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Fatty acid metabolism reprogramming in ccRCC: mechanisms and potential targets

Sze Kiat Tan^{1,2,6}, **Helen Y. Hougen**^{3,6}, **Jaime R. Merchan**^{4,5}, **Mark L. Gonzalgo**^{3,5}, **Scott M. Welford**^{1,5,✉}

¹Department of Radiation Oncology, University of Miami Miller School of Medicine, Miami, FL, USA.

²Sheila and David Fuente Graduate Program in Cancer Biology, University of Miami Miller School of Medicine, Miami, FL, USA.

³Department of Urology, University of Miami Miller School of Medicine, Miami, FL, USA.

⁴Department of Medicine, University of Miami Miller School of Medicine, Miami, FL, USA.

⁵Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA.

⁶These authors contributed equally: Sze Kiat Tan, Helen Y. Hougen.

Abstract

Lipid droplet formation is a defining histological feature in clear-cell renal cell carcinoma (ccRCC) but the underlying mechanisms and importance of this biological behaviour have remained enigmatic. De novo fatty acid (FA) synthesis, uptake and suppression of FA oxidation have all been shown to contribute to lipid storage, which is a necessary tumour adaptation rather than a bystander effect. Clinical studies and mechanistic investigations into the roles of different enzymes in FA metabolism pathways have revealed new metabolic vulnerabilities that hold promise for clinical effect. Several metabolic alterations are associated with worse clinical outcomes in patients with ccRCC, as lipogenic genes drive tumorigenesis. Enzymes involved in the intrinsic FA metabolism pathway include FA synthase, acetyl-CoA carboxylase, ATP citrate lyase, stearoyl-CoA desaturase 1, cluster of differentiation 36, carnitine palmitoyltransferase 1A and the perilipin family, and each might be potential therapeutic targets in ccRCC owing to the link between lipid deposition and ccRCC risk. Adipokines and lipid species are potential biomarkers for diagnosis and treatment monitoring in patients with ccRCC. FA metabolism could potentially be targeted for therapeutic intervention in ccRCC as small-molecule inhibitors targeting the pathway have shown promising results in preclinical models.

✉ Scott.welford@med.miami.edu.

Author contributions

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Competing interests

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Renal cell carcinoma (RCC) has been described as a metabolic disease as metabolic alterations underlie otherwise disparate cancer aetiologies¹. Dysregulations in oxygen, nutrients, iron and energy metabolism are common in RCC¹, suggesting that understanding tumour metabolism could be a key to the development of novel therapeutic strategies. For example, ccRCC (which is the most common subtype of RCC, and accounts for ~80% of renal malignancies²) has a distinct histological phenotype characterized by cytoplasmic lipid deposits that underlie the pathological nomenclature (FIG. 1). The lipid droplets contain different lipid species (fatty acids (FAs), triglycerides and cholesterol esters) and a non-lipid component, glycogen³. Efforts to understand the mechanisms that drive lipid storage in ccRCC have repeatedly revealed a tumour dependency that could potentially be exploited.

Genetically, ccRCC commonly displays inactivation of the von Hippel–Lindau (*VHL*) tumour suppressor through a near universal loss of chromosome 3p, together with either mutation or promoter hypermethylation of the remaining *VHL* allele, showing an important initiating mutation at the convergence of both familial and sporadic tumours¹. *VHL* is a component of an E3 ubiquitin ligase complex that regulates the stability of the hypoxia-inducible factors (HIFs)⁴. In normoxia, prolyl hydroxylase (PHD) enzymes hydroxylate two key proline residues in the oxygen-dependent degradation domains of the HIFs subunits HIF1 α and HIF2 α , enabling recognition by the *VHL* complex for subsequent ubiquitin-dependent degradation. Under oxygen deprivation, or after loss of *VHL*, the HIF α proteins are stabilized and translocate to the nucleus, where they partner with a constitutive HIF1 β to form heterodimeric transcription factors⁵ (FIG. 2). HIF proteins regulate numerous pathways, including cell survival, energy production, and angiogenesis, which are often exploited by cancer cells⁶. Metabolic adaptations in ccRCC are a result of HIF-mediated increases in the production of GLUT1 (*SLC2A1*), hexokinase 2 (*HK2*), lactate dehydrogenase A (*LDHA*) and pyruvate dehydrogenase kinase 1 (*PDK1*), which increase glycolysis and suppress pyruvate entry into the tricarboxylic acid (TCA) cycle⁷ (FIG. 2). To maintain crucial TCA cycle intermediates, ccRCC cells use an anaplerotic process via elevated uptake of glutamine that is converted to glutamate by the HIF-dependent expression of glutaminase 1 (*GLS1*)^{8,9}. Glutamate is then converted into α -ketoglutarate, which, among other outcomes, leads to the increased citrate that fuels lipid synthesis. Concurrently, HIF-driven suppression of carnitine palmitoyltransferase 1 A (*CPT1A*) prevents FA oxidation and results in accumulation of cytoplasmic lipids¹⁰ (FIG. 2).

The lipid droplet formation process is crucial in ccRCC tumorigenesis. Storage of excess FAs is necessary for maintaining endoplasmic reticulum (ER) integrity¹¹, and suppressing lipid reactive oxygen species to prevent lipotoxicity¹². Elevated lipid storage levels might also benefit renal tumours, as elevated phosphatidylcholine can maintain cell membrane fluidity, which enhances metastatic capability¹³, as has been found in other malignancies such as lung carcinoma and glioma^{14,15}. By contrast, the coincident accumulation of glycogen granules in ccRCC, which is also HIF dependent, is currently thought to be dispensable for tumorigenesis suggesting that the lipid component is more important than the other non-lipid component¹⁶. Altered FA metabolism has also been reported in multiple non-renal malignancies, including prostate, breast and lung^{17–19}, and results of several studies have enabled identification of potential therapeutic targets^{20,21}, with a select few potential therapeutic targets progressing to clinical trials²². For example, in breast

cancer, a crosstalk between fatty acid synthase (FASN) and the oestrogen receptor exists whereby FASN inhibition suppresses the tumorigenic effects of oestrogen²³. In prostate cancer, FASN expression is regulated by androgens, but becomes androgen independent in castration-resistant disease²⁰. Thus, as therapeutic strategies for ccRCC continue to evolve, investigating untapped tumour-dependent mechanisms will open up new opportunities for clinical success.

In this Perspective, we discuss the enzymes involved in the intrinsic FA metabolism pathway and the current advances in the development of therapeutic strategies against these targets. We also highlight the potential use of circulating adipokines and lipid species as serum biomarkers for ccRCC diagnosis and treatment monitoring.

Targets in the fatty acid pathway in ccRCC

FAs are important constituents of cell membranes, energy sources, and signalling molecules; they can either be imported from exogenous supply or synthesized *de novo* from cytosolic citrate or acetate^{9,24–27}. ccRCC cells increase both the import and the synthesis of FAs to facilitate metabolic plasticity²⁸, unlike kidney proximal tubule cells, which have been shown to rely more heavily on lipid uptake^{29–33}. ccRCC cells make use of the metabolic advantage of not relying on a single pathway to sustain their rapid proliferation rate, similar to the Warburg elevation of glycolysis even in the presence of abundant oxygen³⁴. However, notably, not all lipid species follow the same paradigm of lipid production in cancer: for example, biosynthesis of cholesterol has been shown to be suppressed in ccRCC tumour cells, causing full reliance on cholesterol uptake³⁵. These seemingly contradicting lipid metabolism pathways demonstrate the complexity of how cancer cells use lipids for tumorigenesis and the need to fully understand them in order to improve development of new treatment strategies. Expression of specialized transporters (such as cluster of differentiation 36 (CD36)) are upregulated to maximize FA uptake across the plasma membrane, and *de novo* lipogenesis enzymes (such as FASN) are overexpressed in cancer cells, including ccRCC³⁶. In addition to synthesis and uptake, the FA pathway includes modification, storage and degradation³⁷. Stearoyl-CoA desaturase 1 (SCD1) expression is upregulated in ccRCC, resulting in increased endogenous FA desaturation, which is required for proliferation when exogenous sources of monounsaturated FAs (MUFAs) are limited^{38,39}. Many FA enzyme alterations occur in ccRCC⁴⁰, and some correlate with clinical outcomes (TABLE 1). For example, upregulation of FASN³⁶ and SCD1 (REF.³⁹) are associated with worse clinical outcomes in patients with ccRCC.

