In this review, results of the recent studies on the biosynthesis and action of estrogen and progestin in normal endometrium and its disorders will be summarized and the new aspects of hormonal therapies in the patients with endometrial carcinoma will be discussed including its future prospectives. We reported that the enzymes responsible for intratumoral estrogen metabolism and biosynthesis are markedly different between human breast and endometrial carcinoma, although both of them are considered “estrogen-dependent malignancies”. In addition, the biological significance of Progesterone receptor (PR) isoforms is considered to differ between endometrial and breast carcinomas. Clinical data concerning Hormone replacement therapy (HRT) and estrogen-dependent cancer risk also support these findings. These basic and clinical findings help to understand the biology and provide the new knowledge for prevention, diagnosis and treatment of human endometrial carcinoma. Specific endocrine treatment of endometrial carcinoma should be explored in future, although aromatase inhibitors are the most effective endocrine treatments of estrogen-responsive breast carcinoma. Retinoid, metabolities of vitamin A, and synthetic peroxisome proliferator-activated receptor (PPAR) γ ligands, which have been used for the treatment of insulin resistance in type II diabetes mellitus, may be the important candidates as drugs not only for prevention but also for possible endocrine treatment of endometrial carcinoma.

Key words: Estrogen, Progesterone, Endometrial carcinoma, Organic cation transporter, Peroxisome proliferator-activated receptor

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1. Introduction

Endometrial carcinoma is one of the most common female pelvic malignancies and its incidence has recently increased [1]. It is well known that uterine endometrial cell proliferation is under the control of both estrogen and progesterone. The results of previous clinical, biological and epidemiological studies have all demonstrated that excessive and/or prolonged exposure to unopposed estrogens increases the risk of endometrial carcinoma, especially that of the endometrioid type [2, 3]. However, it is also true that the great majority of estrogen-dependent carcinomas occur during the post-menopausal period, when the ovaries cease to be functional or produce active sex steroids. Therefore, in situ estrogen metabolism and synthesis play cardinal roles in the development and progression of various human estrogen-dependent epithelial neoplasms, including breast and endometrial carcinomas in postmenopausal patients. Therefore, it is very important to investigate the enzymes responsible for intratumoral estrogen metabolism and biosynthesis. The results of recent studies have all demonstrated that complete blockade of in situ estrogen production could lead to an improvement in the prognosis of breast cancer patients [4, 5]. However, the precise roles of sex-steroid producing enzymes in endometrial carcinoma have remained unclear. On the other hand, the physiological roles of progesterone in the regulation of the glandular epithelium of the endometrium are, in general, considered to antagonize estrogen-mediated cell proliferation and to induce cellular differentiation [6]. Progesterone has been clinically demonstrated to provide some protection against the stimulatory effects of estrogenic agents. For example, hormone replacement therapy using combinations of estrogen and progestin yields a lower risk of endometrial carcinoma, despite an increment in the incidence of breast carcinoma [7, 8].

Both estrogen and progesterone exert their effects through intra-nuclear receptors, estrogen receptors (ER) and progesterone receptors (PR), respectively, which belong to the superfamily of steroid hormone receptors [9]. The expression of ER and PR is generally considered to be coordinated because transcription of the PR gene is induced by estrogen and inhibited by progesterone in the great majority of estrogen responsive cells [10]. Both ER and PR play important roles as the signal mediators of estrogen and progesterone, but the exact biological and clinical roles of these receptors in human endometrial carcinoma have also remained unknown. In this review, the results of the recent studies on the biosynthesis and actions of estrogen and progestin in normal endometria and its disorders will be summarized and the new aspects of hormonal therapies in patients with endometrial carcinoma will be discussed, including its future prospects.

2. Enzyme systems for local biosynthesis or Intracrinology of estrogen

1) Intracrinology: In situ estrogen metabolism and synthesis

Recently, a focus has been given to the importance of in situ estrogen metabolism and synthesis in the etiology and progression of various human estrogen-dependent epithelial neoplasms, including breast and endometrial carcinoma [11]. The results of several studies have demonstrated increased tissue estrogen content in human breasts, compared to serum and/or normal non-neoplastic tissues of the same patients [12–14]. In these studies, the tissue concentrations of estrone (E1), estradiol (E2) and their sulfates were generally several times higher than those found in the plasma or in the area of the normal breast tissues of the same postmenopausal patients, despite markedly low levels of circulating estrogens. These findings all indicated specific intratumoral biosynthesis and accumulation of these hormones.

