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Lipid metabolism reprogramming in renal cell carcinoma

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Abstract

Metabolic reprogramming is recognized as a hallmark of cancer. Lipids are the essential biomolecules required for membrane biosynthesis, energy storage, and cell signaling. Altered lipid metabolism allows tumor cells to survive in the nutrient-deprived environment. However, lipid metabolism remodeling in renal cell carcinoma (RCC) has not received the same attention as in other cancers. RCC, the most common type of kidney cancer, is associated with almost 15,000 death in the USA annually. Being refractory to conventional chemotherapy agents and limited available targeted therapy options has made the treatment of metastatic RCC very challenging. In this article, we review recent findings that support the importance of synthesis and metabolism of cholesterol, free fatty acids (FFAs), and polyunsaturated fatty acids (PUFAs) in the carcinogenesis and biology of RCC. Delineating the detailed mechanisms underlying lipid reprogramming can help to better understand the pathophysiology of RCC and to design novel therapeutic strategies targeting this malignancy.

Keywords

Metabolic reprogramming; Cholesterol; Free fatty acids; PUFA; Renal cell carcinoma

1 Introduction

Renal cell carcinoma (RCC) is the most common type of kidney cancer. In 2020, the USA had approximately 74,000 new cases and 15,000 deaths from RCC [1]. This cancer originates from renal tubular epithelial cells and the most common subtypes are clear

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cell RCC (ccRCC), papillary RCC, and chromophobe RCC. Multiple risk factors such as smoking, obesity, and chronic kidney disease (CKD) have been associated with this malignancy [2].

Surgery is the usual treatment in the majority of patients with localized RCC. However, in 30% of cases, cancer will recur after successful treatment for localized tumors [3]. Five-year survival for localized RCC exceeds 90%, whereas this number for patients with distant metastases is only 13% [4]. Metastatic RCC (mRCC) is refractory to conventional chemotherapy drugs, and effective therapies are limited [2]. Metastatic RCC requires systemic therapy with immunotherapy and/or molecularly targeted therapy [5].

First-line treatment for ccRCC includes immunotherapy with programmed cell death 1 protein (PD-1) checkpoint inhibitors such as nivolumab and pembrolizumab in combination with molecular targeted therapy. The most commonly used molecularly targeted medications in RCC are tyrosine kinase inhibitors which block vascular endothelial growth factor receptors (VEGFR) like axitinib, cabozantinib, and lenvatinib [6–9]. Combination of nivolumab and ipilimumab as anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies can also be considered in the first-line setting [10]. Agents targeting mammalian (mechanistic) target of rapamycin (mTOR) like everolimus can be used mainly in patients with mRCC who have progressed after one previous VEGF-targeted therapy [11]. While targeted therapy options are very limited in this type of malignancy, improved knowledge of disease biology is critically needed for the identification of novel targets.

The prospective analysis of more than 300,000 participants in the National Institutes of Health and American Association for Retired Persons (NIH-AARP) Diet and Health Study showed that excess body weight is a risk factor for development of RCC in both men and women [12]. Another large cohort study with 348,550 participants from 8 countries of the European Prospective Investigation into Cancer and Nutrition (EPIC) revealed the same association [13]. Weight gain between young adulthood (18–35 years of age) and midlife (35–50 years of age) was strongly related to risk of RCC. Moreover, a positive association between waist-to-hip ratio and RCC was observed in women [12]. Mechanistically, RCC is characterized by a high degree of metabolic reprogramming including changes in lipid metabolism (Table 1) [14]. It has been shown that increased endogenous lipid synthesis or exogenous uptake is necessary for neoplastic cell survival and proliferation [14]. Specifically, dysregulation of lipid metabolism is among the most prominent changes in RCC. Furthermore, imbalance in lipid metabolism is likely associated with RCC aggressiveness.

In this review, we focus on lipid metabolism dysregulation associated with RCC and ccRCC as the most common subtype. We highlight the recent evidence implicating deregulated lipid metabolism in RCC development, including alterations in the metabolism of cholesterol, free fatty acids (FFAs), and polyunsaturated fatty acids (PUFAs), as well as lipid storage in RCC, and we will describe how delineating these pathways can offer novel targets for prevention and treatment.

2 Lipid biosynthesis, metabolism, and homeostasis in cancers

The abnormal growth of tumors usually leads to a limited supply of nutrients. To adapt to these challenging conditions, cancer cells often reprogram the metabolism of glucose, proteins, nucleic acids, and lipids. Lipids including sterols, acylglycerols, phospholipids, and triacylglycerol represent a complex group of hydrophobic biomolecules. These biomolecules serve a plethora of biological functions. They are not only responsible for the structural integrity of biological membranes but also are important for energy metabolism and storage, as well as playing a significant role in signal transduction [15].

2.1 Cholesterol

Cholesterol, a member of the sterol category of lipids, is a crucial component of cell membranes. It plays an important role in controlling membrane fluidity and assembly and function of lipid rafts which contain multiple signaling cascades such as RAS, AKT, or SRC that are involved in cancer development [16].

Besides its direct uptake from the diet, cholesterol is synthesized through the mevalonate pathway. This pathway starts with the condensation of acetyl-Coenzyme A (CoA) with acetoacetyl-CoA to generate 3-hydroxy-3-methylglutaryl (HMG)-CoA (Fig. 1). The conversion of HMG-CoA to mevalonate by HMG-CoA reductase is the rate-limiting step in cholesterol biosynthesis. Mevalonate undergoes subsequent reactions to form the isoprenoid farnesyl-pyrophosphate (FPP). FPP is the precursor for squalene that is further converted to cholesterol. FPP is also used to produce geranylgeranyl-pyrophosphate (GGPP). Both FPP and GGPP are essential for post-translational modifications (PTMs) of various proteins, a process called prenylation [17]. Rho GTPases are well-studied prenylated signaling proteins that are part of Ras superfamily. Once Rho GTPase is prenylated, it is delivered and bound to plasma membrane which protect it from degradation and protein misfolding [18]. Increased activity of these proteins is associated with cancer progression and PTM prenylation has been identified as a contributor to tumorigenesis [19, 20].