Key intrinsic fatty acid metabolism enzymes such as ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), FASN, SCD1, CD36, carnitine palmitoyltransferase 1 A, and perilipin (PLIN) proteins have proposed roles in ccRCC and provide potential clinical targets (FIG. 3). HIF2 α inhibitors, such as belzutifan, have the potential to impair the wide array of HIF-regulated metabolic genes, but an approach that directly targets FA metabolism enzymes might offer improved specificity. Improved understanding of the pathway enzymes can, therefore, be expected to accelerate the development of additional treatment strategies.

ATP citrate lyase

ACLY forms a physiological link between carbohydrate metabolism and FA biogenesis by converting the TCA intermediate citrate into acetyl-CoA^{41,42}. ccRCC cells divert glucose into the lactic acid pool through the HIF-dependent activation of *PDK1* and, therefore, rely on the reductive carboxylation of glutamine-derived α -ketoglutarate for citrate production⁹ (FIG. 3). ACLY then acts on the citrate product to generate acetyl-CoA to provide a substrate for the subsequent commitment step in FA synthesis⁴³. VHL deficiency increases ACLY through a HIF-independent mechanism, because the PPAR γ transcription factor that controls *ACLY* expression is another VHL degradation target⁴⁴ (FIG. 2). The PI3K–AKT pathway, which is hyperactive in ccRCC⁴⁵, also contributes to FA synthesis by phosphorylating and activating ACLY^{41,46}. ACLY controls acetyl-CoA synthesis; thus, dysregulated epigenetics, including histone acetylation patterns that are characteristic of ccRCC could be caused by ACLY activity⁴⁷. For example, in pancreatic ductal adenocarcinoma, ACLY modulates cellular acetyl-CoA abundance, which in turn regulates histone acetylation marks (AcH4 and H3K27Ac) in genetic loci that promote tumour progression⁴⁸.

Little is known about the clinical significance of ACLY alterations in ccRCC. ACLY is expressed at higher levels in ccRCC than surrounding non-malignant kidney tissue, based on the results of a small institutional cohort of 33 paired tumour and normal adjacent tissue samples⁴⁹. Tumour mRNA and protein levels of ACLY were higher than in adjacent non-malignant tissues, and correlated positively with T stage and Fuhrman grade⁴⁹. However, increased ACLY expression was associated with favourable outcomes such as overall survival (OS) in patients with ccRCC in an Oncomine query, (HR 0.43, 95% CI: 0.29–0.62)⁵⁰. These seemingly contradictory findings suggest that the role of ACLY in ccRCC needs additional study. The biproduct of ACLY, oxaloacetic acid, was speculated to indirectly inhibit FA synthesis and might provide an explanation for the contradiction⁵¹. Importantly, when ACLY was inhibited in vitro, ccRCC cells showed decreased proliferation and increased apoptosis, demonstrating its potential to be used as a therapeutic target⁴⁹. Two ACLY inhibitors, ETC-1002 and hydroxycitrate, have been studied in clinical trials to reduce low-density lipoprotein-cholesterol in patients with cardiovascular disease and type 2 diabetes, respectively, and have demonstrated favourable toxic effect profiles^{52,53}. In both in vitro and in vivo studies using human hepatoma cells and miniature pigs with atherosclerosis, respectively, the use of these ACLY inhibitors upregulated the expression and activity of hepatic LDL receptor, which ultimately reduced the plasma LDL-cholesterol level and, therefore, could potentially reduce the lipid level in cancer cells^{54,55}. This observation suggests that existing ACLY inhibitors could be repurposed for ccRCC treatment if results of further preclinical studies provide the justification.

Acetyl-CoA carboxylase

ACC is a rate-limiting enzyme in FA synthesis⁵⁶. ACC carboxylates acetyl-CoA to form malonyl-CoA^{56,57} (FIG. 3). Results of a gene expression analysis study showed that *ACC* mRNA is upregulated in ccRCC compared with non-malignant kidney tissue, and the overexpression of *ACC* was associated with poor OS in patients with ccRCC (HR 1.43, 95% CI 1.03–1.99, $P = 0.033$)⁵⁰. In a large multi-omic study of over 400 primary ccRCC

tumours, increased ACC and decreased AMP-activated kinase (AMPK) were found to be the top protein correlates of worse survival⁵⁸. AMPK, thought to be a master regulator of cellular energy balance⁵⁹, directly inhibits ACC and, therefore, the altered ACC:AMPK balance promotes FA synthesis in ccRCC⁶⁰.

An ACC-targeted inhibitor as well as indirect inhibition via AMPK activation have been investigated in preclinical studies. 5-tetradecyloxy-2-furoic acid (TOFA), an allosteric ACC inhibitor, reduces cell growth in both ccRCC and papillary RCC cell lines by inhibiting the mTOR pathway and causing cell-cycle arrest in the G2/M phase⁶¹. To indirectly target ACC, metformin, an oral diabetes medication that activates AMPK²⁹ and reduces lipid accumulation in a kidney fibrosis model⁶², has been used. Metformin was found to similarly inhibit mTOR, induce cell-cycle arrest, inhibit proliferation and cause apoptosis in multiple ccRCC cell lines in several studies^{63–66}. Lipid accumulation might be ACC dependent, but whether the effects of metformin rest solely on the inhibition of ACC is unclear. Metformin also inhibits mitochondrial complex I⁶⁷, which could increase FA oxidation and explain the observed lipid reduction. The interest in the role of metformin in cancer is high, in part owing to the wealth of retrospective data from patients with diabetes. Studies examining the effect of metformin on ccRCC outcomes have been unfortunately limited by selection bias and difficulty controlling important confounding factors⁶⁸. Results of a meta-analysis of 8 retrospective studies demonstrated that metformin improved OS (HR 0.643, 95% CI 0.520–0.795, $P < 0.001$) and cancer-specific survival (CSS) (HR 0.618, 95% CI 0.446–0.858) in patients with RCC and diabetes, but the conclusions are limited by a high level of heterogeneity amongst the studies⁶⁹. Additionally, benefits were more uniformly observed in patients with localized disease than in those with metastatic disease for unknown reasons. Thus, the role of metformin in ccRCC treatment remains to be studied, as the observations justify a prospective study in which proper biological correlates such as ACC phosphorylation could be performed.

