Targeting Fatty Acid Metabolism in Gynaecological Cancers

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Fatty acid (FA) metabolism plays a vital role in promoting the development and progression of gynaecological cancers. Therefore, enzymes involved in FA metabolism are attractive targets in treating these cancer types. Moreover, inhibiting these enzymes can synergistically augment the antitumour effects of chemotherapeutic agents targeting the oestradiol pathway (e.g., selective ER modulators (SERM) and aromatase inhibitors) or to overcome chemotherapeutic resistance against these agents in gynaecological cancers. In addition to the developing pharmacological inhibitors specifically targeting FA metabolism enzymes, interest is also growing in implementing diet-based intervention to supplement conventional chemotherapeutic regime.

fatty acid metabolism obesity gynaecological cancer metabolic modulators

1. CD36 Inhibition

FA uptake is critical in supplying cancers with exogenous FAs for their progression; therefore, targeting the FA transporter CD36 could represent a promising strategy for treating some of these gynaecological cancers. One type of recently studied CD36 inhibitors, known as thrombospondin-1 (TSP-1) mimetic peptides, mimics the structure of CD36 ligands. Although many TSP-1 mimetics have been developed and studied (reviewed in [1]), three were found to have antitumour activity in gynaecological cancers: ABT-510, ABT-526 and ABT898 (**Table 1**). ABT510 is derived from the second properdin type I repeat of the NH2-terminal third of TSP-1 and, in mouse models, it inhibited the growth of epithelial ovarian cancer, as well as increasing its susceptibility to chemotherapeutic drugs [2][3]. Despite its initial promise as a CD36 inhibitor to treat ovarian cancer, it was thereafter abandoned, as phase II clinical trials of ABT510 treatment in advanced renal cell carcinoma [4], soft tissue sarcoma [5] and metastatic melanoma [6] showed it lacked sufficient clinical efficiency. ABT-526 is a GVITRIR heptapeptide based on the second TSP-1 type 1 repeat. It exhibited antitumour activity in dogs bearing the metastasis of mammary carcinoma, with one dog being relapse-free following ABT-526 treatment [7]. More promising are second-generation TSP-1 mimics, such as ABT898, which are more stable and better tolerated [5]. ABT898 regressed established ovarian tumours in animal models and significantly prolonged disease-free survival compared with control animals [8]. Although it is established that the anti-tumorigenic properties of these TSP-1 mimics stem from the ensuing anti-angiogenic effect upon CD36 binding, the inhibition of the FA uptake role of CD36 could also play a role in this regard. Indeed, the binding of TSP-1 to CD36 is known to inhibit the uptake of the long-chain FA myristic acid in a nitric-oxide-dependent manner [9]. The uptake of other long-chain FAs, such as palmitic acid by

CD36, could also be inhibited by TSP-1, operating in parallel with the anti-angiogenic effects of TSP-1 in curbing the growth of gynaecological cancers.

Table 1. A non-exhaustive list of interventions for the main FA metabolism enzymes at various stages of development.

Target Protein	Intervention	Cancer Type	Preclinical Model	Clinical Trial	References
CD36	ABT-526	Breast	Breast cancer-bearing dogs	-	[7]
	ABT898	Ovarian	Xenografts	-	[8]
ACLY	Hydroxycitrate	Breast	In Vitro	-	[10]
	Metformin	Cervical	In Vitro	-	[11]
ACC	TOFA	Ovarian, Breast	Xenografts	-	[12][13]
FASN	Orlistat	Breast, Ovarian	Xenografts	-	[14]
	Rigallocatechin Gallate	Breast	Xenografts	-	[15][16]
	Fasnall	Breast	Xenografts	-	[17]
	TVB-2640	Breast	-	Phase II	[18]
	TVB-3166	Ovarian	Xenografts	-	[19]
	C93	Ovarian	Xenografts	-	[20]
	DHA Supplementation	Breast	In Vitro	-	[21]
ACS	Triacsin C	Breast	In Vitro	-	[22][23]
CPTI	Etomoxir	Breast	Xenografts	-	[24]
	Perhexiline	Breast	Xenografts	-	[25]
	Eugenol	Breast	In Vitro	-	[26]
		Cervical	-	Phase III	[27]

ACLY, ATP-citrate lyase; ACC, acetyl-CoA carboxylase; FASN, Fatty acid synthase; ACS, Acyl-CoA synthetase; CPTI, Carnitine palmitoyl transferase I; DHA, Docosahexaenoic acid.

