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Acetyl-CoA carboxylase-α as a novel target for cancer therapy

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1. ABSTRACT

Acetyl-CoA carboxylases (ACC) are rate-limiting enzymes in *de novo* fatty acid synthesis, catalyzing ATP-dependent carboxylation of acetyl-CoA to form malonyl-CoA. Malonyl-CoA is a critical bi-functional molecule, i.e., a substrate of fatty acid synthase (FAS) for acyl chain elongation (fatty acid synthesis) and an inhibitor of carnitine palmitoyltransferase I (CPT-I) for fatty acid beta-oxidation. Two ACC isoforms have been identified in mammals, i.e. ACC-alpha (ACCA, also termed ACC1) and ACC-beta (ACCB, also designated ACC2). ACC has long been used as a target for the management of metabolic diseases, such as obesity and metabolic syndrome, and various inhibitors have been developed in clinical trials. Recently, ACCA up-regulation has been recognized in multiple human cancers, promoting lipogenesis to meet the need of cancer cells for rapid growth and proliferation. Therefore, ACCA might be effective as a potent target for cancer intervention, and the inhibitors developed for the treatment of metabolic diseases would be potential therapeutic agents for cancer therapy. This review summarizes our recent findings and updates the current understanding of the ACCA with focus on cancer research.

2. INTRODUCTION

Cancer is characterized with uncontrolled cell growth; in cancer cells DNA, protein and fatty acid synthesis are largely increased to meet the need of rapid cell growth and proliferation (1-7). Long chain fatty acids are the precursors for cell energy storage and various lipid species, such as the phospholipids essential for biomembrane synthesis (8). Therefore, increased fatty acid and lipid synthesis is a critical feature of cancer cells, and the lipogenic enzymes in the pathway are potential targets for cancer intervention. Acetyl-CoA carboxylases (ACC) carboxylates acetyl-CoA to malonyl-CoA, representing the rate limiting step in fatty acid synthesis. Malonyl-CoA is an intermediate of the de novo fatty acid synthesis, acting as a substrate of fatty acid synthase (FAS) for acyl chain elongation (9, 10); malonyl-CoA also functions as an inhibitor of carnitine palmitoyltransferase I (CPT-I), regulating fatty acid beta-oxidation (11) (Figure 1). Therefore, functional abnormalities of ACC will block fatty acid synthesis and disturb the energy metabolism, leading to cell damage. ACC is a biotin-dependent, multi-domain enzyme containing biotin carboxylase (BC) and