Fatty acid synthase

FASN is the final enzyme in de novo FA synthesis, and its expression is altered in ccRCC in addition to a wide range of malignancies^{70,71}. FASN condenses seven malonyl-CoA and one acetyl-CoA to produce palmitate^{72–74} (FIG. 3). With multifaceted roles in the anabolic FA pathway and oncogenic metabolism (such as suppression of the oestrogen receptor in breast cancer when FASN is inhibited⁷⁵), FASN has justifiably received the most widespread interest in cancer therapeutics. A role for FASN in RCC was first explored in 2008 (REF.⁷⁶): in a cohort of 120 patients with RCC (93% of whom had ccRCC) who underwent nephrectomy, immunohistochemistry (IHC) staining for FASN showed that positive expression correlated positively with tumour stage ($P = 0.0009$), lymph node involvement ($P = 0.0429$) and distant metastasis ($P = 0.0042$)⁷⁶. Increased FASN expression was associated with reduced CSS (HR 3.736, 95% CI 1.087–12.837, $P = 0.036$)⁷⁶. In a cohort of 126 patients from The Cancer Genome Atlas (TCGA) with localized or metastatic ccRCC, *FASN* upregulation was associated with increased cancer-specific mortality ($P < 0.001$)⁷⁷. Results of a study including a cohort from the International Metastatic Renal Cell Carcinoma Database (IMDC) showed that patients with FASN-positive disease on IHC staining had significantly shorter OS than those with FASN-negative disease (14.5 months

versus 27.5 months; HR 1.71, 95% CI 1.17–2.51, $P=0.005$)⁷⁸. Thus, increased FASN expression is prevalent in ccRCC and has considerable prognostic implications.

The oncogenic functions of FASN have been studied in numerous malignancies^{79,80} FASN is involved in producing phospholipids that participate in detergent-resistant membrane microdomains, which have been implicated in promoting signal transduction of the tyrosine kinase receptors EGFR and HER2 (REF.⁸¹). This implication is important as tyrosine kinase inhibitors are a mainstay of RCC treatment. Results of another study suggested that FASN confers a metabolic advantage to otherwise nutritionally deprived colorectal cancer cells⁸². However, overall, the mechanism by which FASN contributes to cancer remains ambiguous. Nonetheless, FASN is a potential therapeutic target and several pharmacological agents against this enzyme are being investigated. The most well-studied small molecule inhibitor is C75. In multiple ccRCC cell lines, C75 reduced cell viability and growth via cell-cycle arrest, reduced cell migration and increased apoptosis⁸³. In human breast cancer xenograft models in mice, C75 decreased tumour volumes compared with control animals after 28 days⁸⁴. Several mechanisms for the effects were proposed, such as reduced mitogenic signalling of membrane receptors⁸³. Another posited mechanism from the breast cancer studies is that FASN inhibition causes malonyl-CoA accumulation, which has been shown to be cytotoxic to cancer cells;^{20,84} this mechanism could also be important in renal cancer. Other molecules, including orlistat, triclosan, G28UCM and GSK837149A, have been tested and found to be effective in inhibiting the proliferation of ovarian and prostate cancer cells^{85,86} and, therefore, might also be useful in ccRCC. Clinically, old-generation FASN inhibitors have not been successful owing primarily to unselective cytotoxicity and unpleasant off-target effects, including weight loss and anorexia, because the inhibitors act centrally in the hypothalamus⁸⁷. However, a new generation of inhibitors with increased specificity holds the potential to realize clinical efficacy; for example, the FASN inhibitor, TVB-2640, has been tested in a phase I trial in patients with advanced solid tumours and displayed a favourable toxic effect profile²².

Stearoyl-CoA desaturase 1

SCD1 is highly expressed in multiple tumour types^{88–91} and appears to participate in the biology of ccRCC as well³⁹. SCD1 produces MUFAs from saturated FAs (SFAs, such as palmitate) to be incorporated into glycerophospholipids and sphingolipids for cell membranes, or serve as signalling molecules⁹² (FIG. 3). SCD1 is expressed in ccRCC tumour specimens across all stages but is not detected in patient-matched benign tissue³⁹. In 359 patients with ccRCC who underwent primary nephrectomy, SCD1 expression by IHC was significantly higher in malignant than in adjacent non-malignant tissue in 61.6% of the samples ($P < 0.001$). Increased SCD1 expression was also an independent prognostic indicator of reduced OS (HR 2.94, 95% CI 1.44–6.03, $P = 0.003$)⁹³.

The complex balance between the levels of SFAs and MUFAs, and the roles of FAs in cell metabolism underlie the importance of SCD1 in kidney cells. Chronic kidney disease secondary to obesity is associated with lipid metabolism dysfunction, in which excess SFAs induce ER stress, inflammation and apoptosis⁹⁴. A particularly susceptible cell is the proximal tubular epithelial cell, the presumed cell of origin for ccRCC⁹⁵, owing to its

high mitochondrial content. SCD1 has been shown to protect proximal tubule cells from lipotoxicity-mediated apoptosis⁹⁶ and, therefore, might have the same role in ccRCC cells. Additionally, unsaturated FAs might have a role in promoting cancer cell stemness, as shown in ovarian cancer cells⁹⁷, which is broadly associated with therapeutic resistance that is often seen in RCC⁹⁸.

Multiple SCD1 inhibitors exist in the preclinical setting in RCC^{91,99}. Inhibiting SCD1 with either a short-hairpin RNA or the small molecule A939572 in ccRCC cell lines decreased ccRCC proliferation and induced apoptosis³⁹. Adding back the MUFA oleic acid, the principal product of SCD1, rescued the proliferation defect, confirming that MUFA levels, or the balance of unsaturated FAs and SFA, affect tumour cell behaviour³⁹. In addition, high levels of unsaturated FAs might alter responses to anti-angiogenic agents by forming lipid mediators such as cyclooxygenase-derived prostaglandins¹⁰⁰ and lipoxygenase-derived 4-hydroxy-docosahexaenoic acid¹⁰¹, which regulate inflammation and angiogenesis¹⁰². A combination of A939572 and the mTOR inhibitor temsirolimus used in ccRCC treatment displayed synergistic effects in reducing ccRCC growth in vitro and in vivo³⁹. Furthermore, SCD1 and HIF2 α synergistically enhance ccRCC growth, suggesting that the combination of SCD1 and HIF2 α inhibitors might enhance effectiveness over HIF2 α inhibition alone¹⁰³. Overall, the mechanistic relationship between FA regulation and synergistic antitumour growth remains to be elucidated, but early studies suggest that combinatorial drug approaches including the targeting of FA metabolism might have value. Owing to the role of SCD1 in sebum production, many SCD1 inhibitors are associated with considerable adverse effects in animal models⁹⁹. However, two SCD1 inhibitors have been tested in vivo with good tolerance: SSI-4 reduced ccRCC cell proliferation in vitro by inducing ER stress and showed minimal toxic effects in vivo¹⁰⁴; T-3764518 inhibited xenograft renal cancer growth in mice without severe adverse effects¹⁰⁵. Currently, SCD1 inhibitors with acceptable toxic effects are in clinical trials for type 2 diabetes and non-alcoholic steatohepatitis¹⁰⁶. Aramchol inhibits SCD1 in hepatic stellate cells and reduces fibrosis in patients with non-alcoholic steatohepatitis¹⁰⁷. No SCD1 inhibitors have been tested for cancer in the clinical setting, but, as interest in fat metabolism pathways continues to increase, more drugs will probably enter clinical trials.

CD36

CD36, which is also known as FA translocase, is a multifunctional transmembrane protein integral to FA uptake^{108,109}. Acting as a translocase, CD36 can transfer extracellular FAs to cytosolic FA-binding proteins for cell metabolism in a variety of tissues^{110,111} (FIG. 3). Increased CD36 expression has been observed in numerous malignancies, including prostate, breast, brain and gastric cancers and ccRCC^{112–115}. Beyond FA metabolism, CD36 has also been implicated in angiogenesis through binding of thrombospondin-1, inflammation through interaction with Toll-like receptors and metastasis through regulation of integrins and the cytoskeleton¹⁰⁸.