HMG-CoA reductase inhibitor medications, known as statins, can inhibit the production of mevalonate that is the precursor of cholesterol [21–23]. Many studies have investigated antitumor activity of statins, specifically, their ability to inhibit the active form of oncoproteins such as Rho and Ras and their downstream pathways controlling proliferation, migration, invasion, and survival of cancer cells including glioma, prostate, breast, and pancreatic cancer cell lines [24–28].

Intracellular cholesterol can also be acquired through receptor-mediated uptake of plasma lipoproteins. Low-density lipoprotein receptor (LDL-R) is the major receptor involved in exogenous cholesterol uptake. However, very-low-density lipoprotein (VLDL) and high-density lipoprotein (HDL) are other sources of extracellular cholesterol [29, 30]. Once lipoprotein binds to its receptor, it forms an endosome within the membrane which translocates into cells. Following internalization and transport into the lysosome, the cholesterol ester is hydrolyzed by lysosomal acid lipase (LAL) to release the free cholesterol (Fig. 1) [31].

Hypercholesterolemia and a high cholesterol diet have been associated with an increased risk of malignancy in both clinical and experimental studies [32, 33]. Targeting cholesterol metabolism has received increasing attention as a new preventive or therapeutic approach for cancers such as colorectal and prostate malignancies [34], but has not been extensively evaluated in RCC.

2.2 Free fatty acids and polyunsaturated fatty acids

Fatty acids (FAs) are the main building blocks of various lipid species such as acylglycerols, phospholipids, and triacylglycerol. Generally, *de novo* FA biosynthesis occurs in the liver, adipose tissue, and lactating breasts. Other tissues acquire FAs from the bloodstream either as free fatty acids (FFAs) or within lipoprotein forms [35]. However, tumors require a constant supply of FAs for cell proliferation and survival which leads to upregulated *de novo* FA synthesis or lipogenesis and uptake in cancer cells [36, 37].

The *de novo* lipogenesis (DNL) pathway starts from citrate that is generated from glucose and glutamine metabolism in the Krebs cycle. Citrate is cleaved by ATP-citrate lyase (ACLY) to generate acetyl-CoA which is an important building block for FA synthesis (Fig. 1). Acetyl-CoA is later converted to Malonyl-CoA by acetyl-CoA carboxylase (ACC). Both of these molecules are substrates for FA synthase (FASN) needed to generate palmitate (C16:0), the most abundant saturated FA in cells [37]. This saturated 16-carbon FA can be then elongated and desaturated to produce other FAs. Stearoyl-CoA desaturase (SCD) adds a double bond to the Δ9 position of FAs. Oleate (C18:1) is the most prevalent monounsaturated fatty acid (MUFA) generated by SCD (Fig. 1) [38]. While unsaturated and mono-saturated FAs are synthesized in cells, two 18-carbon polyunsaturated fatty acids (PUFAs), linoleic acid (LA, omega-6) and α-linolenic acid (ALA, omega-3), are considered essential FAs that must be supplemented via the diet. These essential dietary PUFAs are desaturated by FA desaturase 1 and 2 (FADS1, FADS2) and elongated by ELOVL FA elongase 5(ELOVL5) to form the long-chain PUFAs arachidonic acid (AA, omega-6) and eicosapentaenoic acid (EPA, omega-3) (Fig. 2). Additional elongation and desaturation of EPA finally result in the production of docosahexaenoic acid (DHA, omega3) [39]. PUFAs are important molecules involved in numerous cell functions. These are substantial components of cell membranes, affecting membrane fluidity. They also serve as active molecules in cell signaling, inflammation, and cell death. The metabolism of AA, the most studied omega-6 PUFA, generates eicosanoids such as prostaglandin E_2 (PGE_2) (Fig. 2) which is considered important contributor to cancer progression [40, 41]. On the other hand, eicosanoids produced from omega-3 PUFAs like PGE_3 have been shown to inhibit tumor growth [42–44].

Cancer cells require increased exogenous FA uptake to sustain their lipid demands. This can be achieved by increased expression of CD36 known as fatty acid translocase. CD36 is a multifunctional transmembrane glycoprotein which has been proposed as a prognostic marker in many cancers [45]. FA binding proteins (FABPs) also promote FA uptake. FABPs are intracellular lipid chaperones that facilitate movement of FFAs intracellularly and serve different roles in tumorigenesis (Fig. 1) [46]. For example, increased FABP3 expression has been shown to have an inhibitory effect on cell proliferation and promotes

apoptosis in embryonic cancer cells [47]. On the other hand, elevated FABP5 enhances tumor progression in pancreatic and colon cancers [48, 49]. Moreover, in ovarian cancer, high FABP4 expression was associated with metastasis [50].

FAs are a valuable source of cellular energy. In cytoplasm, FFAs are conjugated to CoA, followed by a modification to acyl-carnitine by carnitine palmitoyltransferase 1 (CPT1) which is rate-limiting to FA entry into mitochondria (Fig. 1). Once FAs are transported into mitochondria, they are oxidized by β-oxidation generating ATP (Fig. 1). One palmitate molecule (C16:0) can yield 130 molecules of ATP. Several studies have shown that β-oxidation is required, especially under metabolic stress, to render tumors more adaptable to nutrient deprivation [37].