On the other hand, there have been limited and inconsistent data regarding tissue estrogen concentrations in endometrial carcinoma tissues, in contrast to that for human breast carcinoma [15–18]. Bernstein et al. recently examined 78 endometrial carcinomas and detected higher concentrations of E2 in cancer tissue specimens compared with macroscopically normal endometrium [18]. The results of our recent study are generally consistent with those in previous investigations [19]. E2, E1 and testosterone levels in the tumor tissue were several times higher than those in serum. It then becomes important to evaluate the mechanisms and/or conditions responsible for such an intratumoral elevation of estrogens in post-menopausal patients with endometrial carcinoma. Numerous studies have demonstrated that human breast and endometrial carcinoma tissues contained the enzyme systems required
for local biosynthesis of estrogen. Among these enzymes, aromatase, 17β-hydroxysteroid dehydrogenases (17-HSDs), steroid sulfatase (STS) and estrogen sulfotransferase (EST) are the primarily involved in the formation of the biologically active estrogen, estradiol. Figure 1 represents the production/metabolism of sex steroids in human endometrial carcinoma tissues.

2) Aromatase

Aromatase is an enzyme that is located in the endoplasmic reticulum of estrogen producing cells, and catalyzes the circulating androgens, mainly androstenedione and testosterone, into E1 and E2, respectively [4]. Aromatase is a key enzyme in the synthesis of estrogens and its levels in breast carcinoma tissues have been found to be significantly higher than those in benign breast lesions [5]. Expression of aromatase has also been detected in human endometrial carcinoma [20, 21]. Our laboratories previously reported marked aromatase immunoreactivity and mRNA, mainly in the stromal cells or fibroblasts of endometrioid endometrial carcinoma, but not in normal or hyperplastic endometrium [20] (Fig. 2). Aromatase expression was significant, both at the protein and mRNA levels, at the site of frank invasion in endometrial carcinoma, suggesting induction of aromatase expression by tumor-stromal interactions. Recently, Segawa et al. reported a significant correlation between aromatase immunoreactivity in stromal cells and poor prognosis in 55 patients with endometrial carcinoma [21]. This positive linkage indicates that local aromatase expression plays a role in tumor progression through the formation of in situ estrogens. In addition, we previously reported that an aromatase inhibitor suppressed the proliferation of endometrial carcinoma cells, which exhibited aromatase activities in vitro [22]. Aromatase is considered a key enzyme in the synthesis of estrogen in endometrial carcinoma as well as breast carcinoma. However, it is important to note that regulation of aromatase in endometrial carcinoma remains largely unknown.
3) Steroid sulfatase (STS) and Estrogen sulfotransferase (EST)

A major circulating form of plasma estrogen is the biologically inactive form of estrogen, estrone sulfate (E1S). E1S exhibits a relatively long half-life in the peripheral blood, and the levels of E1S are 5 to 10 times higher than those of unconjugated estrogens, such as E1 and E2, during the menstrual cycle and in postmenopausal women [23]. STS hydrolyzes circulating E1S to E1, whereas EST (estrogen sulfotransferase) sulfonates E1 to E1S. It was recently reported that in situ estrogen activity in breast cancer may be primarily regulated by the status of intratumoral STS and EST [24]. Thus, the balance between the levels of intratumoral STS and EST may also play an important role in the regulation of in situ estrogen levels in estrogen-dependent neoplasms. Immunoreactivity to STS was not detected but that to EST was evident in normal human mammary glands. However, STS and EST immunoreactivity was detected in 74% and 44% of breast carcinomas, respectively. STS and EST immunoreactivity were associated significantly with an increased and decreased risk of recurrence, respectively [24]. In normal endometrium, immunoreactivity to STS was not detected but that to EST was evident during the secretory phase of the cycle. Both STS and EST immunoreactivity have been detected in 86% and 29% of endometrial carcinomas cases, respectively. In addition, the STS/EST ratio was associated significantly with poor prognosis in endometrial carcinoma patients [25]. Therefore, increased STS and decreased EST expression in both human breast and endometrial carcinomas may result in the increased availability of biologically active estrogens in situ.