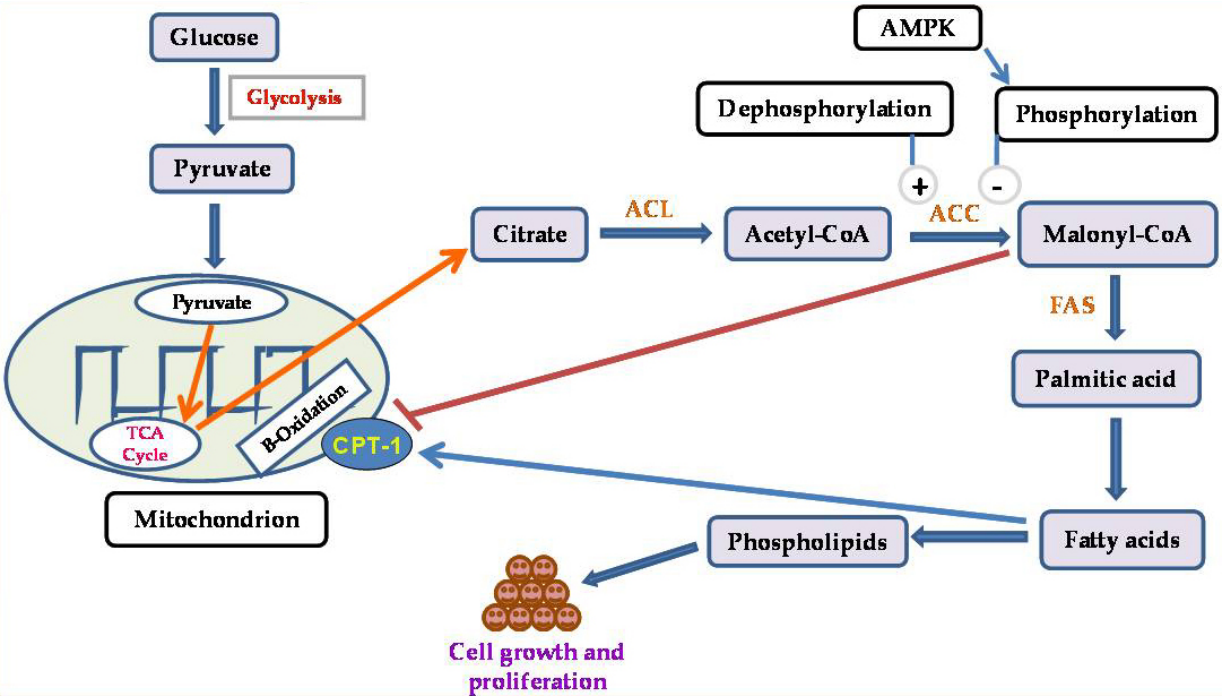

Figure 1. *De novo* fatty acid synthesis. Glucose is converted to pyruvate by glycolysis. In mitochondria pyruvate is converted to acetyl-CoA that enters the tricarboxylic acid (TCA) cycle. Citrate generated in the TCA cycle is transported to cytosol, where it is converted to acetyl-CoA by ATP citrate lyase (ACL). Acetyl-CoA carboxylases (ACC) utilize acetyl-CoA to form malonyl-CoA. This is a rate limiting step in *de novo* fatty acid synthesis. AMP activated protein kinase (AMPK) phosphorylates and deactivates ACC, controlling fatty acid synthesis. Malonyl-CoA is used for acyl chain elongation catalyzed by fatty acid synthase (FAS). Long chain fatty acids are essential components of cellular lipids, such as phospholipids. Malonyl-CoA also inhibits carnitine palmitoyl transferase-1 (CPT-1) that transfers fatty acids into mitochondria for oxidation.

carboxyltransferase (CT) activity in most eukaryotes (12-14). In sequence, BC catalyzes an ATP-dependent carboxylation of biotin with bicarbonate as a CO_2 donor, and the CT promotes the carboxyl transfer from biotin to acetyl CoA, forming malonyl-CoA. Due to its critical role in fatty acid synthesis and energy metabolism, ACC has become an important target for the treatment of metabolic diseases, such as obesity and metabolic syndrome (15-17); and a large amount of ACC inhibitors have been developed for clinical trials (18, 19).

Two ACC isoforms have been identified in mammals, ACC-alpha (ACCA, also termed ACC1) and ACC-beta (ACCB, also designated ACC2) (20, 21). ACCA up-regulation has been recently documented in a variety of human Tumors and is likely to be implicated in the Tumor development and progression (7, 22, 23), or susceptibility (24). In prostate and breast cancer cells, small interfering RNA (siRNA)-mediated silencing of the ACCA gene inhibits fatty acid synthesis, arrests cell cycle and induces caspase-mediated apoptosis (25, 26). More encouraging results were obtained from Swinnen's group (27) and our laboratory (28); inhibiting ACCA activity by soraphen A, an inhibitor of the BC domain, or TOFA, an allosteric inhibitor, induces apoptotic death of breast, lung and colon cancer cells, suggesting ACCA as a potential target for developing novel agents for cancer therapeutics. This is the focus of this review article.