2.3 Lipid reservoir

Excess FAs are incorporated into triacylglycerol or triglyceride (TG) for energy storage in form of lipid droplets (LDs) that can be mobilized by fatty acid oxidation to generate ATP (Fig. 1). Therefore, TGs act as a reservoir for excessive FAs in the cell. Diacylglycerol acyltransferases (DGAT1 and DGAT2) involved in TG synthesis have been studied in tumor carcinogenesis, cancer aggressiveness, chemotherapy resistance, and cancer stem cell invasiveness [51]. Adipose triglyceride lipase (ATGL) is a rate-limiting enzyme in the hydrolysis of TG. Several types of malignancies have been associated with decreased levels of ATGL or deregulated expression of its protein partners [52].

Another component of LD is cholesteryl ester (CE). CE is the product of fatty acid esterification to cholesterol by acetyl-CoA acetyltransferase (ACAT) (Fig. 1). Increased CE is correlated with tumor aggressiveness [53, 54]. In fact, CE accumulation is a hallmark of ccRCC [55].

2.4 Lipid metabolism regulation

Sterol regulatory element-binding proteins (SREBPs) are transcription factors that regulate enzymes involved in cholesterol and fatty acid biosynthesis. When there are sufficient intracellular lipid levels, these proteins are inactive and they are retained in the endoplasmic reticulum (ER) bound to SREBP cleavage-activating protein (SCAP). Insufficient lipid levels in ER activate SREBPs. Their activation requires proteolytic cleavage in Golgi, and translocation into the nucleus. Once inside the nucleus, they bind to the promoter regions of SREBP target genes and initiate gene expression. This process is highly regulated by cellular levels of sterols, insulin, growth factors, and mammalian target of rapamycin (mTOR) signaling [56]. SREBP-1 mainly regulates FA and TG synthesis while SREBP-2 selectively induces the expression of enzymes involved in cholesterol biosynthesis including HMG-CoA reductase (Fig. 1) [57].

Liver X receptor (LXR), a nuclear transcription factor receptor, is another regulator of lipogenesis in cancer. LXR regulates multiple genes related to cholesterol homeostasis and fatty acid biosynthesis and works as a cholesterol sensor in the cell. Oxysterols, derivatives of cholesterol, activate the formation of the LXR complex with retinoid X receptor α (RXRα). Upon activation, this complex induces the expression of genes involved in cholesterol efflux from cells such as the ATP-binding cassette transporter ABCA1 (Fig.

1). In addition, LXR can activate the expression of several lipogenic genes such as FASN and SCD [58].

Peroxisome proliferator-activated receptors (PPARs) are also important regulators for lipid metabolism and storage; e.g., PPAR-α plays a key role in lipid β-oxidation in the liver, while PPAR-γ regulates lipid uptake and storage in the adipose tissue. However, their roles in RCCs are relatively unclear.

3 Cholesterol and RCC

ccRCC, the major RCC subtype, is characterized by lipid and glycogen accumulation, implicating altered fatty acid and glucose metabolism in its etiology. ccRCC cells contain high levels of triglyceride and also cholesterol mainly in the form of CE [59–62]. It can be speculated that cholesterol accumulation is one of the reasons why ccRCC is refractory to treatment. An *in vitro* study showed that the addition of LDL cholesterol to ccRCC cells in culture compromised the efficacy of sunitinib [63]. One of the major mechanisms for increased intracellular cholesterol involves cellular uptake in form of lipoprotein or free cholesterol. Cellular cholesterol can be also *de novo* synthesized from acetyl-CoA via the mevalonate pathway (Fig. 1). In this pathway, HMG-CoA reductase is the rate-limiting step responsible for production of mevalonate which ultimately is converted into cholesterol [64]. Histologic examination of RCC primary specimens showed decreased levels of HMG-CoA reductase [59]. The TCGA-KIRC project dataset also revealed that HMG-CoA reductase gene expression is significantly lower in primary ccRCCs compared to normal tissue [65]. Therefore, cholesterol accumulation in ccRCCs is likely the result of increased uptake rather than excessive biosynthesis from acetate.

3.1 Circulating cholesterol

In clinical studies, preoperative lower serum total cholesterol levels are significantly associated with aggressive tumor characteristics, poor prognosis, and worse overall survival outcomes after surgical removal of tumor [66, 67]. A meta-analysis of nine cohort studies consisting of 15,609 patients concluded that preoperative serum total cholesterol levels are an independent prognostic predictor for patients with surgically treated RCC [68]. Blood cholesterol increases during treatment with the mTOR inhibitor temsirolimus are shown to be a potential predictor of drug efficacy and is associated with longer overall survival [69].

3.2 Cholesterol biosynthesis and statins

The mevalonate pathway has a pivotal regulatory role in cell growth and proliferation. As described before, statins inhibit HMG-CoA reductase and prevent the formation of FPP to reduce cholesterol biosynthesis (Fig. 1) [70]. A few studies demonstrated that statin treatment has an inhibitory effect on RCC. Thompson et al. showed that statins have a profound cytotoxic effect on *von Hippel-Lindau* (*VHL*) gene deficient RCC cell lines (Table 2) [71]. The majority of RCC tumors carry a defective copy of the *VHL* gene that is responsible for ubiquitination and degradation of hypoxia-induced factor (HIF) (Fig. 3) [72]. Therefore, the HIF signaling pathway is overactivated in RCC regardless of oxygenation status. Overactivation of this pathway contributes to the sensitivity to statins. It appears

that statins inhibit tumor initiation and growth of xenografts via inhibition of GTPase isoprenylation [71].

mTOR inhibitors have been approved for the treatment of metastatic RCC because the mTOR pathway is highly activated in this type of malignancy, but unfortunately, the efficacy of these drugs is not as expected due to resistance. Inhibiting mTOR induces feedback activation of the phosphatidylinositol 3 kinase (PI3K)/AKT pathway that results in resistance. Expression levels of phospho-S6 and phospho-AKT can be used as predictive biomarkers of responses to mTOR inhibitors [73]. Hagiwara et al. demonstrated that statins synergistically inhibit the growth of RCC cell lines when combined with mTOR inhibitors (Table 2). Statins sensitize cells to mTOR inhibitors by suppressing KRAS and Rac1 prenylation. This results in hypophosphorylation and activation of retinoblastoma protein, resulting in induction of G1 arrest upon combination therapy [74]. Importantly, statins were shown to improve survival outcomes of patients with metastatic RCC who are treated with targeted therapy such as mTOR inhibitors [75]. Moreover, in a population-based cohort study, use of statins showed to reduce the risk of RCC with hazard ratio of 0.64(95% CI, 0.38 to 0.87) [76]. Hence, statin can be considered for further clinical study in patients with risk factors for RCC or in treatment of RCC.

