Acta Scientiarum
http://www.periodicos.uem.br/ojs/
ISSN on-line: 1807-863X
Doi: 10.4025/actascibiolsci.v42i1.51151

Central cellular signaling pathways involved with the regulation of lipid metabolism in the liver: a review

Rute Lopes[1], Moema Souza Santana[2], Carla Rios da Cruz[2], Rafael Bianchini Fulindi[2], Ana Maria Minarelli Gaspar[1] and Paulo Inácio da Costa[2*]

[1]Instituto de Química, Universidade Estadual Paulista, Araraquara, São Paulo, Brazil. [2]Faculdade de Ciências Farmacêuticas, Universidade Estadual Paulista, Rua Expedicionários do Brasil, 1621, 14801-902, Araraquara, São Paulo, Brazil. *Author for correspondence. E-mail: costapi.unesp@gmail.com

ABSTRACT. The liver is primarily responsible for energy homeostasis and the regulation of lipid, carbohydrate and protein metabolism. Lipid metabolism consists of distributing lipids to peripheral tissues or ensuring their return to the liver to be reprocessed. Additionally, cellular metabolism is regulated by several molecules in different signaling pathways. Lipid homeostasis in the liver is mainly regulated by AKT, AMPK, SREBP, PPAR, and JNK. The PI3K/AKT/mTOR signaling pathway results in the biosynthesis of macromolecules and regulates lipogenesis and the expression of lipogenic genes. AMPK is an energy sensor that regulates metabolism and is activated when stored ATP is depleted, and it is responsible for the suppression of several key lipogenic factors in the liver related to cholesterol and fatty acid synthesis. SREBPs control lipogenic gene expression and cholesterol metabolism and act in the nutritional regulation of fatty acids and triglycerides. The continued activation of SREBPs is associated with cellular stress, inflammation and ultimately steatosis. PPARs are intrinsically important regulators of lipid metabolism. These genes are essential to various metabolic processes, especially lipid and glucose homeostasis, and can play a role in cell differentiation. JNK signaling is related to insulin resistance and its activation results in decreased mitochondrial activity and fat accumulation. Therefore, the study of cell signaling pathways related to lipid metabolism and liver function may help to identify abnormalities and develop strategies to manage and regulate metabolic disorders and resulting complications.

Keywords: lipid synthesis; hepatic molecular routes; fatty acids; steatosis.

Received on November 26, 2019.
Accepted on March 31, 2020.

Introduction

The liver consists largely of hepatocytes, the major scaffold for lipoprotein synthesis, but it also contains many other cell types (Aizawa, Seki, Nagano, & Abe, 2015; La Rosa Rodriguez & Kersten, 2017). The main function of lipid metabolism is to distribute lipids to peripheral tissues or to ensure their return to the liver to be reprocessed (Tang, 2016). The fatty acids in the liver originate from the diet in energy abundant states, from de novo lipogenesis, or are derived from the adipose tissue, and enter the liver as free fatty acids (La Rosa Rodriguez & Kersten, 2017).

The diseases or metabolic disorders related to lipid processing have a large public health impact because of both the increasing population affected worldwide and the potential of these disorders to advance to chronic complications that lead to poor quality of life, in which is associated with increased global expenditures directly connected to those health issues as well as high morbidity and mortality rates (Trogdon et al., 2015). Some of the most important pathological conditions associated with lipid metabolic disorders include type 2 diabetes mellitus, obstructive sleep apnea, coronary artery disease, non-alcoholic steatohepatitis (NASH) and some types of cancer (Tang, 2016). Furthermore, lipid metabolism has been demonstrated to have an important role in cancer cell survival and proliferation under hypoxic conditions (Chen & Li, 2016; Tang, 2016). The central cell signaling pathways related to lipid metabolism include AKT, AMPK, SREBP, PPAR and JNK.

Understanding lipid metabolism and liver function as well as the main signaling pathways connected to these phenomena, is crucial to identify abnormalities and develop strategies to manage and regulate metabolic disorders and metabolic disorder-associated complications.

Methods

This review consists of a systematic review study about the major cell signaling pathways involved with the regulation of lipid metabolism in the liver. The databases Medline (https://www.ncbi.nlm.nih.gov/pubmed), Scopus (https://www.scopus.com) and Web of Science (https://apps.webofknowledge.com) were included in the search. The search was conducted using the descriptors: ("lipid metabolism") AND ("cell signaling" OR "pathway" OR "signaling") AND "steatosis". Studies were restricted to those published from 2014 to 2019, in English language.

Lipids and cell signaling pathways

Cell metabolism is regulated by several molecules in many signaling pathways and consists of biochemical stimuli transmitted to effector molecules, by the inhibition or activation of downstream molecules, to elicit an intended response.

Lipids, particularly fatty acids and cholesterol, constitute an important part of cell membranes and act as signaling factors or metabolic intermediates in many molecular pathways (Shimano & Sato, 2017). A summary of the cellular signaling interactions connected to lipid metabolism in the liver is shown in Table 1.

Table 1. Summary of signaling pathways involved in hepatic lipid processing and resulting metabolic effects.