3. ACC, FATTY ACID METABOLISM, AND METABOLIC SYNDROMES

ACC isoforms, ACCA and ACCB, are encoded by different genes (13, 29). Human ACCA contains 2346 amino acid residues, with a molecular weight of 265 kDa. By alternative splicing, two ACCA isoforms/variants are produced with molecular weight of 257kDa and 259 kDa, respectively (30, 31). ACCB contains 2483 amino acid residues with molecular weight of 280 kDa. The 140 amino acids at N-terminus of ACCB contribute to its subcellular localization at the outer membrane of mitochondria, where it functions as a regulator of fatty acid beta-oxidation via malonyl-CoA (32, 33). ACCA does not have the 140 N-terminal amino acids and is universally distributed in cytosol for fatty acid synthesis (14, 34, 35). Therefore, these two ACC isoforms display distinct affinity and activity to the substrate and allosteric regulators, such as citrate, although they share up to 75% of identity of amino acid sequences (15, 36, 37). Tissue distributions of two ACC isoforms are also diverse, in accordance with their biological functions. In normal tissues, ACCA is mainly expressed in lipogenic tissues, such as liver and adipose, as well as lactating mammary glands. On the other hand, ACCB is preferentially expressed in the tissues with active fat oxidation, e.g., heart and skeletal muscle. The metabolically active liver is also abundant in ACCB (32,

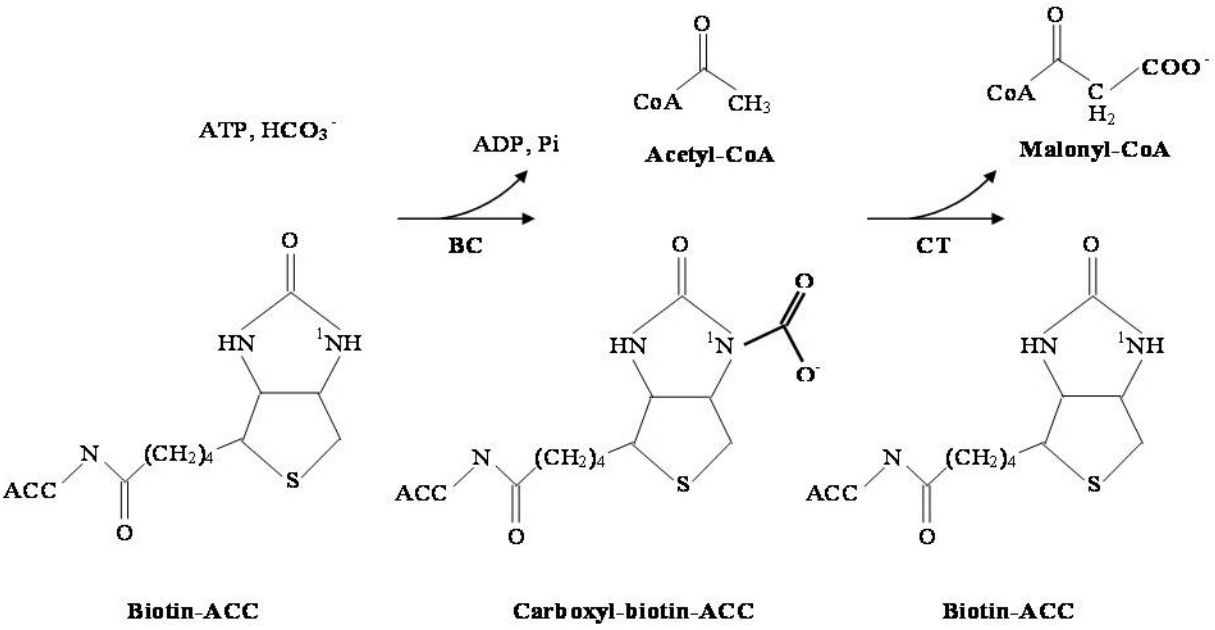

Figure 2. Malonyl-CoA formation by an ACC-catalyzed two-step reaction. Biotin carboxylase (BC) catalyzes the ATP-dependent carboxylation of biotin with bicarbonate as a carbon-dioxide donor (CO_2), followed by carboxyl transferase (CT)-catalyzed carboxyl group transfer to acetyl-CoA to form malonyl-CoA.