4) 17β-Hydroxysteroid Dehydrogenase (17-HSD)

4.1. 17-HSD type 1 & 2

The 17β-hydroxysteroid dehydrogenases (17-HSDs) are enzymes involved in the formation of androgens and estrogens [26]. The enzymes, 17-HSD types 1 and 2 primarily catalyze the reversible interconversion of E1 and E2. Type 1 17-HSD catalyzes the 17β-reduction of biologically inactive E1 to E2 [27, 28], whereas the type 2 isozyme preferentially catalyzes the oxidation of E2 to E1 [29]. Both type 1 and type 2 17-HSD regulate tissue levels of E2 and modulate estrogenic actions in estrogen target tissues, such as the endometrium and breast [30].

Oxidative 17-HSD activity is the preferential biochemical reaction in normal breast tissues, but the reductive 17-HSD pathway generally predominates in breast carcinomas. 17-HSD type 1 immunoreactivity was detected in carcinoma cells in approximately 60% of breast carcinoma tissues, whereas 17-HSD type 2 was not expressed at all [31]. In addition, breast carcinoma patients exhibiting high levels of expression of 17-HSD type 1 mRNA also exhibited increased risk of recurrence of breast carcinoma [32]. Therefore, type 1 17-HSD is considered responsible for regulating the process leading to the accumulation of E2 in human breast carcinomas.

However, 17-HSD type 1 immunoreactivity was not detected in any of the cases with normal endometrium, endometrial hyperplasia or endometrioid endometrial carcinoma [33, 34]. 17-HSD type 1 mRNA expression and enzymatic activity were also absent in all carcinoma cases. In normal endometrium tissues, 17-HSD type 2 immunoreactive protein was detected only in the cytoplasm of glandular cells during the secretory phase. 17-HSD type 2 mRNA was also markedly expressed in the endometrial glandular epithelial cells during the luteal phase, but 17-HSD type 1 mRNA was not detected in any of the phases of the examined endometrium [35]. 17-HSD type 2 immunoreactivity was detected in 75% and 37% of cases of endometrial hyperplasia and endometrioid endometrial carcinoma, respectively. 17-HSD type 2 expression was decreased from normal endometrium (secretory phase) to hyperplasia and finally carcinoma [34]. In addition, there was a statistically significant inverse correlation between the intratumoral E2 concentration and the level of 17-HSD type 2 mRNA in endometrial carcinoma [19]. These results strongly suggest that type 2 17-HSD contributes to the regulation of “intratissue” estrogen levels in normal endometrium and that disruption of the control or regulatory mechanisms of intratissue estrogen levels may be related to the development of endometrial disorders.

4.2. Type 5 17-HSD

Intratumoral E2 concentration may be maintained primarily by aromatization of testosterone in endometrial carcinoma, since 17-HSD type 1 expression is negligible in human endometrioid endometrial carcinoma tissues. Recently, 17-HSD type 5, which catalyzes the reduction of androstenedione to testosterone,
was cloned [36]. 17-HSD type 5 is a member of the aldo-keto reductase (AKR) superfamily, and is formally termed AKR1C3. This enzyme is expressed in various peripheral tissues, liver, prostate, and ovary, and has been also detected in prostate and breast carcinoma tissues [26, 37, 38]. 17-HSD type 5 immunoreactivity was detected in normal mammary gland and breast carcinoma cells in 53% of such cases. Immunoreactivity of 17-HSD type 5 also correlated significantly with that of 5α-reductase, which catalyzes the reduction of testosterone to the biologically active and potent androgen, 5α-dihydrotestosterone (DHT). 17-HSD type 5 is considered to be involved with DHT production in breast carcinomas in situ [5, 37].