Signaling pathways	Cellular regulation	Metabolic effects	References
AKT	- Growth regulation, metabolism control - Glucose metabolism: ↑ glucose transporters on cell surface → glycolysis - ↓ FOXO1: ↓ gluconeogenesis - ↑ PI3K/AKT/mTOR: biosynthesis of macromolecules	- Insulin resistance: FOXO1 activation → ↓ AKT → hyperglycemia and phosphorylation of IRS-1, ↓ GLUT-4 translocation, ↓ glucose transported into cells - Caloric abundance: ↑ mTOR → ↑ lipid droplets	Hirata et al., 2018; Józwiak, Forma, Brys, & Krzeslak, 2014; Manning & Toker, 2017; Semenkovich, Goldberg, & Goldberg, 2016; Welty, Alfaddagh, & Elajami, 2016; Zhang et al., 2018
AMPK	- ↑ demand for energy or caloric restriction: ↓ ATP → ↑ AMP/ATP - SIRT1 acetylation: simulates a caloric depleted state → AMPK activation → ↓ de novo lipogenesis and ↑ insulin sensitivity, lipolysis, and mitochondrial fatty acid (FA) oxidation - TSH → AMPK: ↓ HMG-CoAR and ↓ cholesterol synthesis	- ↓ insulin sensitivity: ↓ AMPK, defective autophagy and ROS generation - Starvation: ↑ autophagy, to ↑ nutrients available to cells → ↑ ULK1 and mTORC1 - AMPK *improves* NASH induced by high-fat-diet: suppression of several key lipogenic factors, such as SREBP-1 (↓ triglyceride synthesis), HMG-CoAR, cholesterol synthesis; and ↑ ACC: ↓ malonyl-CoA, ↓ FFA and VLDL synthesis	Li, Lian, Liu, Hu, & Wang, 2015; Musso, Cassader, & Gambino, 2016; Navarro-Yepes et al., 2014; Sinha, Singh, & Yen, 2018; Su, Cao, He, Guan, & Ruan, 2017; Yang, Vijayakumar, & Kahn, 2018
SREBP	- SREBP-1c phosphorylates genes involved in FA synthesis - Insulin and AKT/mTORC1: activation and nuclear accumulation of SREBP1c → ↑ de novo lipid synthesis and protein synthesis - mTORC1 → LPIN1/SREBP: synthesis of phospholipids (phosphatidylcholine, triglycerides). - AKT: ↓ GSK3β, ↑ SREBP → lipid biosynthesis enzymes	- mTORC1 → SREBP: ↑ cholesterol synthesis and accumulation - Caloric abundance: activated UPR and SREBP → ER stress, inflammation response and steatosis → ↑ lipotoxicity: obesity, diabetes mellitus, atherosclerosis, NAFLD, NASH, and other metabolic disorders	Manning & Toker, 2017; McRae et al., 2016; Musso et al., 2016; Röhrig & Schulze, 2016; Shimano & Sato, 2017
PPAR	- PPAR-α: fatty acid receptor, activated by high levels of triglycerides in the liver → ↑ FA β-oxidation, ↓ lipid accumulation - ↑ lipolysis: ↓ triglycerides, VLDL production and ↑ ApoA-I and ApoA-II (HDL) - Glucagon: ↑ PPAR-α. AMPK (fasting): ↑ PPAR-α → ↑ FA oxidation - Insulin, mTORC1/AKT and S6K2: ↓ PPAR-α → ↑ ketogenesis - PPAR-γ: insulin sensitivity → ↑ adipocytokines, adiponectin, and leptin - PPAR-γ: lipid metabolism, lipogenesis, fat storage and other related effects	- Caloric abundance: PPAR-α activation reverses suppression of autophagy, improving NAFLD - Exercise: ↑ PPAR-δ → lipolytic activity. - PPAR-δ: ↓ LDL and triglyceride, ↑ lipid catabolism and ↓ weight gain - PPAR-γ: adipogenic function → weight gain. Caloric restriction does not induce changes in the activity of PPAR-γ or PPAR-δ	Jahansouz et al., 2018; Janani & Kumari, 2015; Lodhi & Semenkovich, 2014; Pawlak, Lefebvre, & Staels, 2015; Régnier et al., 2018; Welty et al., 2016; Zhang et al., 2018

Signaling pathways	Cellular regulation	Metabolic effects	References
JNK	- JNK: ↓ AKT → SRC altered by saturated FA → insulin resistance - TNF-α: activates JNK → ↓ IKK-β → ↑ serine phosphorylation of IRS-1 → insulin resistance and metabolic syndrome - ↑ Bcl-2/Beclin-1 → ↓ AMPK → ↓ autophagy/JNK/IKK-β	- ↓ JNK: ↓ autophagy → lipid accumulation → NAFLD - JNK: modulate NCOR-1 → ↓ PPAR-α → ↓ mitochondrial activity and ↑ fat accumulation: NASH	Baiceanu, Mesdom, Lagouge, & Foufelle, 2016; Navarro-Yepes et al., 2014; Welty et al., 2016; Yang et al., 2018; Zhang et al., 2018

Key: ↑ increased/stimulation; ↓ decreased/inhibition; → result in.

AKT/PKB

The serine and threonine kinase (AKT), also known as protein kinase B (PKB), is a key regulator of many intracellular signal transduction processes that mediate cell survival (Hirata et al., 2018). There are three AKT isoforms: AKT1, AKT2, and AKT3 (Manning & Toker, 2017). AKT1 is linked to growth regulation, and it is the most prevalent isoform. AKT2 is related to the control of metabolism, and AKT3 is mostly expressed in the brain where it also regulates growth (Semenkovich et al., 2016).

Phosphoinositide 3-kinase (PI3K) is a lipid kinase related to insulin response and cellular metabolism that is activated by extracellular signals. The PI3K/AKT/mTOR signaling pathway is involved in cellular growth and glucose metabolism regulation. AKT influences the activity of enzymes and the transcription factors involved in various pathways (Józwiak et al., 2014; Manning & Toker, 2017).