3.3 Cholesterol uptake

Cholesterol uptake is mediated through different receptors including LDL-R, VLDL-R, and scavenger receptor B1 (SR-B1) (Fig. 1) [29, 30]. A genome-wide association study (GWAS) on RCC demonstrated that a single nucleotide polymorphism (SNP) which maps to the SR-B1 gene is associated with a higher risk of RCC [77]. Indeed, cancer tissues containing excessive cholesterol showed an increased level of SR-B1, a receptor for uptake of HDL-cholesterol [78]. In a mouse xenograft model, lowering HDL-cholesterol intake significantly reduced cholesterol levels in the tumor which suggests that cholesterol accumulation is partly provided through HDL uptake [79]. Conversely, LDL-R, the main receptor involved in cholesterol uptake, is low in malignant renal tissues [80]. However, VLDL-R, an alternative receptor for the uptake of lipoproteins, is upregulated in ccRCC tissues [81, 82]. Following internalization, lipoprotein is hydrolyzed by lysosomal acid lipase (LAL) in lysosomes to release free cholesterol. LAL is upregulated in ccRCC cells and it is associated with lower patient survival [83]. When Wang et al. attempted to block LAL and the utilization of cholesterol esters, this resulted in impaired proliferation and survival of ccRCC cells [83]. These studies demonstrate that lipid accumulation in ccRCC is more dependent on increased lipid uptake than on cholesterol biosynthesis.

3.4 Cholesterol storage

To protect cells from the toxic effects of high free cholesterol levels resulting from LAL hydrolysis, ACAT re-esterifies free cholesterol with FAs for storage inside the cell (Fig. 1). High levels of CE in RCC tumors result from increased activity of this enzyme [59]. In breast cancer, cholesterol biosynthesis is reduced when ACAT mRNA levels and cholesterol esters are elevated [84]. It can be speculated that higher uptake of cholesterol regulates the retention of SREBPs in ER and degradation of HMG-CoA reductase [85].

3.5 Cholesterol metabolism regulation

LXR regulates multiple genes involved in cholesterol transport. LXR facilitates regulatory feedback in the presence of high cholesterol. In one study, Wu et al. evaluated the effects of a LXR agonist in ccRCC cells [78]. Targeting LXR downregulates LDL-R and upregulates expression of ABCA1 also known as cholesterol efflux regulatory protein. This regulatory effect results in reduced intracellular cholesterol and apoptosis of neoplastic cells without an effect on normal renal tubular epithelial HK2 cells. Interestingly, this LXR-agonist showed a large difference in the killing of two RCC cell lines including 786-O, representing a primary ccRCC tumor, and ACHN, with characteristics of metastatic papillary RCC. Expression of HMG-CoA reductase is higher in ACHN compared to 786-O cells, suggesting that ACHN is more dependent on the intracellular biosynthesis of cholesterol. Therefore, a higher dose of the LXR agonist was required to inhibit cell growth of ACHN than 786-O cells. This suggests that ccRCC tumor cells might be more dependent on exogenous cholesterol than other RCC tumors and normal cells, such that LXR may offer a new therapeutic target for ccRCC (Table 2) [78].

In summary, ccRCC, especially *VHL*-deficient tumors, are more dependent on exogenous cholesterol compared to other RCC subtypes. Blocking the uptake of cholesterol, by increasing the cholesterol efflux or decreasing influx into tumors, resulting in higher plasma cholesterol may be a useful strategy for treating RCC patients.

4 FFA metabolism and RCC

4.1 FA biosynthesis

FAs are essential for tumor cell growth to maintain membrane sustainability and provide energy sources during rapid proliferation. Hence, FA biosynthesis is upregulated in tumor cells irrespective of the levels of circulating lipids [86]. Lipidomic studies have shown an increase in utilization of FAs in ccRCC [87]. Moreover, aerobic glycolysis and glutamine utilization are well-known metabolic reprogramming pathways in ccRCC [14]. Teng et al. reported that ACLY is highly expressed in RCC tumors compared to adjacent normal tissue. They also used siRNAs to downregulate ACLY *in vitro* and demonstrated that ACLY knockdown can inhibit RCC cell proliferation and induce apoptosis [88]. In addition, increased levels of ACC protein are associated with worse clinical outcomes of RCC patients [89]. These findings suggest that ACLY and ACC expression levels are partially responsible for increased lipogenesis in RCC. While pharmacological inhibition of these two enzymes attenuated cell growth in other cancers such as lung and prostate cancers [90, 91], chemical agents targeting ACLY and ACC have not been studied in RCC.

Similar to several types of cancer such as breast, prostate, and lung cancer, FASN is overexpressed in ccRCC. FASN overexpression commonly occurs in cancers with higher risk of both disease recurrence and death including ccRCC. FASN hyperactivity is associated with aggressiveness and poor prognosis in ccRCC [92]. The product of FASN (palmitate) is desaturated by SCD to generate MUFA (Fig. 1). Studies revealed that SCD is overexpressed in many malignant cells [93]. In patients with ccRCC, SCD expression is higher in malignant renal cells than in adjacent normal tissues, and patients with higher SCD

have worse overall survival [94, 95]. Inhibiting lipogenic enzymes such as FASN and SCD leads to reduced neoplastic cell proliferation and induction of apoptosis [96]. For example, administration of C75, a pharmacological inhibitor of FASN, significantly inhibited cell growth and triggered programmed cell death *in vitro* and in a xenograft model of RCC (Table 2) [97].