The association between CD36 and ccRCC has been investigated. Results of one investigation showed that CD36 was expressed at higher levels in the cell membranes of 74 ccRCC samples than in 80 non-malignant kidney samples¹¹⁶. Results of another study,

involving a cohort of 367 patients with ccRCC undergoing nephrectomy (10% of patients were M+), showed that high CD36 expression was associated with increased TNM stage and visceral adiposity¹¹⁷. On multivariate Cox regression analysis, patients with high CD36 expression had significantly reduced progression-free survival (PFS) (median PFS of 44 months for medium expression versus 29 months for high expression, HR 3.24, 95% CI 2.15–4.89, $P < 0.001$) and OS (median OS of 80 months for medium versus 52 months for high expression, HR 2.49, 95% CI 1.55–4.00, $P < 0.001$) when controlling for stage and body mass index (BMI)¹¹⁷. Thus, CD36 has potentially meaningful involvement in ccRCC.

Preclinical mechanistic studies of CD36 in ccRCC are notably lacking. Insights from other models suggest that CD36 is regulated by the HIF pathway¹¹⁸, which would explain its elevation in ccRCC. In a cervical cancer xenograft model, CD36 was shown to mediate tumour growth enhancement caused by a high oleic acid diet, which could have obvious ramifications for the obesity-dependent increase in ccRCC tumour incidence¹¹⁹. Oleic acid was found to promote tumour cell proliferation by activating Src kinase and the downstream ERK1–ERK2 pathway in a CD36-dependent manner¹¹⁹. In gastric cancer, palmitic acid uptake via CD36 has been found to induce AKT phosphorylation¹²⁰, which is also elevated in ccRCC¹²¹. Collectively, the data suggest that CD36 is highly likely to have a functional role in ccRCC that is yet to be documented.

CD36 inhibitory strategies are currently under development. A number of peptide strategies have been used in preclinical studies, taking advantage of known binding partners such as TSP-1 and apolipoprotein^{122–124}, but have suffered in early-phase trials from toxic effects or lack of efficacy^{122,123}. Inhibiting CD36 using a monoclonal antibody has demonstrated high efficacy in reducing tumour metastasis in oral squamous cell carcinoma models, with no described adverse effects, suggesting possible promising outcomes in other highly metastatic cancers and ccRCC^{125,126}.

Carnitine palmitoyltransferase 1 A

CPT1A is a mitochondrial outer membrane protein that has an essential role in the transport of long-chain FAs across the membrane for β -oxidation in the mitochondrial matrix¹²⁷. CPT1A is the rate-limiting enzyme in FA transport, which involves transfer of a long-chain acyl group from coenzyme A to carnitine, transport into the inner membrane space in exchange for a free carnitine, and finally reversion to long-chain acyl-CoA by CPT2 on the inner matrix¹²⁸ (FIG. 3). Deficiencies in CPT1A result in hypoketotic hypoglycaemia, hepatomegaly and elevated levels of free FAs with fat accumulation in skeletal muscles¹²⁹.

In ccRCC, CPT1A levels are reduced compared with non-malignant kidney tissue, in concordance with reduced FA oxidation in favour of storage^{10,130}. IHC staining of CPT1A in 50 ccRCC samples and 50 non-malignant kidney samples showed a reduction of CPT1A protein expression in cancer tissue¹³⁰. Mechanistically, CPT1A expression was found to correlate positively with VHL status, and elevated HIF transcriptionally represses *CPT1A* mRNA synthesis¹⁰. Functionally, CPT1A repression is important because exogenously added CPT1A reduced lipid deposition and tumour formation in preclinical ccRCC models both in vitro and in vivo¹⁰. Furthermore, survival analysis using TCGA data showed a

correlation between reduced *CPT1A* expression with reduced OS in patients with ccRCC ($P = 2.58 \times 10^{-6}$)¹⁰.

Therapeutically, *CPT1A* is an atypical target in ccRCC. The preclinical and prognostic data suggest that agents that could elevate expression or activity of *CPT1A* would be beneficial in patients with ccRCC, which precludes the use of *CPT1A* inhibitors such as etomoxir¹³¹. However, currently, no direct approaches to upregulating or relieving the repression of *CPT1A* exist. Inducing FA oxidation to treat ccRCC would align with the demonstration that suppression of FA oxidation is a necessary means for cancer cells to escape from the iron accumulation-induced and lipid peroxidation-induced form of cell death known as ferroptosis¹³². Redox balance in cancer cells is an essential facet of all of the hallmarks of cancer¹³³, and cancer cells invest heavily in regulating antioxidant enzymes to survive high reactive oxygen species production¹³⁴. Glutathione peroxidase 4 (GPX4), an antioxidant enzyme that detoxifies lipid reactive oxygen species, has been shown to be necessary for ccRCC cells to evade ferroptosis and importantly highlights the idea that targeting glutathione biology is an alternative strategy to achieve the same outcome as inducing *CPT1A* activity^{135,136}.

Perilipin proteins

The PLIN proteins comprise a family of five proteins (PLIN1–PLIN5) that are associated with lipid droplets and are involved in lipid droplet function and formation in various tissue types^{137,138} (FIG. 3). Post-translational modifications of PLINs are key to their roles in controlling lipid homeostasis, and differential expression of the five members suggest divergence of function: PLIN1 and PLIN4 are exclusively present in professional lipid-storing cells such as adipocytes^{139,140}; PLIN2 is expressed in immature adipocytes¹⁴¹; PLIN3 is ubiquitously expressed in many tissue types and is present in cell cytosol and lipid droplets¹⁴²; and PLIN5 is exclusively expressed in cells with high energy demand, such as cardiomyocytes¹⁴³. PLIN2 and PLIN3 have been studied in the context of ccRCC. Investigation of the lipid phenotype in tumour cell lines first showed elevated expression of PLIN2 in ccRCC, in which expression was found to be specifically dependent on HIF2 α ¹². In 80 matched tumour–non-malignant tissue pairs, PLIN2 and PLIN3 were found to have higher expression in ccRCC tissue than in non-malignant tissue^{144,145}. However, PLIN2 and PLIN3 expression correlate with disease severity and survival differently: PLIN2 expression decreases with increasing T stage and grade¹⁴⁴, but PLIN3 expression increases¹⁴⁵. In TCGA database, when stratifying by PLIN2 expression, high PLIN2 expression correlated with improved survival (HR 0.586, 95% CI 0.429–0.803, $P = 0.001$)¹⁴⁴, whereas high PLIN3 (REFS.^{144,145}) was associated with worse disease-free survival (77.9 months, 95% CI 69.2–86.6 versus 98.4 months, 95% CI 89.4–107.5, $P = 0.0005$)¹⁴⁵. The high-PLIN3 expression group also had worse OS than the group with low-PLIN3 expression (79.5 months, 95% CI 71.5–86.6 versus 102.5 months, 95% CI 92.4–112.6, $P = 0.0006$)¹⁴⁵.

Structural proteins might not seem to be ideal drug targets, but preclinical studies have shown that PLIN2 depletion in ccRCC cells results in reduced lipid droplets and cell death owing to ER stress, supporting the theory that lipid storage is an essential activity of ccRCC¹². PLINs are heavily post-translationally modified and control of their expression is

key to their function¹⁴⁶, thus, targeting upstream regulators might be a possible approach. The natural compound sulforaphane is an isothiocyanate derived from broccoli with noted protective effects against cancer¹⁴⁷. Sulforaphane targets PLIN2 and PLIN5 through a PPAR γ -dependent mechanism to reduce hepatic lipid droplet formation in a model of non-alcoholic fatty liver disease¹⁴⁸. Clearly, inhibitors of master regulators such as PPAR γ would be expected to have multiple downstream effects, but the concept is still valid and currently untested in ccRCC.