In glucose metabolism, the phosphorylation of PI3K/AKT increases the expression of glucose transporters on the cell surface, which activates hexokinase, the enzyme responsible for glucose phosphorylation and phosphofructokinase-1 activation, ultimately leading to glycolysis (Józwiak et al., 2014). Additionally, AKT activation inhibits forkhead box protein O1 (FOXO1), resulting in the inhibition of gluconeogenesis and the reduction of plasma glucose levels. In insulin resistance, hyperglycemia is caused by the inhibition of AKT through FOXO1 activation. Additionally, the phosphorylation of insulin receptor substrate-1 (IRS-1) reduces insulin signaling and promotes insulin resistance in the liver, muscles, and other tissues by diminishing the activation of PI3K/AKT2, attenuating the insulin-responsive glucose transporter 4 (GLUT-4) translocation to the plasma membrane, and ultimately inhibiting the transport of glucose into cells (Welty et al., 2016).

The overconsumption of nutrients and increased intracellular concentration of lipid droplets are linked to the upregulation of mTOR, a lipophagy inhibitor and catalytic subunit of the mTORC1 and mTORC2 complexes, in the liver. The activation of the PI3K/AKT/mTOR pathway results in the biosynthesis of macromolecules. In contrast, lipophagy is inhibited either by the mTOR complex or by the insulin-induced inhibition of FOXO1 and transcription factor EB (TFEB), which control the transcription of autophagy genes. Lipid usage via lipophagy involves the regulation of other autophagy genes, such as cAMP-response element binding protein (CREB), nuclear farnesoid X receptor (FXR) and peroxisome proliferator-activated receptor-α (PPAR-α). PI3K/AKT regulates lipogenesis and the expression of lipogenic genes in various cell types (Józwiak et al., 2014; Zhang et al., 2018). Cholesterol-lowering agents are linked to decreased PI3K/AKT/mTOR activity and increased autophagy in hepatocytes (Wang, Ding, & Li, 2018).

AMPK

5'-adenosine monophosphate-activated protein kinase (AMPK) is a major energy sensor. It regulates metabolism and is especially associated with glycolysis, which is activated when there is depletion of stored ATP and therefore an increase in the AMP/ATP ratio due to higher demand for energy or caloric restriction (Musso et al., 2016; Navarro-Yepes et al., 2014). AMPK regulates autophagy, which is a way to increase the nutrients available to cells under starvation conditions, by the regulation of Unc-51-like autophagy activating kinase 1 (ULK1) and mTORC1 complexes. AMPK can also be activated via mitochondrial reactive oxygen species (ROS) formation as a result of hypoxia (Navarro-Yepes et al., 2014). Similarly, the inactivation of AMPK induced by reduced insulin sensitivity not only results in defective autophagy but also leads to ROS generation (Yang et al., 2018).

AKT signaling and the AMPK pathway have several shared regulatory steps. AKT is associated with glucose uptake and glycolysis resulting in ATP synthesis, which in turn causes AMPK to remain inactive. AKT can also directly block AMPK activation through the phosphorylation of a C-terminal residue on AMPK, which blocks AMPK phosphorylation by liver kinase B1 (LKB1). These two signaling pathways sometimes

have equivalent roles and other times have opposing roles; for example, both pathways can increase glucose metabolism in response to different stimuli and AKT stimulates anabolic activities for ATP consumption while AMPK halts anabolism to produce ATP. AKT and AMPK also have opposing roles in protein synthesis, lipogenesis, glycogenesis, mTORC1 signaling, and autophagy (Manning & Toker, 2017).

AKT and AMPK pathways affect autophagy in an opposed manner as well. The inhibition of the PI3K/AKT/mTORC1 complex pathway, as a result of growth factor stimulation, leads to the phosphorylation of autophagy-related protein 13 (ATG13), which prevents ATG13 from entering the ULK1 complex and consequently blocks the recruitment of ATG13 to the pre-autophagosomal complex, subsequently inhibiting autophagy. Antagonistically, under conditions of low energy, such as glucose or amino acid starvation, the AMP/ATP ratio increases, leading to AMPK activation, mTOR inhibition, and autophagy activation (Musso et al., 2016; Navarro-Yepes et al., 2014; Park et al., 2016; Sinha et al., 2018).

Silent information regulator T1 (SIRT1) is a protein involved in the activity of proteins and enzymes that are important regulators of glucose and lipid metabolism, as well as energy levels. SIRT1 acetylation simulates a calorie depletion state, resulting in AMPK activation. This effect leads to reduced de novo lipogenesis and increased insulin sensitivity, lipolysis, and mitochondrial fatty acid oxidation (Li, Lian, Liu, Hu, & Wang, 2015; Musso et al., 2016).

Hepatic lipid metabolism is also affected by thyroid hormones when the cAMP-protein kinase A (PKA) and Ca^{2+}/AMPK pathways are activated. Thyroid stimulating hormone (TSH) can increase the phosphorylation of the 3-hydroxy-3-methylglutaryl-CoA reductase enzyme (HMG-CoAR), mediated by AMPK, to inhibit HMG-CoAR activity, which in turn results in reduced cholesterol synthesis (Sinha et al., 2018).

Regarding lipid metabolism, phosphorylated AMPK can also improve high-fat-diet-induced NASH through the suppression of several key lipogenic factors in the liver related to cholesterol and fatty acid synthesis, such as sterol regulatory element-binding protein (SREBP-1), which results in reduced triglyceride synthesis, HMG-CoAR levels, cholesterol synthesis, and ACC enzyme activation, which in turn decreases malonyl-CoA levels and reduces free fatty acids and VLDL synthesis (Musso et al., 2016; Su et al., 2017).