4.2 FA metabolism regulation

Similar to cholesterol metabolism, stimulating LXR promotes fatty acid production. Treatment with an inverse agonist of LXR (Table 2) can downregulate LXR-mediated genes responsible for fatty acid synthesis including FASN and SCD. This leads to impaired cell growth by depleting the FFA content of cells, and also induces cell death in cancer cells but not in normal epithelial kidney cells [78].

4.3 FA transport

Newly synthesized FAs require FABPs for transport into cells (Fig. 1). FABP-5 is upregulated in ccRCC and is associated with poor overall survival in patients [98]. Knockdown of FABP-5 significantly decreased cell proliferation although this did not affect cell migration and invasion of ccRCC cell lines [98]. In addition, FABP-5 levels positively correlate with lipoprotein lipase (LPL) that hydrolyzes FAs from lipoprotein, resulting in increased intracellular FAs which promote tumor progression [99].

4.4 FA oxidation

The excess FAs stored in lipid droplets (LDs) can undergo oxidation and provide a valuable source of ATP. CPT1A, the rate-limiting step in FA oxidation, has shown to be upregulated in several cancers such as prostate, lung, gastric, and breast [100]. On the contrary, Du et al. found that CPT1A is downregulated in ccRCCs compared to normal kidney tissue. As this is observed in *VHL* defective ccRCC cells, this suggests that CPT1A is suppressed in a VHL-dependent manner. Indeed, restoring CPT1A levels in ccRCC cell lines reduces the number of lipid droplets and inhibits tumor growth *in vivo* [101].

Increased *de novo* FFA synthesis or FFA uptake promotes RCC tumorigenesis. In ccRCC tumors, fatty acid catabolism (FA oxidation) is reduced. Treatments that influence the FA accumulation in cells by reducing FA biosynthesis or uptake, or by increasing FA oxidation, could be promising combination therapies in RCC patients.

4.5 PUFA and RCC

In modern western diets, the ratio of the consumed dietary essential PUFAs LA (omega-6) to ALA (omega-3) has surged from 5:1 to more than 10:1 [102, 103]. LA is the predominant PUFA in western diets and this imbalance of omega-6 and omega-3 PUFAs can impact human health and disease [104]. This also suggests the importance of studying the role of dietary intervention in cancer risk and therapy. EPA and DHA are the major omega-3 PUFAs and their high dietary intake has been proposed to reduce the risk of cancer [105–107]. Serum profiling of 112 patients with RCC prior to surgical resection demonstrated that patients with metastatic disease had lower DHA levels compared to patients without

metastasis. Furthermore, patients with DHA levels below the median value showed shorter cancer-specific survival compared to patients with higher levels of DHA in the serum [108].

Several studies showed that co-administration of omega-3 PUFA with chemotherapy drugs is an effective adjuvant in cancer therapy [109]. Regorafenib is a multi-kinase inhibitor used in advanced RCC. In addition to blocking vascular endothelial growth factor receptors to prevent angiogenesis, this drug has an inhibitory effect on soluble epoxide hydrolase (sEH). The DHA metabolite, epoxydocosapentaenoic acid (EDP), is one of the substrates for this enzyme and is converted to a stable diol form. EDP has anti-angiogenesis properties. The combination of DHA and regorafenib was shown to have a synergistic effect in tumor inhibition likely because EDP is increased in cells due to blockage of epoxide hydrolase by regorafenib. As the result, the combination of DHA and regorafenib led to a reduction in angiogenesis and tumor invasiveness *in vitro* and in an animal model [110].

FADS1, a key rate-limiting enzyme in PUFA metabolism, is responsible for biosynthesis of EPA and AA from essential fatty acids (Fig. 2) and its activity is highly dependent on the diet [111]. Studies have shown that FADS1 is aberrantly expressed in many cancers, including colon, pancreas, breast, and laryngeal cancers. Furthermore, the knockdown of FADS1 can inhibit cancer growth [112–116]. Moreover, a lipidomic study revealed that FADS1 is overexpressed in ccRCC specimens. Surprisingly, in the same study, the levels of free PUFAs including AA, EPA, and DHA were lower in malignant tissues [82]. Free PUFAs can be incorporated into phospholipids and TGs, and additional analysis of the lipidomic data revealed that levels of PUFA-phosphatidylethanolamine (PE)/ether-PEs and PUFA-phosphatidylcholine (PC)/ether-PCs were higher in ccRCC tumors than in normal renal tissues. Moreover, PUFA-phospholipids were increased in high-grade compared to low-grade tumor samples [117]. Whether increased PUFA-phospholipids have an impact on tumorigenesis needs further investigation. It is important to note that the nutrient source and the omega-6/omega-3 ratio in the diet can have tremendous potential in cancer prevention and therapy response.

5 Hypoxia, lipid metabolism, and RCC

VHL tumor suppressor gene is located on chromosome 3p25–26 [118]. VHL protein is responsible for ubiquitinylating and degradation of HIFs under normoxic condition [119]. The loss of VHL is the most common feature of ccRCC [120] and can occur through genetic mutation, epigenetic mechanisms, and post translational changes [2, 121]. Oxygen deprivation or absence of VHL leads to increased level of HIFs (Fig. 3). HIFs regulate metabolic pathways related to cellular adaptation to hypoxia such as angiogenesis, glycolysis, and the Krebs cycle to maintain oxygen homeostasis [122]. In addition, HIFs are key regulators of lipid metabolism [123–126]. HIF-1α and HIF-2α are detected in various malignancies and are widely associated with poor prognosis [127]. The 2p21 gene locus to which Endothelial PAS Domain Protein 1 (EPAS1) gene maps and encodes HIF-2α is associated with increased RCC susceptibility that is identified in genome-wide association studies (GWAS) of RCC [77].