In summary, multiple enzymes in the FA metabolism pathway are altered in RCC. Some, such as FASN and SCD1, are better studied as potential targets than others and have inhibitors that are being studied in the clinical setting. Others are being further studied in the preclinical setting. Together, the pathway as a whole offers promise for developing novel cancer therapeutics.

Lipid metabolism-related biomarkers

Lipid metabolism alterations in ccRCC compared with renal epithelia provide the potential for the discovery of biomarkers of the disease, and high-throughput ‘-omic’ technologies, including lipidomic analysis, have been increasingly used to identify biochemical or molecular signatures¹⁴⁹. However, currently, the use of biomarkers as a whole is limited in RCC. In the metastatic setting, the only validated biomarker is the IMDC risk model, which is a composite model of six clinical factors¹⁵⁰. Other biomarkers, including lipid biomarkers, are considered investigational in both localized and metastatic settings. Nonetheless, a prognostic or predictive biomarker could be beneficial in several situations, from active surveillance of small renal masses to consideration of adjuvant therapy after excision of locally advanced tumours.

Adipokines

Adipokines are cytokines released by adipocytes¹⁵¹. Many adipokines have been examined in the context of ccRCC, and three well-studied adipokines have a potential role as serum biomarkers. Adiponectin and chemerin were chosen owing to their established connections with RCC, and leptin owing to its implications in multiple malignancies.

Adiponectin.—Adiponectin is one of the most physiologically active molecules secreted by adipose tissue and stimulates glucose uptake in skeletal muscle, increases FA oxidation in muscle and liver, and has anti-atherosclerotic effects¹⁵². Serum adiponectin levels are low in patients with metabolic syndrome, type 2 diabetes mellitus¹⁵³ and cardiovascular disease¹⁵². Weight loss has been associated with increased adiponectin as well as improved insulin sensitivity^{152,154}. Adiponectin has been studied in detail in the context of cancer owing to the relationship between obesity and several malignancies, such as colorectal and breast cancers^{155–157}. Adiponectin has also been studied in RCC because of its anti-angiogenic properties¹⁵⁸.

Adiponectin levels are reduced in patients with RCC. In one case–control study, patients with RCC (74% ccRCC) had lower serum adiponectin levels than matched healthy individuals after controlling for BMI¹⁵⁹. Similar inverse associations between RCC

incidence and adiponectin levels have been reported in two other studies^{160,161}. One of the studies was a prospective case–control study including 273 patients with incidentally diagnosed RCC and BMI-matched healthy individuals, and the results suggested that high adiponectin levels might be protective against future RCC risk¹⁶⁰. Some evidence also suggests that adiponectin levels correlate inversely with measures of tumour severity, such as tumour size and metastatic disease¹⁶². Results of a meta-analysis of 10 studies showed that adiponectin is lower in patients with RCC than in healthy individuals, but serum adiponectin levels did not correlate with stage, grade or subtype^{160,163}.

In terms of long-term clinical outcomes, the association between adiponectin and survival has been examined. Measurement of adiponectin before nephrectomy in 131 patients with various stages of cancer showed that each 1- $\mu\text{g/ml}$ increase in preoperative adiponectin resulted in an 8% decrease in hazard of death (0.92, 95% CI 0.86–0.98, $P=0.007$) after controlling for tumour characteristics but not body composition variables¹⁶⁴. Notably, in another study involving 129 patients undergoing nephrectomy mostly for localized ccRCC, low serum adiponectin was associated with reduced OS ($P=0.035$) but not CSS ($P=0.3$)¹⁶⁵. This observation is interesting because adiponectin is inversely associated with obesity and insulin resistance; thus, the association with OS but not CSS suggests that adiponectin levels might be predictive of mortality from metabolic disorders rather than RCC¹⁶⁵. Moreover, this inference is consistent with the short follow-up duration (30 months) in a cohort of patients with mostly localized RCC, which has relatively low mortality¹⁶⁵. In the metastatic setting, the adiponectin receptor 1 (AdipoR1) was investigated in a study involving 127 patients with RCC (71% ccRCC) receiving sunitinib. Low receptor expression correlated significantly with disease progression compared with patients with high expression over a 64-month follow-up period (40.0% versus 11.1%, $P=0.02$; median PFS 19.5 months versus 37.8 months, $P=0.001$). On Cox regression analysis, after controlling for cancer-specific features including IMDC score, low adiponectin levels remained a significant predictor of PFS (HR 0.55, 95% CI 0.31–0.98, $P=0.042$)¹⁶⁶. Overall, adiponectin levels are reduced in patients with RCC and might be associated with survival, but no threshold has been suggested, limiting its use as a biomarker.

Leptin.—The connection of leptin with adiposity is well-established. Leptin suppresses appetite and promotes metabolic activity when it binds to receptors in the brain as a ‘satiety’ hormone^{167,168}. Patients with congenital leptin deficiency have symptoms such as severe obesity and insulin resistance¹⁶⁹. Leptin is elevated in the serum of patients with BMI ≥ 25 kg/m^2 compared with those with BMI < 25 kg/m^2 and has a contrasting biological function to adiponectin^{167,170}.

Leptin has tumorigenic effects that have been demonstrated in several malignancies¹⁷¹. In breast cancer, chronic leptin treatment reduces reactive oxygen species levels and apoptosis in MCF-7 cells¹⁷². Leptin also mediates tumour–stromal interactions between breast cancer cells and tumour-associated macrophages via stimulation of IL-8 and IL-18 synthesis in order to promote metastasis¹⁷². However, the role of leptin in ccRCC is not well studied, and most evidence showed no association between leptin and RCC¹⁷³. Serum leptin levels were shown to inversely correlate with RCC risk in one study¹⁷⁴, but in other studies and meta-analyses no association between serum leptin levels and RCC was found^{161,164,173,175}.

Thus, serum leptin does not seem to be a good candidate as a serum biomarker for ccRCC, despite its well-studied role in adiposity.

Chemerin.—Chemerin is a multifunctional adipokine that both promotes adipocyte differentiation and increases fat deposition in mature adipocytes¹⁷⁶. Systemically, chemerin has been linked to obesity and metabolic syndrome¹⁷⁶. Chemerin is also involved in inflammation, promoting chemotaxis of macrophages and dendritic cells¹⁷⁷. Serum chemerin correlates positively with levels of many pro-inflammatory cytokines, such as tumour necrosis factor (TNF)- α , IL-6 and C reactive protein (CRP)¹⁷⁸. Inflammation is associated with many cancers, but the combination of lipid regulation and inflammation makes chemerin an ideal candidate to have a role in ccRCC. Chemerin expression has been shown to be elevated in ccRCC tumour tissue, in which it promotes lipid droplet formation, resulting in increased expression of HIF1 α and HIF2 α mRNA, which are responsive to SFAs such as palmitate^{12,179}. The mechanism yields a positive feedback loop because HIF2 α then suppresses FA oxidation via downregulation of CPT1A and further induces chemerin¹² (FIG. 3). A similar effect was also observed in hepatocellular carcinoma cells, in which *HIF1A* mRNA level was upregulated transiently when treated with palmitate¹⁷⁹. Thus, chemerin depletion results in drastic lipid reprogramming in ccRCC, leading to excess FA catabolism that induces mitochondrial dysfunction and ferroptosis¹⁸⁰.