36, 38, 39). In these tissues, ACCB regulates fatty acid oxidation and becomes a main target for the management of metabolic diseases (see below).

In eukaryotic cells, ACC belongs to a family of biotin dependent carboxylases, containing 3 domains in a single polypeptide, i.e., biotin carboxylase (BC), carboxyl transferase (CT) and biotin carboxyl carrier protein (BCCP) (40, 41). However, in bacteria, there are three individual protein subunits (BC, CT-α/β, and BCCP) that form a multimeric complex (42, 43). This protein complex in Escherichia coli (E. coli) is unstable and readily dissociates (42). However, the dissociated subunits retain the capability of catalyzing corresponding reactions (20) and thereby, *E. coli* ACC has been an optimal protein model for studying the crystal structure and reaction sequence of ACC in detail. ACC proteins are highly conserved among living organisms, particularly in its BC domain. For instance, human ACCA shows 37% of amino acid sequence similarity to the BC subunit of *E. coli* and 63% to that of yeast (44). The CT domain is relatively less conserved with approximately 45% of sequence identity even among the eukaryotic cells. This phenomenon may be ascribed to different evolutionary pressures that these three domains face (44).

ACC structure has been extensively investigated and provides important information for the development of specific inhibitors. The crystal structure of BC subunit of E. coli, characterized in 1994 (45), has been a paradigm of structural studies. Fully folded BC molecule consists of three domains: N-terminal domain, "B-domain" and C-terminal domain. The active site is constituted of residues Glu^{211}, Glu^{288}, Asn^{290}, Arg^{292}; Lys^{116}, Lys^{159}, His^{209}, Glu^{276}, Gly^{165}, and Gly^{166} (46-49). Yeast CT domain contains two sub-domains (N and C domains). These two domains share similar polypeptide backbone folds with a central beta-beta-alpha super helix, but have different function, such as the binding to adenine base of acyl-CoA (35). Residues in CT active site are highly conserved, such as Arg^{1954} for recognizing the carboxyl group of malonyl-CoA and carboxybiotin (35). Biotin carboxyl carrier protein (BCCP), a central site of the carboxylation and trans-carboxylation reactions, is composed of C-terminal domain (biotin domain) and N-terminal domain. The residues 77-156 of E. coli BCCP subunit (called BCCPsc, a subtilisin Carlsberg digestion product) act as a carboxyl acceptor and donor in the biotin carboxylase and carboxyl transferase-catalyzed reactions. This peptide forms two sets of four anti-parallel beta strands, designated as beta1- beta8. These beta strands are remarkably symmetric at three levels and are described as a capped beta sandwich with a quasi-dyad axis of symmetry. X-ray crystallographic and multidimensional nuclear magnetic resonance (NMR) studies show that eight amino acid residues present upstream of the biotinylated lysine constitute a structure called the “thumb”, which plays an essential role in the BCCP function and is a useful motif for identifying the biotin in this multifunctional ACC (50). The structure of the N-terminus of the BCCP remains unclear; it may play a role in dimerization and interaction with the other subunits in prokaryotic organisms (51).

ACCs catalyze the carboxylation of acetyl-CoA to malonyl-CoA by two consecutive steps (15, 20) (Figure 2). In this reaction, BC catalyzes adenosine triphosphate (ATP)–dependent carboxylation of a biotin group covalently linked to a lysine residue in BCCP, a carboxyl ‘carrier’, followed by CT-catalyzed transfer of the carboxyl