5.1 Hypoxia and lipid droplets

Increase in levels of HIFs contributes to the accumulation of LDs within ccRCC cells (Fig. 3). Surplus of FFA specially PUFA can react with reactive oxygen species (ROS) and cause lipid peroxidation which is harmful to the cells [128]. Channeling FAs to LDs is a mechanism for the cells to prevent lipid peroxidation [129]. These cytoplasmic vesicles are needed for energy homeostasis and release of lipid species during membrane synthesis and cell proliferation [129]. HIF-1α and HIF-2α knockdown lead to a reduction in lipid droplets in ccRCC cell lines [101, 129]. Perilipin2, LD coat protein, is abundantly expressed in non-adipose tissue. This protein is overexpressed in ccRCC tumor samples and is a marker of cellular lipid accumulation. Qiu et al. demonstrated that upregulation of Perilipin2 is due to HIF-2α activation (Fig. 3). The HIF-2α/Perilipin2 lipid storage axis suggests a model to protect tumor cells against endoplasmic reticulum stress [130]. A transgenic mouse model of ccRCC with expression of constitutively activated HIF-1 α also showed elevated level of perilipin2 that indicates lipid storage in LDs [131].Taken together, LD accumulation supports a potential drug target for cancer.

5.2 Hypoxia and TG

Hypoxia also reduces lipolysis in cancer cells by inhibiting ATGL, an important lipase on LDs controlling TG homeostasis (Fig. 3). Hence, it promotes LD formation, attenuates reactive oxygen species (ROS) production, and sustains cancer cell survival [125]. Blocking TG synthesis by inhibiting DGAT enhances apoptosis and represses the proliferation of ccRCC tumor cells *in vivo*. A low level of oxygen increases the incorporation of saturated fatty acid in TGs to protect the cells from the toxic buildup of free saturated FAs *in vitro.* These data suggest that TG incorporation into LDs plays an important role in reducing the availability of specific FAs for metabolism, and promotes cell viability [132].

5.3 Hypoxia and PUFAs

HIF-2α also plays an important role in regulating cellular PUFA levels. HIF-2α depletion demonstrates a remarkable reduction in free PUFAs and PUFA-TGs compared with TGs containing saturated/mono-unsaturated fatty acyl chains (SFA/MUFA-TAGs) *in vitro*. In addition, HIF-2α depletion results in a lower amount of PE-containing PUFA chains (AA and DHA). While HIF-2α activity strongly affects the level of PUFAs, free SFA/MUFAs are less impacted by HIF-2α activity [117].

5.4 Other effects of hypoxia

In the previous sections, we reviewed how cholesterol uptake is increased in RCC cells due to overexpression of VLDL receptors which result in accumulation of lipid droplets. This exogenous uptake of cholesterol is reduced when HIF-1α is downregulated with siRNA [81]. Moreover, we discussed that lipogenesis genes like FASN and SCD are upregulated in RCC. In other cancers such as breast cancer, FASN is upregulated by hypoxia, followed by activation of SREBP-1, the major transcriptional regulator of the FASN gene [126]. Nonetheless, the association of hypoxia and FASN, and SCD upregulation in RCC, requires further investigation.

6 Targeting lipid metabolism in RCC

Lipid metabolism reprogramming in RCC (Table 1) offers unique vulnerabilities and opportunities for therapeutic targeting. Whereas clinical trials have targeted lipid metabolism in cancers such as breast, colon, and lung [46, 133], research on RCC is limited to preclinical studies. FASN has received widespread attention as a therapeutic target since it is overexpressed in most cancer types [37]. The oral FASN inhibitor, TVB-2640 was tested in a phase I clinical trial in patients with advanced-stage solid tumors. The combination therapy of TVB-2640 with taxane increased the time to progression specifically KRAS mutated in non-small cell lung, breast, and ovarian cancers. FASN inhibition was associated with predictable and manageable safety profile with non-serious, reversible adverse events [134]. This therapeutic is used in combination therapy in two ongoing phase II clinical trials on astrocytoma and HER2-positive breast cancer [135, 136]. Since FA biosynthesis is upregulated in RCC, FASN inhibitor can be considered for clinical trial in this cancer type.

Another well-known example involves HMG-CoA reductase inhibitors. Statins are being repurposed for cancer patient care and are being tested extensively in clinical trials for assorted cancers [133]. Although a cohort study showed that use of statins is associated with a reduced risk of RCC [76], there are no clinical studies demonstrating the effects of statins in treating RCC.

As mentioned in previous section, HIFs play crucial role in pathophysiology of ccRCC and they are directly influencing lipid metabolism. An ongoing phase II clinical trial is evaluating the efficacy of HIF-2α, PT2385, on VHL disease-associated ccRCC tumors [137]. The result of this clinical trial may provide useful information on design of study blocking HIF-2α and the effect of that on lipid metabolism in progression of ccRCC.

In this review, we summarized studies that showed targeting lipid metabolism in RCC can be beneficial in treating this disease (Table 2). Collectively, these offer compelling evidence in support of the need for more clinical studies that target lipid metabolism in this cancer type.

7 Summary and future directions

Studies discussed here highlight altered lipid metabolism as an important metabolic phenotype of RCC. During kidney damage, renal epithelial cells reprogram their metabolic pathways to increase lipid accumulation. Understanding the mechanisms behind this condition can provide us with new insights into the basis for increased cancer risk associated with kidney disease. We provided a graphic summary of lipid reprogramming in RCC (Table 1). There is a close relationship between lipid metabolism and oncogenic signaling to promote cell proliferation and survival. Novel therapeutic approaches to target fatty acid or cholesterol homeostasis of cancer cells, either through blocking biosynthesis or uptake, have shown promising results *in vitro* and *in vivo*. This review was designed to facilitate a greater understanding of lipid biology in cancer to identify potential treatment strategies to overcome the limitations of chemotherapy in metastatic RCC, particularly ccRCC. Although 70% of all RCC malignancies are ccRCC, more research clearly needs to be done in papillary and chromophobe RCC, as well.