Increased chemerin expression in ccRCC correlates significantly with poor patient outcomes according to TCGA data when patients are stratified according to upper-third versus lower-third of chemerin mRNA expression ($P = 9.02e-07$); furthermore, plasma chemerin is also elevated in patients with ccRCC compared with healthy individuals, suggesting a potential use of chemerin as a circulating biomarker¹². Chemerin might, therefore, be part of the protumorigenic effects of obesity in renal cancer. Chemerin has attractive therapeutic potential as a circulating target, because a monoclonal antibody or a small molecule approach can affect tumour inhibition without the need to enter into tumour cells. Chemerin antagonism could also affect the immune-suppressive tumour microenvironment, which is thought to decrease the effectiveness of current checkpoint therapies¹⁸¹.

Serum lipid species as biomarkers

The overt lipid metabolic reprogramming in ccRCC raises the prospect of using serum lipids themselves as biomarkers. However, few studies to date have explored this concept, and most of the results are inconsistent. In a discovery-based lipid profiling study including 112 patients with ccRCC of various stages and 52 healthy individuals, a 16-lipid panel from serum enabled patients with ccRCC to be distinguished, and a 26-lipid panel distinguished early-stage (I and II) from late-stage (III and IV) disease with 77–95% accuracy¹⁸². The lipid components included were lyso-glycerophospholipids, phospholipids and SFAs. However, further validation is necessary to determine prognostic potential. Results of another exploratory study of a broad portfolio of serum metabolites (amino acids, bile acids, vitamins, FAs and lipids) in a cohort of 28 patients, the majority of whom had RCC (89%), receiving immune checkpoint inhibitor therapy for metastatic disease showed that 9 of 10 metabolites associated with response to therapy were very-long-chain FAs (VLCFAs)¹⁸³. VLCFAs are carboxylic acids with at least 22 carbons and have been proposed to be

involved in regulated cell death^{184,185}. The observational nature of this study means that potential mechanisms for the association between VLCFA levels and treatment response were not explored, but a connection to peroxisome signalling in immune T cells was suggested. Overall, the paucity of data currently limits the use of serum lipids as biomarkers.

Some evidence exists for an association between tissue FA levels and prognosis. Certain classes of FAs seem to be more concentrated in tumour tissue than in normal tissue¹⁸⁶. In one study, 47 ccRCC samples were compared with paired non-malignant renal cortex and 8 tissue lipid biomarkers with high signal intensity in tumours were identified¹⁸⁵. Among the candidate biomarkers, low maximum intensity ratio values of oleic acid correlated with shorter PFS than high maximum ratio values¹⁸⁵. However, the study was limited by the small cohort.

In summary, tumour or circulating lipid biomarkers have shown some correlation with clinical outcomes in RCC, but currently published studies are too small to draw firm clinical conclusions. Larger, prospective studies will be necessary to validate any useful prognostic or predictive tools in the clinical setting in ccRCC.

The obesity paradox

Obesity is associated with increased cancer incidence^{187–189} and poor outcomes in several malignancies¹⁹⁰, and is one of the few known risk factors for RCC^{187,191–193}. The causal relationship of obesity and cancer is not fully defined, but one theory is that increased body size leads to increased oxidative stress¹⁹⁴ and increased inflammation, which are both associated with carcinogenesis¹⁹⁵. Numerous adipocyte-linked molecules such as adipokines, insulin and insulin-like growth factor, interleukins, and gastric inhibitory polypeptides could also promote tumorigenesis¹⁹⁶. The effect is probably multifactorial, rather than dependent on a single mechanism.

Paradoxically, ccRCC disease incidence is increased in individuals with obesity, but patients with obesity and ccRCC tend to have more favourable outcomes than patients with a BMI within the 'normal' range¹⁹⁷. This 'obesity paradox' has been demonstrated in multiple disease states including localized and metastatic settings^{198–200}. For example, in localized disease, patients with obesity who underwent nephrectomy in a single-institution retrospective study had improved median 5-year recurrence-free survival (90.7% versus 84.9%, $P < 0.001$)¹⁹⁸. Consistent with the paradox, recurrence-free survival was also improved with increasing BMI on multivariate analysis (HR 0.93, 95% CI 0.89–0.97, $P = 0.002$)¹⁹⁸. This phenomenon might be driven by the fact that patients with obesity tend to present with a low-stage and low-grade disease⁷⁷, although results of other studies involving patients with localized disease show a persistent, independent positive effect of BMI on improved OS and CSS after correcting for stage and grade¹⁹⁹. A considerable difference in survival was observed in the metastatic setting as well: for patients receiving first-line targeted therapy in the IMDC, the median OS was 25.6 months for patients with BMI ≥ 25 kg/m², compared with 17.1 months among patients with BMI < 25 kg/m² (adjusted HR 0.84, 95% CI 0.73–0.95)⁷⁸. In the immunotherapy era, the phenomenon has been borne out as well. Patients in the IMDC receiving PD1–PDL1 immune checkpoint inhibitors have

a 1-year OS of 79% in the high-BMI group compared with 66% in the low-BMI group (adjusted HR 0.75, 95% CI 0.57–0.97, $P = 0.03$)²⁰⁰.

FA molecular changes that might underlie a potential mechanism of the obesity paradox have been studied. The first of these is FASN-mediated; FASN is generally reduced in individuals with obesity and might independently mediate survival⁷⁷. Results of a study including 126 patients with ccRCC who underwent nephrectomy in a single institution showed that patients with obesity had a decreased cancer-specific mortality ($P < 0.05$)⁷⁷. Genomic analysis showed that patients with obesity (BMI ≥ 30) had lower tumour FASN expression than those with a BMI within the ‘normal’ range, and was associated with improved CSS in TCGA ($P < 0.001$)⁷⁷. In another study that included 145 patients with localized or metastatic ccRCC from a single institution, improved cancer survival independent of BMI was observed in the low-FASN cohort with a 3-year follow-up duration based on logrank analysis (logrank = 14.9, $P < 0.001$)³⁶. Cox regression analysis controlling for clinical characteristics including tumour grade, stage, size and clinical metastasis showed an HR of 1.88 (95% CI 1.021–3.460, $P = 0.043$)³⁶. In the same study, the LinkedOmics and The Cancer Protein Atlas were analysed and FASN expression was shown to be negatively correlated with OS in both databases. Thus, reduced tumour FASN expression as a BMI-dependent variable could be one mechanistic driver of the improved clinical outcomes shown by patients with obesity.

Tumour and adipose microenvironments have also been investigated in the context of the protective effect of adiposity in patients with RCC. Using the cohort from the COMPARZ trial (patients with metastatic RCC receiving pazopanib or sunitinib), immune cell infiltration in tumour tissues and peritumoural fat was examined using gene expression analyses²⁰¹. No significant difference in the degree of immune cell infiltration was found between patients with obesity and those with a BMI within the ‘normal’ range, but the tumours from patients with obesity expressed lower levels of immune checkpoint molecules and had decreased PDL1 expression. This mechanism might explain the improved survival seen in patients with obesity receiving ICIs²⁰⁰, but the data are immature. Furthermore, tumours from those with obesity had higher angiogenic scores than those with a BMI within the ‘normal’ range in a separate cohort receiving nephrectomy for localized RCC²⁰¹. One hypothesis from the data would be that improved vascularization in tumours leads to improved drug delivery and/or immune access. However, no direct mechanistic studies comparing tumours from individuals with different BMIs have been conducted to establish whether fundamental biological differences exist.