Recent studies have implicated CD36 in promoting the resistance of breast cancer towards tamoxifen, a widely used selective ER modulator for treating ER+ breast cancer. Liang et al., found that the CD36 protein expression was higher in tamoxifen-resistant MCF-7 (MCF7/TAMR) than their non-resistant counterpart, suggesting the role of CD36 in mediating tamoxifen resistance in MCF7/TAMR [28]. Indeed, knocking down CD36 in MCF7/TAMR via siRNA restored sensitivity towards tamoxifen, as evidenced by tamoxifen regaining the ability to inhibit the growth of MCF7/TAMR. These results poInt. to a treatment strategy where ER+ breast cancer patients are administered simultaneously with tamoxifen and CD36 inhibitors to overcome tamoxifen resistance. This strategy, however, may not be effective in all tamoxifen-resistance breast cancer types, since in the same study, Liang et al., found MDA-MB-231, an ER-negative tamoxifen-resistant breast cancer cell line, had lower CD36 protein expression than non-resistant MCF7 [28]. Therefore, utilising the tamoxifen-CD36 inhibitor combination might require stratifying breast cancer patients based not only on tamoxifen resistance, but also on both CD36 and ER expression levels.

2. ATP-Citrate Lyase (ACLY) Inhibition

Numerous natural and synthetic ACLY inhibitors are available (reviewed in [29]) but only a few have been tested in gynaecological cancers. Hydroxycitrate (HCA) was found to reduce the cancer stem cell population of mammary breast cancer cell lines (HMLE and HMLER), suggesting it may reduce tumour initiation [10]. Besides, metformin, together with caffeic acid, reduced the protein level of ACLY in cervical carcinoma SiHa/HTB-35 cells, impairing FA synthesis and sensitising SiHa/HTB-35 to the action of cisplatin (**Table 1**) [11]. This combination effect suggests ACLY could have a role modulating the response of cancer cells towards certain chemotherapeutic agents, at least in cervical cancer. Interestingly, inhibiting ACLY reduced the intracellular citrate level and cell viability of breast cancer cell lines more effectively than inhibiting citrate transport protein (CTP) [30], but whether inhibiting both CTP and ACLY produces a synergistic antitumour effect is underexamined. Targeting ACLY, however, may not be a viable long-term treatment option, as cancer cells can upregulate acetyl-CoA synthetase (ACCS) to produce acetyl-CoA from acetate, obviating the need for citrate as a source of acetyl-CoA for FA synthesis [31]. This bypassing could be overcome by inhibiting ACLY together with ACCS simultaneously, but whether this approach results in favourable clinical outcomes needs further investigation.

Few studies have investigated the effect of ACLY inhibitors in influencing the effect of tamoxifen on breast cancer cells. Ismail et al., found that co-treating MCF-7 with HCA and tamoxifen reduced MCF-7 viability and promoted apoptosis to a greater degree than when either one was used alone [32], suggesting their antitumour effects are acting synergistically when used in combination. This evidence could prompt a clinical trial, investigating whether the synergistic effect of ACLY inhibitors and tamoxifen can be translated clinically in breast cancer patients, which, if successful, could motivate lowering the therapeutic dosage of tamoxifen required, so as to lessen the side-effects undergone by tamoxifen-treated patients [33]. Apart from that, other investigators have demonstrated the potential use of targeting ACLY in overcoming drug resistance in several cancer types, such as hepatocellular carcinoma [34] and ovarian cancer [35]. Therefore, it would also be interesting to investigate the potential of using the tamoxifen-ACLY inhibitor combination in overcoming tamoxifen-resistance in breast cancer. Nevertheless, the possibility of the breast cancer cells gaining resistance towards this tamoxifen-ACLY inhibitor combination should be borne in

mind, since Ismail et al., found elevated levels of triglycerides in the co-treated MCF-7 [32], suggesting a compensatory mechanism to acquire FAs, without the need for citrate-originating acetyl-CoA.