Table 1. Summary of ACC regulation at different levels

Regulation	Factors	References
Transcriptional level	SREBP1: androgens, thyroid, insulin, AMPK;	(30, 32, 64-65)
	LXR/RXR complex: thyroid	(67)
Translational level	PI3K/AKT/mTOR signaling pathway: human epithelial growth factor receptor- 2 (HER2)	(75)
Post-translation level		
Protein stability	ACC-TRB3-COP-1 complex: mediating the ubiquitination and proteasome degradation of ACCA and ACCB;	(86)
Enzyme activity	ACCA- AKR1B10 complex: blocking ACCA ubiquitination and degradation	(87)
Phosphorylation	AMPK: phosphorylating and inactivating both and ACCB;	(92, 95)
	PKA: phosphorylating and inactivating ACCB, ACCA (in vitro);	(52, 104-106)
	BRCA1-pACCA complex: blocking the dephosphorylation of the ACCA	(108-109)
Allosteric	Palmitoyl-CoA: inactivating ACC	(7)
	Citrate: activating ACC	(114)

group from biotin to acetyl-CoA forming malonyl-CoA. The malonyl CoA produced by ACCA is used by FAS to synthesize long chain fatty acids for energy storage and synthesis of cellular lipid species, such as triacylglycerides (TG), phospholipids, and cholesterol (14). The heart and skeletal muscle do not have significant *de novo* fatty acid synthesis due to the lack of FAS; and the malonyl-CoA synthesized by ACCB localized in mitochondria regulates mitochondrial fatty acid uptake and oxidation through allosteric inhibition of carnitine palmitoyltransferase I (CPT-I), a key enzyme in mitochondrial fatty acid oxidation (52-54). Therefore, ACCs and their product malonyl-CoA play a crucial role in energy metabolism and cell growth and proliferation (11, 55).

Several metabolic disorders, such as obesity, diabetes and metabolic syndrome, are attributed or related to the imbalance of fatty acid storage and oxidation, involving ACCs in the pathogenesis of these diseases (56-60). In ACCB deficient mice, fatty acid oxidation is elevated and body fat content and body weight are reduced, indicating its potential as a target for treatment of metabolic diseases (15, 61, 62).

4. REGULATION OF ACC EXPRESSION AND ACTIVITY

Due to the importance of ACC in fatty acid synthesis and energy metabolism, its expression and activity in mammalian cells are strictly regulated at multiple levels (Table 1).

4.1. ACC expression is regulated at both transcriptional and translational levels

ACCA is encoded by a single gene, but its expression is controlled by three consecutive promoters designated PI–PIII, which are located upstream of exons 1, 2, and 5A, respectively (30, 63). These promoters demonstrate distinct roles in constitutive or inducible expression in response to a variety of factors (32, 64). ACCA expression at the promoter level is exerted via a group of transcription factors controlled by glucose, insulin, thyroid hormones and catabolic hormones (30, 32, 64). The transcription factors involved include sterol-regulatory-element binding protein-1 (SREBP1) (65, 66), liver X receptor/retinoid X receptor complex (67), and PPARγ co-activator (PGC) (31, 68). SREBP1 is a key lipogenic transcription factor. As an effector of both mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K) pathways, SREBP1 regulates the expression of ACCA, as well as other lipogenic enzymes in adipose tissues (23, 65, 69-74). The ACCA expression is also regulated at the translational level. In breast cancer cells with over-expression of human epithelial growth factor receptor- 2 (HER2), the ACCA protein is enhanced through the translational activation mediated by PI3K/AKT/mTOR signaling pathway, rather than transcriptional activation (75).

ACCB expression is controlled by a single promoter and mainly regulated by PPARα, MyoD, Myf4 and Myf6 (76, 77). AMP-activated kinase (AMPK) also regulates ACCA/B expression, but the regulatory mechanisms remain unclear (78-81). AMPK regulates the activity of some key transcriptional factors, such as SREBP-1c (82, 83), and co-activator p300 (84), which may affect ACC expression. In addition, ACCA/B expression is also affected by feeding. ACCA/B in the liver is decreased in response to starvation and elevated by re-feeding (85).