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Abbreviations

HMG	3-Hydroxy-3-methylglutaryl
CoA	Acetyl-Co enzyme
ACAT	Acetyl-CoA acetyltransferase
ACC	Acetyl-CoA carboxylase
ATGL	Adipose triglyceride lipase
ALA	α-Linolenic acid
AA	Arachidonic acid
ABCA1	ATP-binding cassette transporter
ACLY	ATP-citrate lyase
CPT1	Carnitine palmitoyltransferase 1
CE	Cholesteryl ester
CKD	Chronic kidney disease
COX	Cyclooxygenase
ccRCC	Clear cell RCC
DNL	*De novo* Lipogenesis
DG	Diacylglycerol
DGAT	Diacylglycerol acyltransferase
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
ELOVL5	ELOVL fatty acid elongase 5
ER	Endoplasmic reticulum
EPAS1	Endothelial PAS domain protein 1
sEH	Epoxide hydrolase
EDP	Epoxydocosapentaenoic acid

FPP	Farnesyl-pyrophosphate
FA	Fatty acid
FABPs	Fatty acid binding proteins
FADS1	Fatty acid desaturase 1
FADS2	Fatty acid desaturase 2
FASN	Fatty acid synthase
FFAs	Free fatty acids
GWAS	Genome-wide association study
GGPP	Geranylgeranyl-pyrophosphate
HDL	High-density lipoprotein
HIF	Hypoxia-induced factors
LA	Linoleic acid
LDs	Lipid droplets
LPL	Lipoprotein lipase
LXR	Liver X receptor
LDL-R	Low-density lipoprotein recepto
LAL	Lysosomal acid lipase
mTOR	Mammalian target of rapamycin
mRCC	Metastatic RCC
MUFA	Monounsaturated fatty acid
PPARs	Peroxisome proliferator-activated receptors
PC	Phosphatidylcholine
PE	Phosphatidylethanolamine
PI3K	Phosphatidylinositol 3 kinase
PUFAs	Polyunsaturated fatty acids
PTM	Post-translational modification
PGE_2	Prostaglandin E_2
ROS	Reactive oxygen species
RCC	Renal cell carcinoma

RXRα	Retinoid X receptor α
SR-B1	Scavenger receptor B1
SNP	Single nucleotide polymorphism
SEH	Soluble epoxide hydrolase
SCAP	SREBP cleavage-activating protein
SCD	Stearoyl-CoA desaturase
SREBPs	Sterol regulatory element binding proteins
TGF-β	Transforming growth factor-β
TG	Triglyceride
VEGF	Vascular endothelial growth factor
VLDL	Very-low-density lipoprotein
VHL	Von Hippel-Lindau

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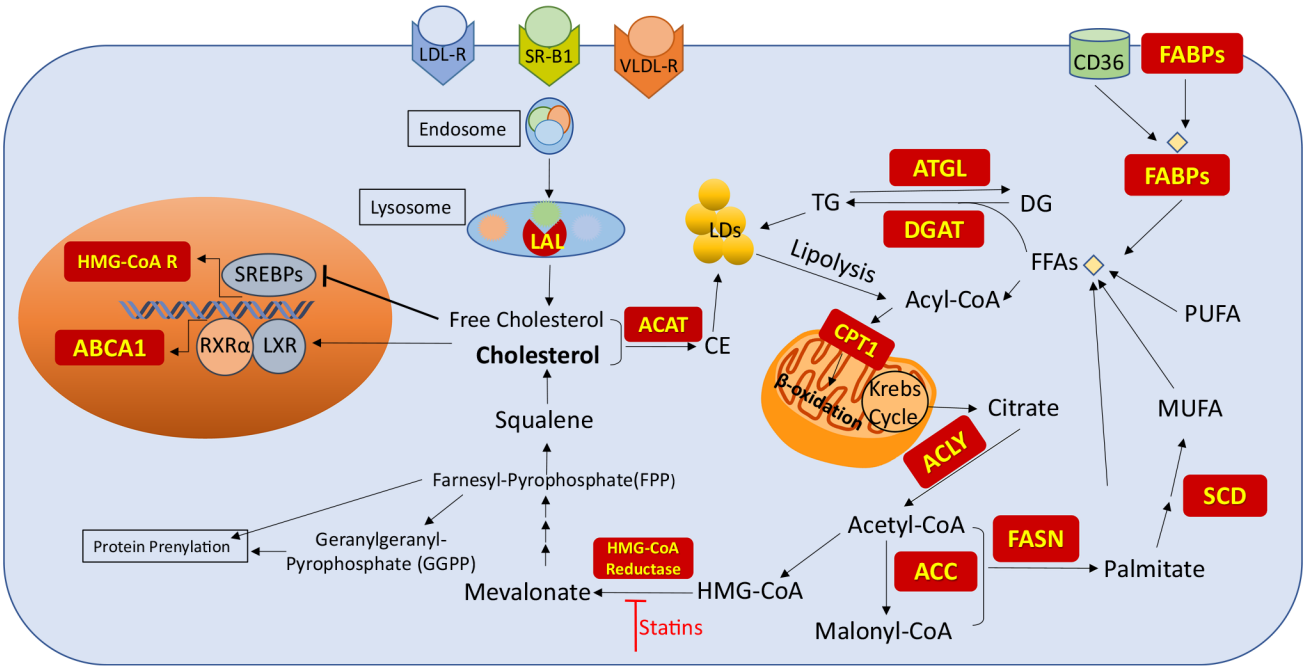


Fig. 1.