3. Acetyl-CoA Carboxylase (ACC) Inhibition

ACC inhibitors, such as TOFA, are found to retard the growth of breast [13] and ovarian [12] cancer, but none have reached the clinical trial phase for the treatment of gynaecological cancers (**Table 1**). However, the ACC inhibitor NDI-010976 may be investigated as a potential gynaecological cancer treatment. It reduced de novo lipogenesis in overweight adult male subjects in a randomized, double-blind, crossover study [36]. Although inhibiting ACC may have clinical benefits in treating gynaecological cancers, this method should be approached with caution, as several tumour types have been reported to have their growth accelerated when ACC is inhibited [37].

So far, the role of the ACC inhibitor and its impact on the pro-carcinogenic activity of oestradiol has received little attention, probably stemming from the focus on FASN instead of ACC as the key enzyme to target FA synthesis in cancer. Nevertheless, studies suggest ACC may be a valuable additional target in treating breast cancer patients undergoing treatment with aromatase inhibitors. Du et al., deprived SUM44, an invasive lobular breast cancer cell line, of oestrogen long term to mimic aromatase inhibition and also treated these long-term oestrogen-deprived cells (SUM44 LTED) with TOFA to inhibit ACC [38]. They found, compared with the parental controls, TOFA more greatly inhibited the cell growth of SUM44 LTED, suggesting the potential use of ACC inhibitors to supplement the aromatase treatment of breast cancer. Nevertheless, the effectiveness of the aromatase inhibitor-ACC inhibitor combination might be influenced by the Human Leucocyte Antigen (HLA) typing of the invasive lobular breast cancer, given that Du et al., also found the cytotoxic effect of TOFA was not enhanced in MM134 LTED, another invasive lobular breast cancer cell line but of a different HLA typing from SUM44 [39], compared with their parental controls [38].

4. Fatty Acid Synthase (FASN) Inhibition

Pharmacologic FASN inhibitors are classified based on the FASN domain targeted, that is, whether they target the β-ketoacyl synthase or thioesterase domain [40]. Orlistat, a well-studied irreversible inhibitor of the thioesterase domain, is shown to exhibit antitumour properties in various breast and ovarian cancer cell lines (**Table 1**) [14]. It is also a well-established anti-obesogenic agent, shown to reduce weight by about 3% in obese and overweight people compared with their placebo counterparts [41]. This weight-losing effect suggests another mechanism through which orlistat may lower the risk of gynaecological cancers, in concert with its FASN inhibitory activity. Natural FASN inhibitors are also available, the most studied of which is epigallocatechin gallate (EGCG), shown to inhibit the growth of breast cancer cells in vivo and in vitro [15][16]. Intriguingly, selective FASN inhibitor Fasnall operates by targeting co-factor binding to FASN, not by competing with substrate intermediate of FASN. It had potent anticancer activity in various breast cancer cell lines and in MMTV-Neu in vivo model of $HER2^+$ breast cancer, with favourable pharmacokinetics and tolerance profiles [17]. Notably, it had a synergistic effect on tumour shrinkage when combined with carboplatin. Such synergistic effects suggest Fasnall can be used together with

carboplatin in the clinical treatment of breast cancer to improve their efficacy [17]. TVB-2640 is a first-in-class FA inhibitor used in a Phase I trial to investigate its efficiency in lowering metabolic markers associated with non-alcoholic fatty liver disease in obese men [42]. TVB-2640 is part of an ongoing phase II clinical trial that seeks to determine how effective it is in combination with paclitaxel and trastuzumab in treating ER2+ breast cancer metastases [18]. C75 is a synthetic FASN inhibitor found to exert antitumour effects in breast [43][44], ovarian [45] and endometrial [46] cancer. Given it demonstrated anti-carcinogenic properties in a broad range of gynaecological cancers, it could be a suitable candidate drug for clinical trials investigating its efficacy and effectiveness in these cancer types.