4.2. ACC protein stability is mediated by protein-protein complexes

In addition to rigid control in the expression, ACC stability is mediated by protein-protein complexes. Two key protein complexes have been identified thus far to regulate ACC stability. One is the ACC-TRB3-COP-1 complex that mediates the ubiquitination and proteasome degradation of ACC protein (86). Tribbles 3 (TRB3), a mammalian homolog of Drosophila tribbles (TRB), triggers the degradation of ACC in adipose tissues by recruiting E3 ubiquitin ligase constitutive photomorphogeneic protein 1 (COP1) to ubiquinate ACC. In this process, TRB3 acts as an adaptor promoting ACCA and COP1 interaction and thereby ACC ubiquitination. TRB3 stimulates the ubiquitination of both ACCA and ACCB isoforms.

Our data demonstrated that AKR1B10 (aldo-keto reductase family 1 B10) associates with ACCA blocking its ubiquitination and degradation (87). AKR1B10 is a protein overexpressed in hepatocellular carcinoma and non-small cell lung cancer (88-90). In breast cancer cells, AKR1B10 is upregulated along with the tumorigenic transformation of human mammary epithelial cells. Accordingly, AKR1B10 knockdown mediated by RNAi dramatically decreases ACCA protein levels and inhibits lipid synthesis in breast and colon cancer cells, representing a novel regulatory mechanism of ACCA activity and lipid metabolism (87). It remains unclear whether this mechanism is unique to cancer cells or also occurs in normal cells. ACCA also binds to breast cancer protein-1 (BRCA1) that blocks the dephosphorylation and activation of ACCA, but does not affect its stability.

4.3. ACC activity is modulated by phosphorylation and allosteric mechanisms

ACC exists as active/dephosphorylation and inactive/phosphorylation forms (52, 91). Active ACC self-associates forming multimeric filamentous complexes. Upon phosphorylation, ACC dissociates to inactive monomers. The phosphorylation of ACCA at Ser79, Ser1200 and Ser1215 is carried out largely by AMP-activated kinase (AMPK), inhibiting fatty acid and lipid synthesis and thus inducing apoptosis (92-95). A variety of stress signals and adipokines, such as leptin and adiponectin, are involved in the regulation of phosphorylation-dephosphorylation of the ACCA through AMPK pathway (21, 96-100). AMPK also phosphorylates and inactivates ACCB (101-103). Considering its regulation on ACC expression as described above, AMPK appears as a key regulator of ACC activity, affecting fatty acid synthesis and oxidation through a rapid (ACC phosphorylation) or slower (ACC expression) mechanism.

In cultured cell, protein kinase A (PKA) phosphorylates ACCA at Ser77 and Ser1200 and results in a modest inactivation of its enzyme activity (52, 104-106). Compared to ACCA, ACCB is a far better substrate of the PKA in response to isoprenaline treatment in cardiac myocytes or leptin in endothelial cells (107). However, this mechanism needs to be confirmed in vivo.

ACC phosphorylation and dephosphorylation is also regulated by BRCA1, a tumour suppressor (108, 109). BRCA1 associates with phosphorylated/inactive ACCA through its BRCT tandem domain at C-terminus, blocking the dephosphorylation at Ser^{79} and Ser^{1263} residues. BRCA1 mutations that occur in up to 90% of hereditary breast cancer abolish this association, thus leading to ACCA activation and breast cancer susceptibility (110-113).

The complexity and strictness of ACC regulation are also reflected on allosteric modulations by local metabolites. Palmitoyl-CoA, the FAS end-product, promotes inactive conformation of the ACCA, diminishing the malonyl-CoA production (7). On the contrary, citrate, a precursor of acetyl-CoA allosterically activates the ACCA, stimulating fatty acid synthesis and storage (114).

5. ACCA EXPRESSION AND LIPOGENESIS IN CANCER CELLS

Enhanced lipogenesis is a common feature of cancer cells. Recent studies have revealed that in Tumor cells, newly synthesized lipids are mainly phospholipids, the major components of cell membranes, meeting the need of rapid cell division (115-117). The newly synthesized lipids are enriched with saturated or monounsaturated fatty acids and tend to partition into detergent resistant membrane microdomains or rafts, mediating cell migration, signal transduction, and intracellular trafficking (118-124). Therefore, fatty acid synthesis and lipogenesis are critical to cancer cell growth and proliferation.