In normal human endometrium, 17-HSD type 5 immunoreactivity was detected in 19% and 25% of proliferative and secretory phase endometria, respectively. However, 17-HSD type 5 immunoreactivity was detected in 50% and 69% of cases of endometrial hyperplasia and endometrioid endometrial carcinoma, respectively. 17-HSD type 5 expression was increased significantly throughout normal endometrium, hyperplasia and finally carcinoma. In addition, there was a statistically significant inverse correlation between intratumoral testosterone concentration and aromatase mRNA level in endometrial carcinoma [19]. Testosterone produced by 17-HSD type 5 in the tumor tissue may be finally aromatized to E2 by aromatase, which is also overexpressed in human endometrial cancer tissues. Therefore 17-HSD type 5 is considered one of the key enzymes in the local regulation of estrogen concentrations in endometrial malignancy.

3. Sex-steroid receptors

1) Estrogen receptors

The biological effects of estrogens are mediated through the estrogen receptors (ER). ER is expressed in a great majority of breast and endometrial carcinoma tissues. To date, two ERs (ERα and ERβ), which are encoded by different genes, have been detected [39]. ERα and ERβ differ markedly in the N-terminal A/B domains, exhibiting only about 20% amino acid identity. They also differ substantially in the hormone-binding domain. The differences in the A/B domains suggest that the transcriptional activation of different estrogen-responsive genes by ERα and ERβ may play different roles in carcinogenesis. It is well known that the presence of ERα in breast and endometrial carcinoma is associated with a less aggressive phenotype [39–41]. However, the roles of ERβ in the development and growth of these tumors have not been as completely elucidated. The ratio of ERα/ERβ differed between normal and cancerous tissues and a higher ERα/ERβ ratio was reported in breast and endometrial carcinoma [42–44]. ERβ mRNA was detected in 36% of endometrial carcinoma cases, whereas ERα mRNA hybridization signals were detected in 80% of those cases. ERβ was co-expressed with ERα and the estrogenic effects were considered to occur predominantly through ERα in endometrial carcinomas [43].

2) Progesterone receptors

The status of the progesterone receptor (PR) in endometrial and breast carcinoma has been considered an independent prognostic factor of the patients [40, 45]. Progesterone receptor (PR) is present in two isoforms, termed PRA and PRB. These isoforms are translated from the same gene, following initiation of transcription from different promoters [46]. There have been several studies, which have reported individual effects of PR isoforms. PRA can repress PRB activity in cells in which PRA was not transcriptionally active, and PRA might be associated with a cell- and promotor-specific repressor of PRB [47]. In addition, microarray analyses of human breast cancer cells expressing either PRA or PRB have confirmed that each of the PR isoforms has a unique set of target genes, with little overlap [48]. These functional and transcriptional differences suggest that the development, invasiveness, and metastatic potential of carcinoma cells can be influenced by the PR status of the tumor cells. In breast carcinoma, a significant proportion of tumors expressed very low levels of PRB and consequently exhibited a high PRA/PRB ratio [49]. PRA predominated in invasive ductal carcinoma [50]. In addition, breast carcinoma patients with PRA-rich tumors were generally associated with poorer disease-free survival rates or adverse clinical outcomes [51]. PRA overexpression was also associated with altered adhesive properties.

Reduced expression of either one or both of the PR isoforms has been observed in the great majority of endometrial carcinomas, compared with hyperplastic or
Several studies have demonstrated that PRB was more common than PRA in endometrial carcinoma [53, 54]. Very recently, we reported that cases negative for either one or both of the PR isoforms were associated significantly with shorter disease-free and overall survival of the patients [54]. In addition, multivariate analysis demonstrated that an absence of PRA immunoreactivity was an independent risk factor in disease-free survival of the patients. The results of our study indicated that the loss of expression of PR isoforms, especially that of PRA, may result in more aggressive biological characteristics in human endometrioid endometrial carcinoma that can play important roles in the prognosis and/or recurrence, in these patients.

In summary, these results all indicated that the biological significance of PR isoforms differ markedly between endometrial and breast carcinomas.