SREBP

SREBPs are nuclear transcription factors that control the expression of enzymes involved in fatty acid biosynthesis. SREBPs are synthesized as precursors bound to the endoplasmic reticulum (ER) membrane and are complexed with SREBP cleavage-activating protein (SCAP), which promotes the translocation of SREBPs to the Golgi, where they are cleaved to then move into the nucleus. SREBPs present three active isoforms after cleavage: SREBP-1a, SREBP-1c, and SREBP-2. SREBP-2 is the main regulator of intracellular cholesterol homeostasis, while SREBP-1c phosphorylates genes involved in fatty acid synthesis (McRae et al., 2016; Musso et al., 2016).

SREBP1c is expressed in most tissues, controlling lipogenic gene expression, and acting in the nutritional regulation of fatty acids and triglycerides in organs such as the liver, while SREBP-1a is mostly expressed in the heart, intestinal epithelium, macrophages and bone marrow dendritic cells, where it activates global lipid synthesis in rapidly growing cells. SREBP-2 regulates the transcription of genes related to cholesterol metabolism in every tissue (Shimano & Sato, 2017). An abundance of cholesterol in the ER membrane causes SCAP to bind to the products of insulin-induced genes (INSIGs), causing the SREBP-SCAP complex to be confined to the ER. The membrane-bound transcription factor site-1 protease (MBTPS1) and MBTPS2 are transferred from the Golgi to the ER membrane and activate SREBP-1, as a consequence of reduced phosphatidylcholine levels (Röhrig & Schulze, 2016).

The cleavage of SREBPs has been shown to be stimulated by the PI3K/AKT/mTOR pathway (Boyd & Ye, 2018). The activation and nuclear accumulation of SREBP-1c by the insulin and AKT/mTORC1 signaling pathways in the liver enhances de novo lipid synthesis and is also related to protein synthesis throughout cell growth processes (Manning & Toker, 2017; Röhrig & Schulze, 2016). mTORC1 regulates anabolism by inducing lipid, nucleotide and protein synthesis, therefore hindering catabolic processes such as autophagy. mTORC1 activation also increases cholesterol synthesis and uptake through the regulation of SREBP-2, causing cholesterol accumulation (Musso et al., 2016).

After the activation of the mTORC1 pathway, SREBP is regulated by phosphatidate phosphatase lipin 1 (LPIN1), an enzyme that converts phosphatidic acid into diacylglycerol and is involved in the synthesis of phospholipids, such as phosphatidylcholine, or triglycerides. The AKT phosphorylation pathway inhibits the

glycogen synthase kinase 3β (GSK3β), further inducing SREBP processing and improving its stability to promote the expression of lipid biosynthesis enzymes (Röhrig & Schulze, 2016).

Cholesterol and fatty acid homeostasis vary in different nutritional states; SREBP-1 and SREBP-2 are activated under conditions of energy abundance, whereas in energy depleted states, they are inhibited. ER stress may be initiated by SREBP-1 activation as well as protein synthesis. To reestablish homeostasis, the unfolded protein response (UPR) is activated; however, in addition to the existing ER stress, SREBP-1c continues to be activated, establishing the conditions for cellular stress, inflammation response and ultimately steatosis. The resulting lipotoxicity is a feature that characterizes obesity, diabetes mellitus, atherosclerosis, non-alcoholic fatty liver disease (NAFLD), NASH, and other metabolic disorders (Shimano & Sato, 2017). In NAFLD, SREBP-2 might be atypically activated, stimulating excessive cholesterol accumulation (Zhang et al., 2018).

Hepatosteatosis may also be caused by the stimulation of TSH receptors expressed in hepatocytes via SREBP-1c. Thyroid hormone induces the expression of HMG-CoAR and farnesyl pyrophosphate synthetase (FDPS) to stimulate hepatic cholesterol synthesis, upregulates LDL receptor levels to increase cholesterol efflux from peripheral tissues, and intensifies HDL metabolism by stimulating cholesteryl ester transfer protein (CETP) activity (Sinha et al., 2018). Figure 1 schematizes the studied pathways association with hepatosteatosis.

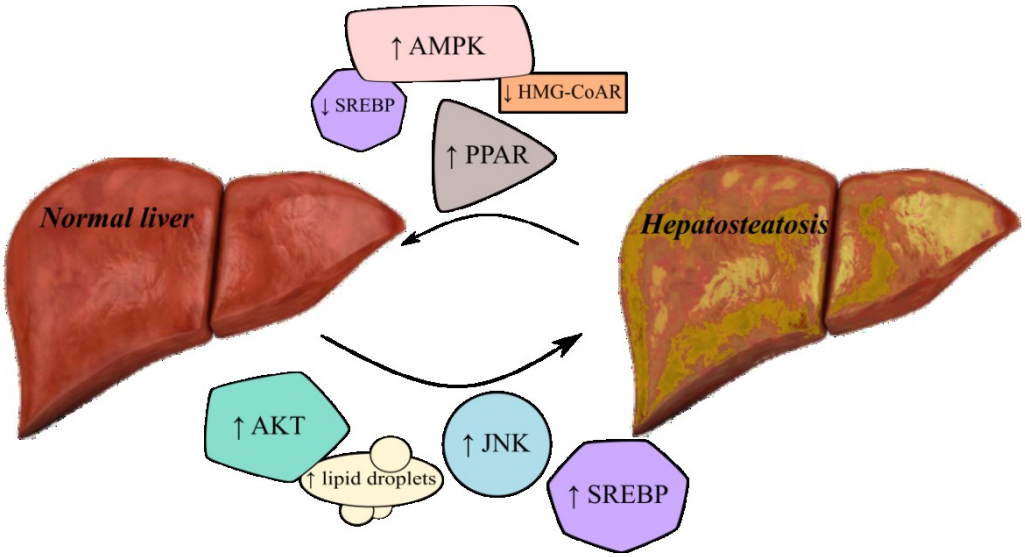

Figure 1. The role of cell signaling molecules regarding steatosis.