As a rate-limiting enzyme of fatty acid synthesis, the ACCA's role in cancer development and progression has attracted the attention of cancer researchers. It has been found that ACCA is overexpressed in human cancers, such as breast, prostate, and liver carcinoma (7, 22, 23, 125, 126). In breast cancer, ACCA upregulation was detected at early stages, ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS) (22); and in prostate cancer, ACCA mRNA level was enhanced concomitantly with FAS, as demonstrated by RNA array hybridization complemented with *in situ* hybridization (126). Interestingly, in hepatocellular carcinoma ACCA upregulation was accompanied with FAS and ATP citrate lyase, two lipogenic enzymes (23). Our recent studies have revealed that ACCA, along with AKR1B10, is highly upregulated during the tumorigenic transformation of human mammary epithelial cells (87). These results suggest that lipogenic enzymes are universally upregulated to meet the enhanced lipid requirements.

ACCA polymorphisms/mutations have been recognized in its encoding and regulatory regions and potentially correlate with the breast cancer susceptibility. Olga M, et. al (24) investigated the polymorphisms/mutation of PIII-controlled mammary gland lactation-induced ACCA isoform in breast and ovarian cancer and found that ACCA alleles with variations in regulatory regions influence ACCA expression and thus the breast cancer risk. The clinical significance of encoding region mutations of the *ACCA* needs to be elucidated.

The role of ACCA in the growth and survival/death of cancer cells has been functionally evaluated by two approaches. Using RNA interfering technology, several studies from different laboratories have shown that small interfering RNA (siRNA)-mediated *ACCA* silencing decreases fatty acid synthesis, impairs mitochondrial potentials, and thus results in oxidative stress and apoptotic cell death in breast, colon and prostate cancer cells; and more importantly, the cell death induced by ACCA knockdown could be reversed by supplementing the medium with palmitic acid (16:0), the end-products of fatty acid synthesis pathway, indicating the importance of fatty acids in cancer cell growth and survival (25, 26, 127). Similar results are observed in our AKR1B10 silencing study. AKR1B10 associates with ACCA and blocks its degradation through the ubiquitin-dependent pathway. AKR1B10 knockdown with specific siRNA promotes ACCA degradation, thus leading to fatty acid/lipid depletions, oxidative stress and cell death (unpublished data). On the contrary, *ACCA* silencing does not affect the growth and survival of non-malignant cells (26).

From the point of view of cancer therapeutics, Beckers and colleagues (27) reported more promising data that exposing LNCaP and PC-3M prostate cancer cells to soraphen A, a macrocyclic polyketide inhibitor of the BC domain, induces growth arrest and cell death. Our recent study further revealed that TOFA (5- (tetradecyloxy)-2-furancarboxylic acid), an allosteric inhibitor of ACCs, induces the apoptosis of lung (NCI-H460) and colon (HCT-8 and HCT-15) cancer cells, indicating that ACCA activity influences cell survival in broad types of cancer (28). Like ACCA silencing, ACC inhibitors have no significant cytotoxicity to premalignant BPH-1 prostate cells. Therefore, it appears that cancer cells have become dependent on ACCA for a sufficient supply of fatty acids to meet their rapid proliferation and survival needs; and the

small molecule ACC inhibitors may be potent cancer therapeutic agents.