### 4. New Aspects with Hormone-Related Drugs

1) **Progestin Therapy**

The standard or conventional therapy for early endometrial carcinoma is established through staging laparotomy with total abdominal hysterectomy and bilateral salpingo-oophorectomy, which deprives these patients of any potential for fertility. Therefore, a more conservative medical treatment may be considered in young patients who may wish to preserve their fertility. Approximately 3–5% of patients with these neoplasms are under age of 40, some of whom have been treated with progestin, especially with high dose of MPA, alone as a primary endocrine therapy for both atypical endometrial hyperplasia and endometrioid endometrial adenocarcinoma. This approach is by no means a standard therapy and should not be recommended routinely, even when the patients desire. However, this approach has been supported by several reports in patients desiring to maintain fertility, despite the fact that the subsequent success rate of pregnancy is not necessarily high [55, 56]. The initial response rate of MPA ranged from 55% to 100% for endometrial carcinoma and 70 to 100% for atypical hyperplasia [55, 56]. In a recent multi-center study, Ushijima et al. reported the results of 17 cases of atypical endometrial hyperplasia and 28 cases of endometrioid endometrial carcinoma [57]. Complete response was detected in 64% of overall patients. Nine cases became pregnant and six cases delivered babies.

Atypical hyperplasia and endometrial carcinoma, especially of the well-differentiated endometrioid type, often express PR, and their growth is suppressed by progestin. In general, the effect of progestin is considered to be mediated through PR, because the response rate to MPA in PR-positive carcinoma was higher (70%) compared with PR-negative tumors (16%) [58]. We previously demonstrated that the *in situ* abundance of 17-HSD type 2, which catalyzes the conversion of the potent estrogen, E2, to an inactive form, E1, and PR, especially PRB, can predict the responsiveness of patients with endometrioid endometrial carcinoma to progestin treatment [59]. We also demonstrated that 17-HSD type 2 was only detected in the cytoplasm of the glandular cells during the secretory phase, but not in the proliferative phase endometrium [19, 34]. In addition, progestin stimulates the expression of 17-HSD type 2 in epithelial cells of human endometrial tissue [60]. Progestin may exert a potent anti-estrogenic effect in the endometrium by inducing 17-HSD type 2 and thereby promoting the regression of endometrial proliferative disease.

2) **Progestin Therapy & the Organic Cation Transporter SLC22A16**

Adriamycin is one of the key drugs for treatment of endometrial cancer. However, the molecular mechanisms by which anticancer drugs enter cells across the plasma membranes are much less clear. Recently, SLC22A16, which is one of newly-isolated organic cation transporters, was demonstrated to be responsible for uptake and transport of adriamycin into cells [61]. SLC22A16 mRNA, normally expressed in adult testis and bone marrow and fetal liver, has also been detected in various cancer cell lines, particularly cell lines derived from the liver and colon. Okabe et al. demonstrated that Xenopus oocytes injected with SLC22A16 cRNA imported adriamycin in a saturable and dose-dependent manner, and SLC22A16 over-expressing leukemic cells became significantly more sensitive to adriamycin treatment in cytotoxicity assays [61]. Very recently, we examined the expression of SLC22A16 in human endometrium and its disorders [62]. Immunohistochemical analysis demonstrated that the SLC22A16 protein was highly expressed in endometrium during the normal secretory phase, but
that its level was significantly reduced during the pro-
liferative phase. SLC22A16 protein was detected in 59 of 124 (48%) endometrial cancer specimens and 3 of 7 (43%) endometrial carcinoma cell lines. There was also a significant positive correlation between SLC22A16 and progesterone receptor expression (Fig. 3). Furthermore, SLC22A16 mRNA levels were increased in endometrial cancer cell lines in the presence of progesterone. These results suggest that it may be possible to use progestins to increase the response of endometrioid endometrial carcinoma to adriamycin-based chemotherapeutic regimens through SLC22A16 expression.