PPAR

The transcription of genes responsible for metabolic regulation is controlled by various transcription factors that are susceptible to altered nutrient conditions, including peroxisome proliferator-activated receptors (PPARs), which can be classified as PPAR-α, PPAR-δ, and PPAR-γ (Kersten & Stienstra, 2017; McMullen et al., 2014; Welty et al., 2016).

PPARs are intrinsically important regulators of lipid metabolism. They are transcription factors that shift to the nucleus following activation by ligands, forming heterodimers with binding partners such as retinoid X receptors (RXR), and then binding to specific DNA sequences known as PPAR response elements (PPREs) in the promoters of target genes, where they substitute corepressors with coactivators to finally activate the expression of the target gene. These genes are essential to various metabolic processes, especially lipid and glucose homeostasis, and can play a role in cell differentiation (Janani & Kumari, 2015; Lodhi & Semenkovich, 2014; Régnier et al., 2018).

PPAR-α

PPAR-α is mainly expressed in the liver where it regulates lipid metabolism, especially during fasting. It is also expressed in the large and small intestines, heart, kidneys, spleen and in white and brown adipose tissues, where it regulates fatty acid oxidation, ketogenesis, adipogenesis, energy balance, and triglyceride metabolism and storage (Feng et al., 2016; Jahansouz et al., 2018; McMullen et al., 2014).

PPAR-α is a fatty acid receptor and a major regulator of hepatocyte and fatty acid homeostasis. It acts as a nutritional sensor, activated by high levels of circulating triglycerides in the liver, which in turn activates the expression of genes involved in fatty acid β-oxidation and inhibits lipid accumulation. PPAR-α is also a transcriptional regulator of genes involved in fatty acid transport and in peroxisomal and mitochondrial β–oxidation. PPAR-α phosphorylation reduces triglyceride levels by increasing lipolysis, inducing LPL to catalyze the hydrolysis of triglycerides into free fatty acids and monoacylglycerol; PPAR-α inhibits VLDL production and stimulates the production of ApoA-I and ApoA-II, which are associated with HDL (Musso et al., 2016; Pawlak et al., 2015; Su et al., 2017).

During fasting, fatty acid oxidation in the hepatic and peripheral tissues increases, producing acetyl-CoA, which is converted into ketone bodies to provide energy for peripheral tissues. Then, PPAR-α upregulates mitochondrial HMG-CoA synthetase, which in turn catalyzes the reaction of acetyl-CoA and acetoacetyl-CoA to produce HMG-CoA and CoA (Pawlak et al., 2015). Additionally, glucagon stimulates PPAR-α activity. Insulin, along with the mTORC1/AKT/PKB pathway and its downstream effector S6K2, inhibits PPAR-α through the recruitment of nuclear receptor corepressor 1 (NCOR1), hence increasing ketogenesis. Hepatic PPAR-α activity can also be stimulated by AMPK during fasting. Fatty acid oxidation is increased by adiponectin through AMPK-dependent PPAR-α activation (Pawlak et al., 2015; Régnier et al., 2018).

PPAR-α agonists increase human SREBP-1c transcriptional activity through interacting with a direct repeat-1 element in the SREBP-1c promoter, and it also acts on SREBP-1c transcription through cross-regulation with the LXR signaling pathway (Pawlak et al., 2015). Finally, SIRT1 connects cell metabolism to PPAR-α activity (Régnier et al., 2018).

PPAR-α agonists and omega-3 reduce plasma triglyceride levels and LDL particles, and synthetic PPAR-α agonists may be very useful in the treatment of NAFLD and cardiovascular diseases (Pawlak et al., 2015; Welty et al., 2016). In previous studies, dietary abundance and PPAR-α activation reversed the normal suppression of autophagy. This resulted in increased autophagic lipid degradation and represents a potential pharmacological target to inhibit several chronic liver diseases related to lipid accumulation (Zhang et al., 2018).

PPAR-δ

PPAR-δ (or PPAR-β) is expressed in most cells and tissues, particularly in adipose tissue, where it promotes lipid usage by stimulating genes involved in fatty acid oxidation (Jahansouz et al., 2018; Janani & Kumari, 2015; McMullen et al., 2014).

PPAR-δ activation lowers LDL and triglyceride levels, mitigating triglyceride accumulation in the liver and adipose tissue, increasing lipid catabolism and consequently decreasing weight gain. Exercise upregulates PPAR-δ, which in turn helps with fatty acid and lipolytic activity. Currently, there are no pharmacological agonists for PPAR-δ (Welty et al., 2016). The simultaneous activation of PPAR-α and PPAR-δ initiates weight gain and fat accumulation due to PPAR-γ agonism. The combination of PPAR-δ and PPAR-γ agonists, in turn, can alleviate insulin resistance and regulate glucose metabolism (La Rosa Rodriguez & Kersten, 2017; Feng et al., 2016).

