cinoma have remained in dispute. Further studies, including the possibility of application and indication of aromatase inhibitors, are required to establish an aromatase inhibitor treatment as one form of endocrine therapy of endometrial carcinoma in postmenopausal patients. The results of *in vitro* studies may help to achieve improved clinical responses in patients with endometrial carcinoma, who are treated with aromatase inhibitors.

1.2.3. Retinoids

Retinoids, metabolites of vitamin A, have been demonstrated to play an important role in *in situ* estrogen metabolism through the regulation of steroid hormone receptors and 17-HSDs. Retinoids are considered to be effective chemopreventive as well as chemotherapeutic agents in a variety of human epithelial and hematopoietic neoplasms, including breast carcinoma (Kudelka et al., 1993; Evans and Kaye, 1999). Kudelka et al. (1993) reported clinically favorable results following retinoid-based treatment of the patients with cisplatin-resistant metastatic endometrial carcinoma. 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 (Ito et al., 2001). Retinoid is considered to be involved in the modulation of *in situ* estrogen metabolism by stimulating the expression of 17-HSD type 2. In addition, it has been discovered that expression of retinoic acid receptor (RAR) β is frequently silenced in epithelial carcinogenesis, which has led to the hypothesis that RARβ could act as a tumor suppressor. Therefore, we studied the effects of retinoic acid on cell proliferation and the expression of RARs using AM580 (a RAR specific agonist) in the Ishikawa endometrial cancer cell line. *In vitro*, cell growth was inhibited and RARβ mRNA was significantly induced by AM580, compared with vehicle controls (Tanabe et al., 2008). Our results suggest that retinoid may be one of the important candidates as a new endocrine-related agent in endometrial carcinoma. However, further studies such as clinical investigations are of course necessary.

1.2.4. Peroxisome proliferator-activated receptor (PPAR) ligand

Peroxisome proliferator-activated receptor (PPAR) is a member of the nuclear hormone receptor superfamily of transcription factors. PPARγ, a subfamily of PPARs, plays essential roles in the regulation of lipid homeostasis, adipogenesis, insulin resistance, and in the development of various organs (Ceil and Shuldiner, 2002; Barak et al., 1999). Synthetic PPARγ ligands, known as thiazolidinediones (TZDs), have been used for the treatment of insulin resistance in type II diabetes mellitus. In addition, results of various *in vitro* studies have demonstrated that PPARγ ligands exhibit a potent antiproliferative activity for a wide variety of neoplastic cells (Koeffer, 2003).

The expression and effectiveness of PPARγ have been extensively studied in various human malignancies but little is known about PPARγ in uterine endometrial carcinoma. In addition, the effects of PPARγ agonists on endometrial carcinoma have largely been unknown, although obesity, excess estrogen, type II diabetes, and hypertension are important risk factors for endometrial carcinoma (Berstein et al., 2004; Inoue et al., 2004). Therefore, we examined the expression of PPARγ mRNA and protein in normal endometria and its disorders (Ota et al., 2006). 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. In addition, the PPARγ agonist, 15d-PGJ_2 inhibited cell proliferation and induced p21 mRNA in endometrial carcinoma cell lines. These results did suggest that synthetic PPARγ ligands should be important drug candidates, not only for prevention but also for endocrine treatment of endometrial carcinoma.

PPARs function as transactivation factors following heterodimerization with retinoid X receptors (RXRs), and bind to specific response elements of various target genes (Mangelsdorf and Evans, 1995). Recently, several studies demonstrated that the combination treatment of PPARγ ligands and RXR ligands (retinoids) enhance the antitumor effects compared to each treatment alone in breast cancer cells (Bonofiglio et al., 2009; Papi et al., 2009). In addition, PPARγ and RXR agonist synergistically suppress proliferation of immortalized endometrial stromal cells (Wu and Guo, 2009). These results all suggest that the combination therapy of PPARγ and RXR ligands may provide a critical strategy for the treatment of endometrial carcinoma in the future.

2. Ovarian carcinoma

Ovarian carcinoma is the leading cause of death in the great majority of developed countries. Estrogen has been implicated in the etiology and progression of some ovarian carcinoma. Human ovarian carcinoma occurs in a similar population of peri- and postmenopausal women as those with breast and endometrial carcinoma, and the great majority of human ovarian carcinomas express estrogen receptor (Rao and Slotman, 1991).

Therefore, a focus has been given to the importance of *in situ* estrogen metabolism in the development and progression of ovarian carcinoma as well as breast and endometrial carcinomas. Aromatase is the key enzyme of *in situ* estrogen metabolism and the frequency of aromatase expression ranged from 33% to 81% in ovarian cancer tissues (Watanabe et al., 1995; Cunat et al., 2005; Li et al., 2008). We previously detected marked aromatase immunoreactivity and mRNA, mainly in the stromal cells of ovarian carcinoma (Kaga et al., 1996). Aromatase immunoreactivity was pronounced at sites of frank invasion. On the other hand, aromatase expression has been reported to be also present in epithelial ovarian cancer cells (Cunat et al., 2005). Therefore, ovarian epithelial or carcinoma cells and stromal cells may both produce estrogen through aromatase expression. Those findings provide a basis for ascertaining an effectiveness of aromatase inhibitor in ovarian carcinomas. We previously examined the biological changes in ovarian carcinoma tissues before and after aromatase inhibitor treatment (Sasano et al., 1999). Four of nine human ovarian carcinoma demonstrated decreased [^{3}H] thymidine uptake or Ki-67 labeling following aromatase inhibitor treatment. The responsive cases tended to be associated with higher aromatase and ERα than the unresponsive cases did.

In clinical studies, aromatase inhibitor treatment has been demonstrated to elitic clinical response rates up to 35.7% of the patients and stable disease of rates of 20–42% in patients with recurrent ovarian carcinoma (Bowman et al., 2002; Smyth et al., 2007; Li et al., 2008). Since aromatase inhibitor treatment cannot benefit all the patients with recurrent ovarian cancers, it should be important to identify those patients who do have aromatase inhibitor-responsive cancers. In a phase II trial of the aromatase inhibitor (letrozole) in the patients with recurrent ovarian carcinoma, CA125 response was associated with estrogen receptor expression (Bowman et al., 2002; Smyth et al., 2007). In addition, increased expression of aromatase was significantly associated with CA125 response on letrozole treatment (Walker et al., 2007). Those studies did show aromatase inhibitors have some therapeutic activity against recurrent ovarian carcinoma. Further studies should be however, required to establish an aromatase inhibitor treatment as one form of endocrine therapy of human epithelial ovarian carcinoma in postmenopausal patients.

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