3) Aromatase inhibitor

Aromatase inhibitors are considered the most effec-
tive endocrine treatments in the postmenopausal pa-
tients with estrogen-dependent breast carcinoma [4]. The large multi-center trials all demonstrated that aromatase inhibitors contributed significantly to improved disease-free survival and good tolerability in breast carcinoma patients [4, 5]. There remain some contro-
versies as to whether or not aromatase inhibitors are effective in patients with endometrial carcinoma, although intratumoral aromatase activity is more fre-
quently detected in endometrial endometrioid carcino-
ma than in breast carcinoma [22, 63, 64]. We pre-
viously examined the biological changes in endo-
metrial carcinoma tissues before and after aromatase inhibitor treatment. Five of 15 human endometrial
carcinoma demonstrated decreased [3H] thymidine up-
take or Ki-67 labeling following aromatase inhibitor treatment [22]. Berstein et al. reported similar results [63]. A Gynecologic Oncology Group Study (GOG) was not able to demonstrate distinct clinical efficacy with aromatase inhibitor treatment. Partial responses were detected in 9% of 23 unselected patients with re-
current or persistent endometrial carcinoma, most of which had poorly differentiated tumors [64]. Recent-
ly, a multi-center phase II trial for letrozol was con-
ducted in 32 recurrent or advanced endometrial carci-
nomas in postmenopausal women, and one of 28 (4%) case had a complete response, two (7%) were associ-
ated with partial responses, and 11 out of 28 (39%) patients had a stable disease for a median duration of 7 months [65]. Therefore, the roles of aromatase inhibitors in well-differentiated hormone-receptor-
positive or hormone-sensitive endometrial carcinoma remain in dispute. Further studies, including the possi-
bility of application and indication of aromatase inhib-
itors, are required to establish an aromatase inhibitor therapy as one form of endocrine treatment of endo-
metrial carcinoma in post-menopausal patients.

4) Retinoids

Retinoids, metabolites of vitamin A, have been demonstrated to play an important role in in situ estrogen metabolism through the regulation of steroid hor-
monoreceptors and 17-HSDs. In a breast carcinoma cell line, retinoids increased the level of 17-HSD type
ITO et al. revealed a significant correlation between retinoic acid receptor α and 17-HSD type 1 expression in breast carcinoma [67]. In addition, retinoids are considered to be effective chemopreventive and chemotherapeutic agents in a variety of human epithelial and hematopoietic neoplasms [68, 69]. Kudelka et al. reported clinically favorable results following retinoid-based treatment of patients with cisplatin-resistant metastatic endometrial carcinoma [69]. We previously reported that retinoids markedly increased the level of 17-HSD type 2 mRNA in a time- and dose-dependent manner in an endometrial carcinoma cell line [33]. We also detected a significant correlation between retinoid X receptor γ and 17beta-HSD type 2 expression in endometrial carcinoma. Our results suggest that retinoid is involved in the modulation of in situ estrogen metabolism by stimulating the expression of 17-HSD type 2 and may be one of the important candidates as a new endocrine-related agent in endometrial carcinoma. However, further clarification remains necessary.

5) Peroxisome proliferator-activated receptor (PPAR) ligand

Peroxisome proliferator-activated receptor (PPAR) is a member of the nuclear hormone receptor superfamily of transcription factors. PPARs function as transactivation factors following heterodimerization with retinoid X receptors (RXRs), and bind to specific response elements of various target genes [70]. PPARs have a subfamily of three different isoforms: PPARα, PPARβ/δ, and PPARγ. PPARγ plays important roles in the regulation of lipid homeostasis, adipogenesis, insulin resistance, and in the development of various organs [71, 72]. The naturally occurring PPARγ ligand, 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2), activates PPARγ at micromolar concentrations in humans in vivo [73]. Synthetic PPARγ ligands, known as thiazolidinediones (TZDs), have been used for the treatment of insulin resistance in type II diabetes mellitus. In addition, TZDs have been proposed in differentiation-mediated therapy of various human carcinomas associated with high levels of PPARγ [74]. Various in vitro studies have demonstrated that PPARγ ligands exhibit a potent anti-proliferative activity for a wide variety of neoplastic cells [75]. A PPARγ agonist was reported to inhibit the proliferation of carcinoma cells, and phase II clinical trials using PPARγ ligands have recently been performed as a novel therapeutics for patients with advanced breast carcinoma, histologically-confirmed prostate carcinoma, liposarcoma, and metastatic colon carcinoma [76].