PPAR-γ

PPAR-γ is only expressed in a limited number of cells and tissues. It is highly abundant in adipose tissue, but it is also found in the liver, muscle, colon, and macrophages. PPAR-γ regulates adipogenesis and the balance between glucose and lipid oxidation (La Rosa Rodriguez & Kersten, 2017).

Adipose PPAR-γ protects the liver and skeletal muscle tissues against excess lipids and maintains normal organ function (Janani & Kumari, 2015).

PPAR-γ is involved in the regulation of insulin sensitivity via stimulating the secretion of adipocytokines, adiponectin, and leptin in adipocytes, which are mediators of insulin action in peripheral tissues (Janani & Kumari, 2015; Lodhi & Semenkovich, 2014). PPAR-γ is also involved in lipid metabolism, lipogenesis, fat storage, adipokine production, thermogenesis, and adipocyte survival, differentiation and function (Lodhi & Semenkovich, 2014).

Due to its adipogenic function, increasing PPAR-γ activity causes weight gain; however, caloric restriction does not induce changes in the activity of PPAR-γ or PPAR-δ (Jahansouz et al., 2018; Janani & Kumari, 2015).

JNK

The activation of the Jun N-terminal kinase (JNK) signaling pathway is crucial for the autophagic process, contributing to Beclin-1 expression, which modulates autophagy dysregulation and p53 phosphorylation. The inhibition of JNK suppresses autophagy and attenuates insulin resistance. Autophagic dysfunction may lead to excessive lipid accumulation in the liver, contributing to the progression of NAFLD (Zhang et al., 2018).

JNK signaling inhibits AKT in the insulin cascade. In this case, insulin resistance may occur when the membrane distribution of proto-oncogene tyrosine-protein kinase SRC is altered by saturated fatty acids, which causes the stimulation of JNK signaling (Welty et al., 2016; Yang et al., 2018). TNF-α signaling activates intracellular JNK and inhibits nuclear factor kappa-B kinase subunit β (IKK-β), which leads to increased activating phosphorylation of serine on IRS-1 instead of normal tyrosine phosphorylation. Thus, an adipocyte product can cause insulin resistance and metabolic syndrome (Welty et al., 2016). The autophagy and JNK/IKK-β signaling pathways are inhibited when the interaction between B-cell lymphoma 2 (Bcl-2) and Beclin-1 is increased, and AMPK activation is decreased. Moreover, when JNK phosphorylates Bcl-2, autophagy is stimulated (Navarro-Yepes et al., 2014).

The JNK pathway is presumed to be involved in the impaired activity of oxidative phosphorylation in advanced steatosis and NASH. JNK activation during steatosis-associated ER stress can modulate NCOR-1 activity, inhibiting PPAR-α and subsequently causing decreased mitochondrial activity and facilitating fat accumulation (Baiceanu et al., 2016). Figure 2 summarizes the cell signaling pathways involved in lipid metabolism, as previously described.