In contrast to the relationship between altered FA metabolism with the obesity paradox, other lipid species have less clear associations with obesity and outcome. Elevated LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) are both associated with a reduced risk of developing ccRCC²⁰², whereas individuals with obesity tend to have high LDL-C but low HDL-C²⁰³. Thus, how cholesterol mediates RCC risk is unclear. Furthermore, increased preoperative serum HDL-C correlated with improved OS in a series of 308 patients with ccRCC eligible for surgery (HR 0.32, 95% CI 0.13–0.78, $P = 0.013$)²⁰⁴. Thus, in summary, the contribution of obesity in ccRCC outcome is still far from clear and warrants further investigation.

Future perspectives

Altered metabolism is well recognized as a hallmark of cancer. FA metabolism is grossly disrupted in ccRCC²⁰⁵, which has a lipid phenotype, affecting tumour growth and therapeutic resistance, and is obviously connected with the histological definition of clear-cell tumours. Understanding the mechanisms of FA metabolism in ccRCC oncogenesis might lead to novel personalized treatment strategies. Historically, therapeutic approaches in ccRCC have focused on tyrosine kinase inhibition using sunitinib, pazopanib or cabozantinib, with moderate but limited success^{206,207}. The FDA approval of a HIF2 α small molecule inhibitor (belzutifan) has great promise for further improving patient outcomes, but HIF2 α inhibitors also cause anaemia and fatigue, which might be a result of the broad roles of HIF targets^{208,209}; thus, developing additional treatment modalities for ccRCC is imperative. Currently, no actively targeted lipid metabolic pathways in ccRCC clinical management exist, but as possibly one of the most appropriate tumours for a metabolic approach, future investigations should be aimed at this tumour-specific characteristic²⁰⁹. Moreover, the different cell types that comprise the tumour microenvironment have been shown to have different metabolic characteristics, adding complexity but also revealing potentially targetable pathways²¹⁰.

Conclusions

Multiple lipid metabolism pathway alterations that drive lipid deposition are associated with ccRCC. Historically, the value of excess lipids in ccRCC has been confined to its use in a histological definition. However, FA metabolic rewiring has now been established as a necessary adaptation of ccRCC tumour cells, which reveals a possible metabolic vulnerability. The fact that lipid storage is a dramatic biological difference between tumour and non-malignant tissue provides an important therapeutic window if appropriate inhibitors with acceptable toxic effect profiles (in the kidney or elsewhere) can be developed. Currently, numerous attractive targets have been discovered, including enzymes, structural proteins and secreted molecules, each with their own advantages and disadvantages. Preclinical studies improve understanding of the mechanisms that define ccRCC, meaning new pharmacological approaches are bound to emerge.

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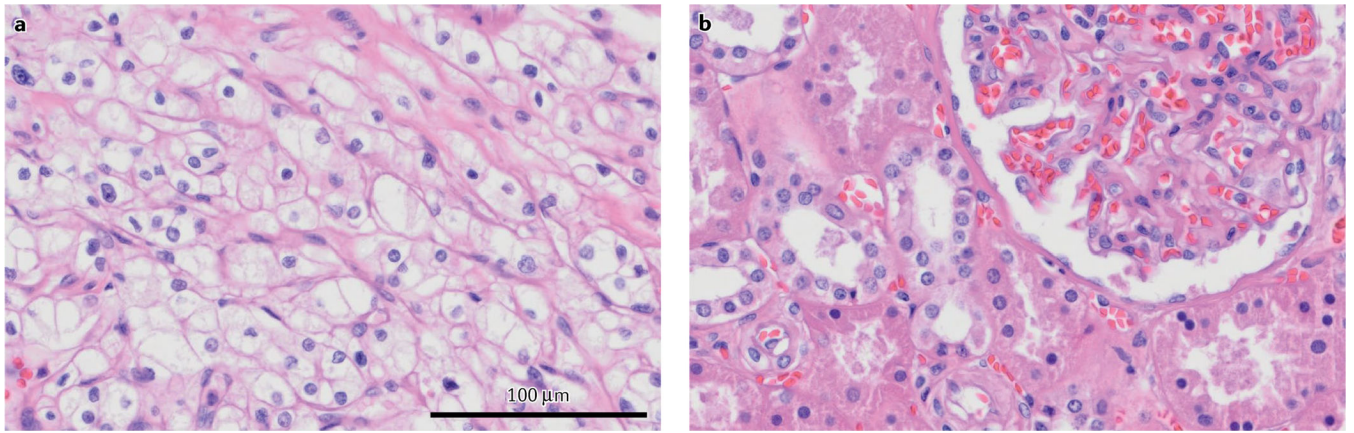


Fig. 1 | H&E staining of ccRCC and normal adjacent kidney tissues.

a | The 'clear' cytoplasm seen in clear-cell renal cell carcinoma (ccRCC) tissue sections compared with **b** | non-malignant adjacent tissue shows the washout of lipid and glycogen content during histological preparation, which also gives the name to this disease.

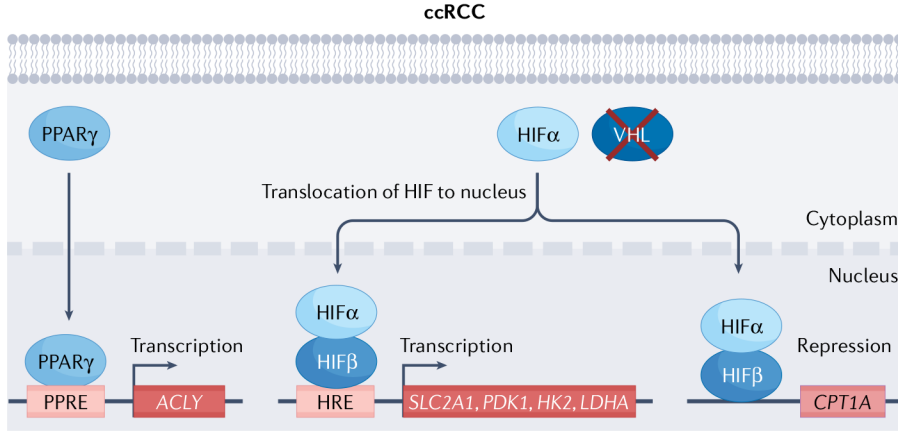


Fig. 2 |. VHL and HIF pathway regulation in ccRCC.

In clear-cell renal cell carcinoma (ccRCC), von Hippel–Lindau (VHL) inactivation leads to hypoxia-inducible factor (HIF)1 α and HIF2 α stabilization irrespective of oxygenation status (although HIF1 α protein lost in roughly 30% of ccRCC, and HIF2 α has been argued to be the driving oncogenic subunit^{211–213}). Stabilized HIF α translocates to the nucleus, dimerizes with HIF β and functions as a transcription factor through binding to conserved hypoxia response elements (HREs) present in hypoxia-responsive genes, such as *SLC2A1*, *PDK1*, *HK2* and *LDHA*, HIF α translocation and dimerization with HIF β also results in repression of *CPT1A* transcription. VHL inactivation also results in stabilization of PPAR γ , which translocates to nucleus to bind to PPRE, activating transcription of lipogenic gene *ACLY*. *CPT1A*, carnitine palmitoyltransferase 1A; *SLC2A1*, glucose transporter 1; *HK2*, hexokinase 2; *LDHA*, lactate dehydrogenase A; *PDK1*, pyruvate dehydrogenase kinase 1; PPAR γ , peroxisome proliferator-activated receptor- γ ; PPRE, PPAR response elements.