The expression and effectiveness of PPARγ has been extensively studied in various human carcinomas but little is known about PPARγ in uterine endometrial carcinoma. In addition, obesity, excess estrogen, type II diabetes, and hypertension are important risk factors for endometrial carcinoma [77, 78], but the effects of PPARγ agonists on endometrial carcinoma are largely unknown. Very recently, we examined the expression
of PPARγ mRNA and protein in normal endometria and its disorders [79]. PPARγ immunoreactivity was detected in 11/23 (48%) cases of proliferative phase endometrium, 14/19 (74%) cases of secretory phase endometrium, 27/32 (84%) cases of endometrial hyperplasia, and 67/103 (65%) cases of carcinoma. PPARγ immunoreactivity was significantly lower in endometrial carcinoma than in secretory phase endometrium and in endometrial hyperplasia. There was a significant positive association between the status of PPARγ and p21 expression in endometrial carcinoma (Fig. 4). In addition, the PPARγ agonist, 15d-PGJ2 inhibited cell proliferation and induced p21 mRNA in endometrial carcinoma cell lines. Our findings suggest that the PPARγ ligand, 15d-PGJ2, exhibits antiproliferative activity against endometrial carcinoma. These results strongly suggest that synthetic PPARγ ligands should be important drug candidates, not only for prevention but also for endocrine treatment of endometrial carcinoma.

5. Hormone replacement therapy (HRT) and the risk of malignancies

Hormone replacement therapy (HRT) has been available for many years. HRT is the most effective intervention to date for the relief of estrogen-deficiency symptoms after menopause. The use of HRT has increased among postmenopausal women worldwide [80]. However, the risk of malignancies associated with HRT remains controversial.

The possible increased risks of endometrial carcinoma associated with exogenous estrogen in postmenopausal women were postulated in the 1970s. This risk of endometrial carcinoma increases in a dose- and time-dependent manner in women receiving estrogen alone (ERT; estrogen replacement therapy). Estrogens at higher levels and over the long-term increased the risk of endometrial carcinoma 5-fold and beyond [81]. Several studies have reported that the addition of progestin to estrogen (HRT; hormone replacement therapy) reduced the increased incidence of endometrial carcinoma associated with unopposed estrogen [81–83]. The Women’s Health Initiative (WHI) study randomized 16608 women; 8506 were treated with HRT and 8102 received placebo [84]. Endometrial carcinomas were observed in 22 patients of the HRT group (0.06%), corresponding with a hazard ratio of 0.83 (95% CI 0.47–1.47) [85]. Similar results were found in the Heart and Estrogen/Progestin Replacement Study (HERS) and the Million Women Study (MWS) [86, 87]. Considering the recent results of the WHI-, HERS-, and MWS-studies, the available data have clearly demonstrated that combined HRT reduced the risk of development of human endometrioid endometrial carcinoma.

However, the WHI study recently demonstrated the possible increasing risks of breast cancer associated with HRT. The WHI study showed that women receiving estrogen plus progestin (HRT) exhibited an increased risk of invasive breast carcinoma (hazard ratio (HR), 1.24; 95% CI, 1.01–1.54), although women receiving estrogen alone (ERT) demonstrated no increased risk of occurrence of invasive breast carcinoma (HR, 0.77; 95% CI, 0.59–1.01) [84, 88, 89]. These clinical data suggest that the biological roles of estrogen and progestin in tumorgenesis are different between the endometrium and breast, although both are considered “estrogen-dependent tissues”.

6. Conclusion

The enzymes responsible for intratumoral estrogen metabolism and biosynthesis are markedly different between human breast and endometrial carcinoma, although both are considered “estrogen-dependent malignancies”. 17-HSD type 1 plays an important role in the regulation of high E2 levels in breast carcinoma tissues, while 17-HSD type 1 was not detected and 17-HSD types 2 and 5 are essential for the maintenance of E2 concentrations in endometrial carcinoma tissues (Fig. 1). In addition, the biological significance of the PR isoforms differs between endometrial and breast carcinomas. Clinical data concerning HRT and estrogen-dependent cancer risk also support these findings. These basic and clinical findings help to understand the biology and provide the new knowledge for the prevention, diagnosis and treatment of human endometrial carcinoma. Although aromatase inhibitors are the most effective endocrine treatments for estrogen-responsive breast carcinoma, specific endocrine treatment of endometrial carcinoma should be considered in the future. However, this awaits further investigations for clarification.
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