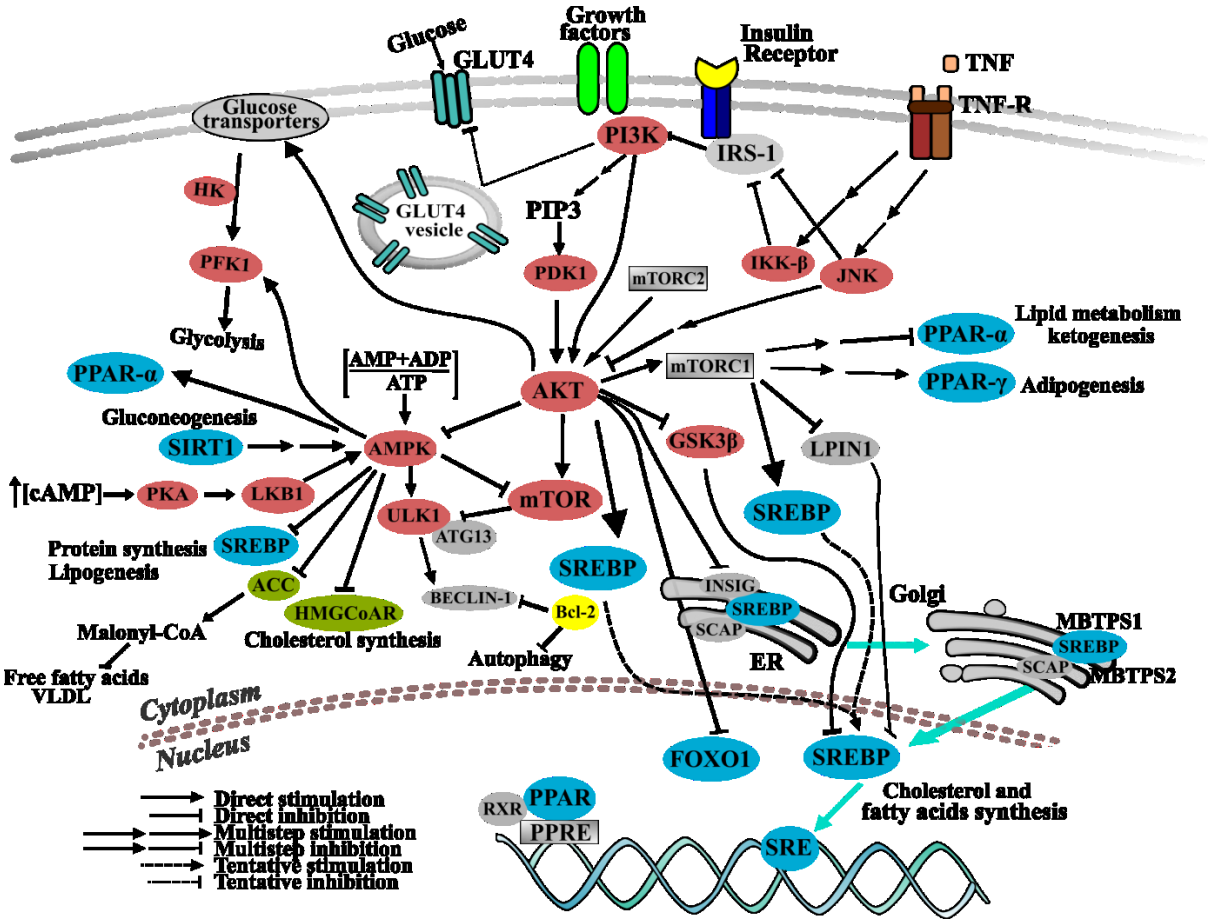

Figure 2. Cell signaling pathways involved in lipid metabolism.

Conclusion

Metabolic disorders have a distinct potential to advance to chronic complications, such as insulin resistance, type 2 diabetes, and NAFLD. Nevertheless, there have been substantial advances in the understanding of the mechanisms of lipid metabolism. These advances, together with the acquired knowledge in the field of cell signaling pathways related to carbohydrate and lipid processing, provide

deeper insight into the metabolism of fatty acids, triglycerides, lipoprotein, and lipids. These are important tools that should be addressed when studying the effects of new strategies to provide education regarding the importance of nutrition and exercise or when developing effective therapeutic interventions.

Acknowledgements

The authors acknowledge financial support by CAPES/FCFAr-UNESP/PADC (Process: 250 - 10/2017) and FAPESP (Process: 2017/04500-9). This study was financed in part by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil* (CAPES) – Finance Code 001.

References

Aizawa, Y., Seki, N., Nagano, T., & Abe, H. (2015). Chronic hepatitis C virus infection and lipoprotein metabolism. *World Journal of Gastroenterology, 21*(36), 10299–10313. doi: 10.3748/wjg.v21.i36.10299

Baiceanu, A., Mesdom, P., Lagouge, M., & Foufelle, F. (2016). Endoplasmic reticulum proteostasis in hepatic steatosis. *Nature Reviews Endocrinology, 12*(12), 710–722. doi: 10.1038/nrendo.2016.124

Boyd, R. A. B., & Ye, J. (2018). SREBPs in lipid metabolism, insulin signaling, and beyond. *Trends in Biochemical Sciences, 43*(5), 358–368. doi: 10.1016/j.tibs.2018.01.005

Chen, Y., & Li, P. (2016). Fatty acid metabolism and cancer development. *Science Bulletin, 61*(19), 1473–1479. doi: 10.1007/s11434-016-1129-4

Feng, L., Luo, H., Xu, Z., Yang, Z., Du, G., Zhang, Y., ... Li, Y. (2016). Bavachinin, as a novel natural pan-PPAR agonist, exhibits unique synergistic effects with synthetic PPAR-γ and PPAR-α agonists on carbohydrate and lipid metabolism in db/db and diet-induced obese mice. *Diabetologia, 59*(6), 1276–1286. doi: 10.1007/s00125-016-3912-9

Hirata, N., Suizu, F., Lennikov, M. M., Tanaka, T., Edamura, T., Ishigaki, S., ... Noguchi, M. (2018). Functional characterization of lysosomal interaction of Akt with VRK2. *Oncogene*, *37*, 5367-5386. doi: 10.1038/s41388-018-0330-0

Jahansouz, C., Xu, H., Hertzel, A. V., Kizy, S., Steen, K. A., Foncea, R., ... Bernlohr, D. A. (2018). Partitioning of adipose lipid metabolism by altered expression and function of PPAR isoforms after bariatric surgery. *International Journal of Obesity, 42*(2), 139–146. doi: 10.1038/ijo.2017.197

Janani, C., & Kumari, B. D. R. (2015). PPAR gamma gene - a review. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 9*(1), 46–50. doi: 10.1016/j.dsx.2014.09.015

Józwiak, P., Forma, E., Brys, M., & Krzeslak, A. (2014). O-GlcNAcylation and metabolic reprograming in cancer. *Frontiers in Endocrinology, 5,* 145. doi: 10.3389/fendo.2014.00145

Kersten, S., & Stienstra, R. (2017). The role and regulation of the peroxisome proliferator activated receptor alpha in human liver. *Biochimie, 136*, 75–84. doi: 10.1016/j.biochi.2016.12.019

La Rosa Rodriguez, M. A. d., & Kersten, S. (2017). Regulation of lipid droplet-associated proteins by peroxisome proliferator-activated receptors. *Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids, 1862*(10B), 1212–1220. doi: 10.1016/j.bbalip.2017.07.007

Li, X., Lian, F., Liu, C., Hu, K.-Q., & Wang, X.-D. (2015). Isocaloric pair-fed high-carbohydrate diet induced more hepatic steatosis and inflammation than high-fat diet mediated by miR-34a/SIRT1 axis in mice. *Scientific Reports, 5,* article n. 16774. doi: 10.1038/srep16774

Lodhi, I. J., & Semenkovich, C. F. (2014). Peroxisomes: a nexus for lipid metabolism and cellular signaling. *Cell Metabolism, 19*(3), 380–392. doi: 10.1016/j.cmet.2014.01.002