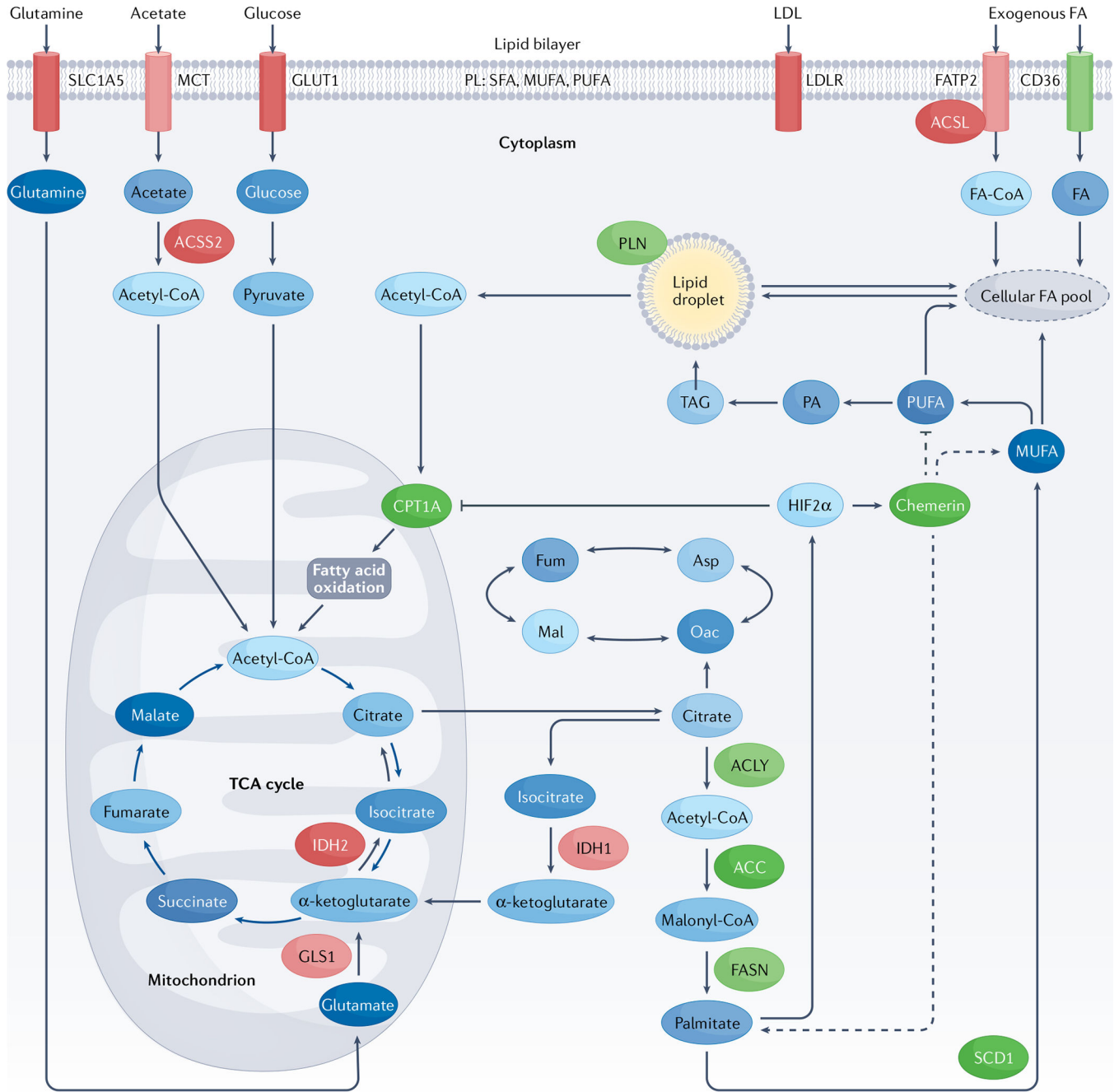


Fig. 3 | Fatty acid metabolism pathways in clear-cell renal cell carcinoma and potential therapeutic targets.

Fatty acids (FAs) are the products of de novo lipogenesis, are carboxylic acid molecules with an unbranched aliphatic chain, and can be either saturated or unsaturated²⁹. In de novo lipogenesis, cells synthesize citrate from glucose, acetate and glutamine. Palmitate (16:0 FA) is produced via a multistep process: through the action of ATP-citrate lyase (ACLY), citrate is cleaved into oxaloacetate and acetyl-coenzyme A (acetyl-CoA). In the cytosol, acetyl-CoA is irreversibly carboxylated to form malonyl-CoA via acetyl-CoA carboxylase (ACC), which is the rate-limiting step. FA synthase (FASN) later elongates the malonyl-CoA into

long-chain FAs. Palmitate can then be further elongated by FA elongases (such as ELOVL6) or desaturated by stearoyl-CoA desaturase (SCD). Exogeneous FAs can be transported into cells by CD36 located on the plasma membrane. Both exogenously and endogenously sourced FAs can be stored as triacylglycerol (TAG) in lipid droplets. FAs can alternatively be transported into mitochondria via carnitine palmitoyltransferase 1 A (CPT1A) for mitochondrial β -oxidation, providing an energy source through the production of ATP. The highly relevant targets that are described in this Review are highlighted in green. ACC, acetyl-CoA carboxylase; ACLY, ATP-citrate lyase; ACSL, long-chain acyl-CoA synthetase; ACSS2, acyl Co-A synthetase-2; Asp, aspartate; FASN, FA synthase; FATP2, fatty acid transport protein 2; Fum, fumarate; GLS, glutaminase; GLUT1, glucose transporter 1; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; Mal, malate; MCT, monocarboxylate transporter; MUFA, monounsaturated FA; Oac, oxaloacetate; PA, phosphatidic acid; PL, phospholipid; PUFA, polyunsaturated FA; SFA, saturated FA; TCA, tricyclic acid cycle.

Fatty acid pathway enzymes implicated in renal cell carcinoma-related alterations and their prognostic values

Table 1 |

Fatty acid pathway enzyme	Mechanism of action	Clinical significance	Small-molecule targeting agents	Refs.
FASN	Condenses seven malonyl-CoA and one acetyl-CoA to produce palmitate	Positive correlation with T stage (pT3-4), grade, lymph node involvement, distant metastasis and microvascular invasion Reduced overall survival Negative correlation with cancer-specific survival	CD97 Orlistat Triclosan G28UCM GSK837149A	35,49,76
ACC	Carboxylates acetyl-CoA to produce malonyl-CoA	Reduced overall survival	Metformin TOFA	49
ACLY	Produces acetyl-CoA from citrate	Positive correlation with T stage and Fuhrman grade Improved overall survival	None	48,49
SCD1	Desaturates palmitate to form monounsaturated fatty acids	Reduced overall survival	A939572	38
CD36	Transport fatty acids across membrane	Positive correlation with TNM stage and visceral adiposity Reduced progression-free survival and overall survival	None	117
CPT1A	Transports long-chain fatty acids across mitochondrial membrane for fatty acid oxidation	Improved overall survival	None	10,49
PLIN3	Lipid droplet protein	Positive correlation with TNM stage and tumour grade Reduced disease-free survival and overall survival	None	145
PLIN2	Lipid droplet protein	Negative correlation with prognosis	None	144

ACC, acetyl-CoA carboxylase; ACLY, ATP citrate lyase; CD36, cluster of differentiation 36; CPT1A, carnitine palmitoyltransferase 1 A; FASN, fatty acid synthase; PLIN, perilipin.