Interestingly, inhibition of FASN in gynaecological cancers by agents, such as cerulenin and C75, also impairs oestradiol-induced nuclear accumulation of ER and downregulates ER expression [45], reinforcing the antitumour effects of FASN inhibition by diminishing the pro-tumorigenic signalling emanating through the ER pathway, which could also reduce the impact of oestradiol-induced upregulation of FASN [47]. Coupling FASN inhibitors to inhibitors of aromatase, the enzyme converting androgens into oestrogens, could serve as potential therapeutic strategy in aromatase inhibitor-treated ER+ breast cancer patients to recurrence, which is due to the ability for aromatase inhibitors, such as anastrozole, to upregulate ER-dependent FASN protein expression in this cancer type by inhibiting ubiquitin-mediated FASN protein degradation [48].

5. Acyl-CoA Synthetase (ACS) Inhibition

Owing to its importance in permitting FAs to be utilised for both catabolic and anabolic downstream processing, blocking FA activation by inhibiting ACS might also serve as an effective approach to treat gynaecological cancers. However, few drugs have been developed to target ACS, a situation most likely arisen due to the existence of numerous ACS isoforms, which might necessitate separate drugs to be specifically made for each isoform. Nevertheless, drugs found to be specific for certain ACS isoforms do exist, such as thiazolidinediones, a drug targeting PPARγ for the treatment of type 2 diabetes and involved in potent-specific inhibition of ACSL4 [49]. Therefore, thiazolidinediones could be potential therapeutic agents in the treatment of breast cancer, a cancer type in which ACSL4 was found to play a role promoting its malignancy and chemoresistance. Investigators also found inhibiting ACSL4 in the presence of chemotherapeutic drugs can have a synergistic antitumour effect, demonstrated by treating MDA-MB-231 with triacsin C alongside cisplatin, doxorubicin or paclitaxel (**Table 1**) [22]. Additionally, other non-cancer drugs may be repurposed for targeting ACS in cancer cells, such as aspirin, which was found to suppress the abnormal lipid metabolism of HCC cells through inhibiting acyl-CoA synthetase long-chain family member 1 (ACSL1) [50]. This, however, may not be clinically beneficial in treating breast cancers, as a population-based study demonstrated that long-term use of low-dose aspirin marginally increased the risk of breast cancer [51], but this does not preclude its potential in treating other gynaecological cancers.

Among the myriad ACS isoforms, ACSL4 has been given the most attention so far for inhibition studies, given the mounting evidence on its pro-carcinogenic role. Indeed, Wu et al., investigated the role of ACSL4 in promoting resistance against tamoxifen in breast cancer. Specifically, they found overexpressing ACSL4 reduces the cytotoxic effect of tamoxifen in MCF-7 and SKBr-3, suggesting inhibiting ACSL4 could overcome tamoxifen resistance in

breast cancer [52]. Indeed, through ERα inverse agonist XCT-790 and triacsin C co-treatment, Dattilo et al., found the co-treatment synergistically reduced the proliferation of MDA-MB-231 [23]. However, XCT-790 also acts as a mitochondrial uncoupler, independent of its ERα-related activity, possibly being responsible instead for its synergism with triacsin C in breast cancer [53]. Which activity mode of XCT-790 is acting synergistically with triacsin C needs to be ascertained, as it could impact whether this treatment combination can be administered to ER-negative breast cancer patients.

6. Carnitine Palmitoyltransferase (CPTI) Inhibition

FA oxidation provides cancer cells the ATP and NADPH needed to support their uncontrollable proliferation, making this process an attractive target for gynaecological cancer therapy. Few CPTI inhibitors are available, namely, perhexiline [25], etomoxir [24][54][55], and Eugenol [26], all of which showed antitumorigenic effect when used to treat breast cancer in vitro and in vivo (**Table 1**). Although etomoxir is not clinically approved for any gynaecological cancers, investigators found chemically inhibiting CPTI with etomoxir, together with glutaminase with CB-839, a drug currently in Phase I/II, decreased cell proliferation and migration of CB-839-resistant TNBC cells more than inhibiting only either enzyme alone [24]. This effective dual combination may open up a possibility of conducting a clinical trial to investigate whether etomoxir and CB-839 could be used simultaneously to improve the treatment of aggressive breast cancer. Nevertheless, it should be borne in mind that etomoxir might not affect all cancer types the same way. Some cell lines of several cancer types, including MCF7 and HeLa, did not experience any reduction in proliferation when treated with etomoxir [56]. Furthermore, etomoxir was also found to exhibit an off-target effect with complex I of the electron transport chain being targeted at high doses of etomoxir [56]. This unintended consequence should be considered when determining the appropriate dose for clinical trials and cancer studies, should its intended target be only CPTI. Recently, a reversible CPTI inhibitor ST1326 was found to reduce the proliferation of chronic lymphocytic leukaemia cells [57] and could be considered for targeting CPTI in gynaecological cancers. Eugenol, as one of the components of a topical antiviral spray AV2, was found to be marginally more effective in regressing HPV-associated precancerous lesions of the cervix in a low-resource setting Phase III clinical trial, though the regression rate did not achieve statistical significance. This resource-restricted outcome may be rectified with a larger sample size and by repeating the clinical trial in a high-resource setting [27].