Lipid metabolism. Acetyl-CoA is the starting material in cholesterol and FFA biosynthesis. Cholesterol and FFA can also be provided from exogenous resources. The red boxes are the proteins involved in lipid regulation

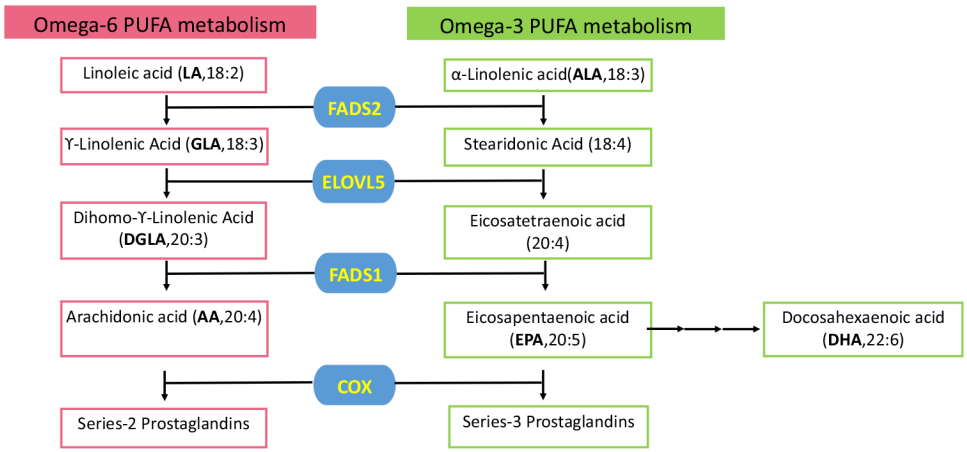


Fig. 2.

PUFA metabolism pathway. Linoleic acid and α-Linolenic acid are the essential PUFA provided from food. Other PUFA can either be obtained from diet or synthesized in the body. Blue boxes represent the enzymes involved in PUFA metabolism

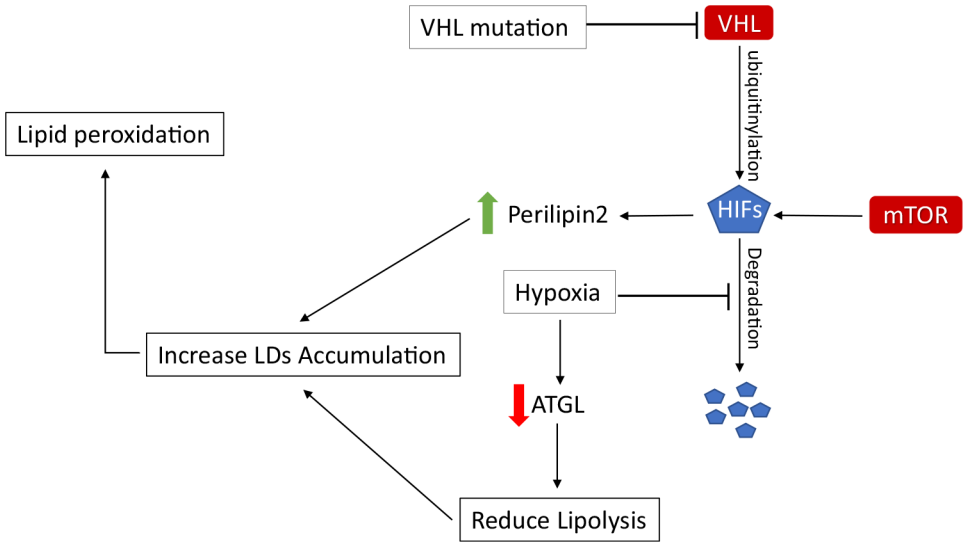


Fig. 3.

HIF pathway in ccRCC. VHL mutation, mTOR activation, and hypoxia cause an increase of HIFs in the cell. This event ultimately leads to LD accumulation

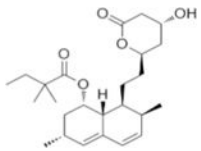
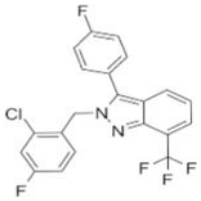
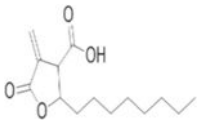
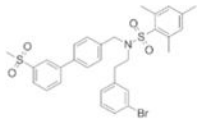
Table 1

Lipid reprogramming in RCC. This table depicts lipid dysregulation in RCC and the proteins that are involved in different pathways

Lipid reprogramming in RCC tumors	Mechanism	References
Decreased cholesterol biosynthesis	↓HMG-CoA Reductase	59,65
Increased cholesterol uptake	↑VLDL-R ↑SR-B1	78,81,82
Increased fatty acid biosynthesis	↑ACC ↑ACLY ↑FASN ↑SCD ↑FADS1	82,88,89,92,94,95
Increased fatty acid uptake	↑FABP-5	98,99
Reduced fatty acid catabolism	↓CPT1A	101
Reduced Lipolysis	↓ATGL	125
LDs Accumulation	HIF-α stabilization	101,129,130

Table 2

Inhibitors targeting lipid metabolism in RCC as cited in the main text.

Compound	Structure	Mechanism of Action	Observed effect		References
			In vitro	*In vivo*	
Statins [a]		HMG-CoA reductase inhibitor	Growth inhibition of 786-O, RCC4 and RCC10 cell lines	Tumor growth inhibition of 786-OT1 xenograft	71,74
LXR-623		LXR agonist	Growth inhibition of 786-O and ACHN cell line		78
SR9243		LXR inverse agonist	Growth inhibition of 786-O and ACHN cell lines	Tumor growth inhibition of 786-O xenograft	78
C75		FASN inhibitor	Growth inhibition of 769P, Caki-1 and KU20–01 cell lines	Tumor volume reduction of Caki-1 xenografts	97

[a] Molecular structure of Simvastatin is shown here as statin representative