6. ACCA AS A POTENTIAL TARGET FOR CANCER THERAPEUTICS

The upregulation of ACCA in cancer cells and its critical role in cell growth and survival lead to a notion that ACCA may be a potential target for cancer intervention. Due to the regulatory role of malonyl-CoA in fatty acid beta-oxidation, ACCs have long been used as a therapeutic target for obesity, diabetes, dyslipidemia; and metabolic syndrome, and a variety of inhibitors have been developed (15, 33, 44). Preclinical and clinical studies have demonstrated that the ACC inhibitors reduce fatty acid synthesis and triglyceride (TG) levels and enhance the fatty acid oxidation, favorably affecting the metabolic conditions/syndromes. To date, several lines of structurally diverse ACC inhibitors have been developed, including substituted bipiperidylcarboxamides (e.g., CP-640186), polyketide natural product fungicides (e.g., soraphen A), aryloxyphenoxypropionate and cyclohexanedione herbicides (e.g., haloxyfop), fatty acyl-CoA mimetics (e.g., TOFA), and bisubstrate and acylsulfonamide analogues (e.g., CABI-CoA) (19). Although isozyme-nonselective, several inhibitors have been extensively investigated in terms of the inhibitory kinetics and crystal structures in combination with biotin carboxylase or carboxyltransferase (128, 129), allowing for development of more effective derivatives.

TOFA (5- (tetradecyloxy)-2-furancarboxylic acid) is a representative of fatty acyl-CoA mimetics, reducing fatty acid synthesis by inhibiting ACCs when converted to a CoA derivative (TOFyl-CoA) (19, 33, 130, 131). It has been demonstrated that TOFA can reduce lipid synthesis and TG secretion in cultured hepatic cells and the plasma TG levels and body weight in animals (130-135). As a hypolipidemic agent, TOFA shows more potent inhibition than natural fatty acid, oleate (136). In cancer cells that are more dependent on cellular lipid synthesis, TOFA effectively induces apoptotic cell death, indicating its potential as an antiTumor agent or as a backbone for the development of more effectual inhibitors (28).

CP-640186, an N-substituted bipiperidylcarboxamides, is a more potent, metabolically stable analog of CP-610431 (137). This class of ACC inhibitors is isozyme-nonselective and thus inhibits fatty acid synthesis and increases fatty acid oxidation in cultured cells and experimental animals.

Soraphen A is a natural polyketide isolated from myxobacterium Sorangium cellulosum (138, 139). This product shows strong inhibitory activity to eukaryotic ACCs and induces cell death (138-140), but not to bacteria ACC (141). Soraphen A inhibits ACC activity by interacting with the BC domain at an allosteric site and thus disrupting the oligomerization (142).

Due to the distinct function of ACCA and ACCB in fatty acid synthesis and oxidation, ACCB-selective inhibitors have been developed by the structure–activity study and used in clinical trials (143). However, isozyme-nonselective ACC inhibitors appear more potent in the point of view of cancer intervention. By targeting both ACCA and ACCB, the isozyme-nonselective inhibitors may effectively prevent potential compensatory reactions (137). For instance, ACCB knockout mice demonstrate increased muscle fatty acid oxidation, reduced hepatic fat mass and whole body fat, but the adipose tissues are compensated by increasing ACCA-mediated fatty acid synthesis (15). Nevertheless, the studies involved in the development and use of ACC inhibitors have accumulated a large amount of valuable preclinical and clinical data that will substantially facilitate the development of ACC inhibitors as antiTumor agents. The pioneer work carried out by Beckers and colleagues (27) as well as our group (28) has provided promising preliminary data for this exploration.

7. CONCLUSION

Increased lipogenesis is an important feature of cancer cells and most likely contributes to the development and progression of cancer. Limiting fatty acid supply deprives cancer cells of critical lipids, thus suppressing cell proliferation and inducing apoptosis. ACCA upregulation has been observed in breast, prostate, ovary, lung, and colon cancer cells and tissues, thus being a potential target for cancer intervention. Recently initiated studies on small chemical ACC inhibitors in cancer cells have set up a new milestone in developing novel antiTumor agents; and the well documented data on ACC inhibitors in metabolic disease clinics will substantially hasten the transition of these small chemicals to cancer clinics, although more preclinical studies on the cancer basis are certainly required. However, it is imperative to note that ACCA mutations occur in breast cancer tissues (24), which may alter the binding and inhibitory activity of the inhibitors. A comprehensive perspective study is warranted to understand the effects of ACCA mutations on the action of inhibitors.

8. ACKNOWLEDGEMENT

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