Similar to most other enzymes involved in FA metabolism, little is known about how CPTI could influence the pro-tumorigenic properties of oestradiol. Nevertheless, current evidence implicates CPTI in modulating the resistance of breast cancer against SERM. Duan et al., found that MCF7/TAMR had higher basal expression of CPTI than parental controls and their CPTI expression became higher than their respective baseline when both were treated with endoxifen, another SERM developed to address tamoxifen-resistant breast cancer [58]. Furthermore, in both untreated and endoxifen-treated MCF7/TAMR, inhibiting AMPK via compound C and siRNA knockdown lowered CPTI expression, while, in contrast, the expression was increased when inhibiting AKT with MK2206. These results suggest CPTI could be involved in promoting SERM resistance in breast cancer, which is positively and negatively regulated by the AMPK and AKT pathway, respectively. However, these results need to be confirmed by

determining whether SERM-resistance in untreated and endoxifen-treated MCF7/TAMR could be abrogated by knocking down or inhibiting CPTI.

7. Omega-3 Fatty Acids Supplementation

Aside from pharmacological interventions, dietary intervention is worth exploring, specifically in supplementing and, therefore, enhancing well-tested cancer therapies. Omega-3 FAs, such as eicosapentaenoic and docosahexaenoic acids (EPA and DHA, respectively) are among the nutrients heavily studied for their potential use in this approach. Indeed, consumption of omega-3 FAs is associated in numerous studies with the decreased risk of multiple cancer types, including gynaecological cancers [59][60], accomplished primarily through their anti-inflammatory action [61]. Indeed, the use of omega-3 FAs to inhibit the progression of gynaecological cancer may be more beneficial in obese patients, as rats given high-fat diets had lower NF-κB mRNA levels and DNA binding than control-diet rats when both were treated with omega-3 FAs [62]. Other than their anti-inflammatory properties, omega-3 FAs could also retard the growth of gynaecological cancers by interfering with the action of oestradiol, directly or indirectly, in dysregulating FA metabolism in these cancers. Huang et al., found DHA abrogated the FASN upregulation and pAkt/Akt increase in MCF7 induced by oestradiol, while also inhibiting oestradiol-induced promotion of the SREBP isoform SREBP-1 protein expression and these abrogations were further enhanced upon adding the Akt inhibitor LY294002 [21]. Pro-tumorigenic impact of oestradiol on FASN in breast cancer could, therefore, be significantly inhibited with DHA supplementation in combination with Akt-inhibiting agents (**Table 1**). However, it remains uncertain whether, in addition to SREBP-1, the abrogation of oestradiol-induced FASN by DHA could also be, in part, due to the effect of DHA on PPARs, since PPARs are also known to be both activated by DHA or its downstream metabolites [63], and involved in regulating FA metabolism, including FA synthesis [64]. Nevertheless, intake of omega-3 FAs, however, should be accompanied with caution, as excess consumption is linked to several adverse effects, including the increased risk of prostate cancer [65], another hormone-responsive cancer type, which may also imply the elevated risk of gynaecological cancers. Therefore, optimising the omega-3 FAs intake of each patient is paramount, to avoid such side effects when administering omega-3 FAs, alone or together with established cancer treatments, to fully take advantage of the tremendous therapeutic potential of omega-3 FAs [66].

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