Manning, B. D., & Toker, A. (2017). AKT/PKB signaling: navigating the network. *Cell, 169*(3), 381–405. doi: 10.1016/j.cell.2017.04.001

McMullen, P. D., Bhattacharya, S., Woods, C. G., Sun, B., Yarborough, K., Ross, S. M., ... Andersen, M. E. (2014). A map of the PPARa transcription regulatory network for primary human hepatocytes. *Chemico-Biological Interactions, 209*, 14–24. doi: 10.1016/j.cbi.2013.11.006

McRae, S., Iqbal, J., Dutta, M. S., Lane, S., Nagaraj, A., Ali, N., & Waris, G. (2016). The hepatitis C virus-induced NLRP3 inflammasome activates the sterol regulatory element-binding protein (SREBP) and regulates lipid metabolism. *Journal of Biological Chemistry, 291*(7), 3254–3267. doi: 10.1074/jbc.M115.694059

Musso, G., Cassader, M., & Gambino, R. (2016). Non-alcoholic steatohepatitis: emerging molecular targets and therapeutic strategies. *Nature Reviews Drug Discovery, 15*(4), 249–274. doi: 10.1038/nrd.2015.3

Navarro-Yepes, J., Burns, M., Anandhan, A., Khalimonchuk, O., Del Razo, L. M., Quintanilla-Vega, B., … Franco, R. (2014). Oxidative stress, redox signaling, and autophagy: cell death versus survival. *Antioxidants & Redox Signaling, 21*(1), 66–85. doi: 10.1089/ars.2014.5837

Park, J.-M., Jung, C. H., Seo, M., Otto, N. M., Grunwald, D., Kim, K. H., … Kim, D.-H. (2016). The ULK1 complex mediates MTORC1 signaling to the autophagy initiation machinery via binding and phosphorylating ATG14. *Autophagy, 12*(3), 547–564. doi: 10.1080/15548627.2016.1140293

Pawlak, M., Lefebvre, P., & Staels, B. (2015). Molecular mechanism of PPARα action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease. *Journal of Hepatology, 62*(3), 720–733. doi: 10.1016/j.jhep.2014.10.039

Régnier, M., Polizzi, A., Lippi, Y., Fouché, E., Michel, G., Lukowicz, C., … Montagner, A. (2018). Insights into the role of hepatocyte PPARα activity in response to fasting. *Molecular and Cellular Endocrinology, 471*, 75–88. doi: 10.1016/j.mce.2017.07.035

Röhrig, F., & Schulze, A. (2016). The multifaceted roles of fatty acid synthesis in cancer. *Nature Reviews Cancer, 16*(11), 732–749. doi: 10.1038/nrc.2016.89

Semenkovich, C. F., Goldberg, A. C., & Goldberg, I. J. (2016). Disorders of Lipid Metabolism. In S. Melmed, K. S. Polonsky, P. R. Larsen & H. M. Kronenberg (Eds.), *Williams textbook of endocrinology* (13th ed., p. 1660–1700). Philadelphia: Elsevier. doi: 10.1016/B978-0-323-29738-7.00037-X

Shimano, H., & Sato, R. (2017). SREBP-regulated lipid metabolism: convergent physiology — divergent pathophysiology. *Nature Reviews Endocrinology, 13*(12), 710–730. doi: 10.1038/nrendo.2017.91

Sinha, R. A., Singh, B. K., & Yen, P. M. (2018). Direct effects of thyroid hormones on hepatic lipid metabolism. *Nature Reviews Endocrinology, 14*(5), 259–269. doi: 10.1038/nrendo.2018.10

Su, W., Cao, R., He, Y. C., Guan, Y. F., & Ruan, X. Z. (2017). Crosstalk of hyperglycemia and dyslipidemia in diabetic kidney disease. *Kidney Diseases, 3*(4), 171–180. doi: 10.1159/000479874

Tang, Q.-Q. (2016). Lipid metabolism and diseases. *Science Bulletin, 61*(19), 1471–1472. doi: 10.1007/s11434-016-1174-z

Trogdon, J. G., Murphy, L. B., Khavjou, O. A., Li, R., Maylahn, C. M., Tangka, F. K., … Orenstein, D. (2015). Costs of chronic diseases at the state level: the chronic disease cost calculator. *Preventing Chronic Disease, 12*(E140), 1-9. doi: 10.5888/pcd12.150131

Wang, Y., Ding, W.-X., & Li, T. (2018). Cholesterol and bile acid-mediated regulation of autophagy in fatty liver diseases and atherosclerosis. *Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids*, *1863*(7), 726–733. doi: 10.1016/j.bbalip.2018.04.005

Welty, F. K., Alfaddagh, A., & Elajami, T. K. (2016). Targeting inflammation in metabolic syndrome. *Translational Research – The Journal of Laboratory and Clinical Medicine, 167*(1), 257–280. doi: 10.1016/j.trsl.2015.06.017

Yang, Q., Vijayakumar, A., & Kahn, B. B. (2018). Metabolites as regulators of insulin sensitivity and metabolism. *Nature Reviews - Molecular Cell Biology, 19*(10), 654–672. doi: 10.1038/s41580-018-0044-8

Zhang, Z., Yao, Z., Chen, Y., Qian, L., Jiang, S., Zhou, J., Zheng, S. (2018). Lipophagy and liver disease: new perspectives to better understanding and therapy. *Biomedicine & Pharmacotherapy, 97*, 339–348. doi: 10.1016/j.biopha.2017.07.168