Unravelling the role of fatty acid metabolism in cancer through the FOXO3-FOXM1 axis

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ABSTRACT

Obesity and cachexia represent divergent states of nutritional and metabolic imbalance but both are intimately linked to cancer. There is an extensive overlap in their signalling pathways and molecular components involved such as fatty acids (FAs), which likely play a crucial role in cancer. Forkhead box (FOX) proteins are responsible of a wide range of transcriptional programmes during normal development, and the FOXO3-FOXM1 axis is associated with cancer initiation, progression and drug resistance. Free fatty acids (FFAs), FA synthesis and \( \beta \)-oxidation are associated with cancer development and progression. Meanwhile, insulin and some adipokines, that are up-regulated by FAs, are also involved in cancer development and poor prognosis. In this review, we discuss the role of FA metabolism in cancer and how FA metabolism integrates with the FOXO3-FOXM1 axis. These new insights may provide leads to better cancer diagnostics as well as strategies for tackling cancer development, progression and drug resistance.

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1. Introduction

Obesity is a worldwide epidemic caused by the failure of the human body to match rates of energy intake with rates of energy expenditure, such that energy consumption exceeds energy expenditure and excess calories are stored primarily as fat in adipose tissue (Calle and Kaaks, 2004). In 2014, 39% of adults in the world were overweight (BMI \( \geq 25 \text{ kg/m}^2 \); 39% of men and 40% of women) and 13% were obese (BMI \( \geq 30 \text{ kg/m}^2 \); 11% of men and 15% of women). Thus, nearly 2 billion adults worldwide are overweight and, of these, more than half a billion are obese (World Health Organisation, 2014). Besides the economic and social implications, obesity is associated with an increased risk of developing a number of health problems such as type 2 diabetes mellitus, hypertension, dyslipidaemia (Xu et al., 2015), cardiovascular diseases, gastrointestinal diseases, kidney diseases, endocrine changes, infertility, bone and joint diseases, pulmonary diseases and cancer (Deng et al., 2016). The association of obesity with cancer has been documented over a considerable range of cancer types, and appropriately, obesity is increasingly recognized as a growing cause of preventable cancer risk (Deng et al., 2016).

Another lipid and energy metabolism-related condition strongly associated with cancer is cachexia. It is depicted as involuntary weight loss that cannot be reversed by nutritional intervention (Tsoli and Robertson, 2013) and is observed in up to 80% of cancers (Porporato, 2016). Cachexia is characterized by skeletal muscle wasting and atrophy of the adipose tissue (Petruzzelli and Wagner, 2016), such that fat is lost more rapidly than lean tissues. Ultimately, cachectic patients present high levels of blood fatty acids (FAs), glycerol and triacylglycerol (TAG). This results partly from reduced food intake, and partly through stimulation by tumour-associated factors and systemic inflammatory cytokines/adipokines, such as interleukin (IL)-1, IL-6 and tumour necrosis factor alpha (TNF-\( \alpha \)) (Petruzzelli and Wagner, 2016), that function by inhibiting lipogenesis and/or promoting lipolysis (Fearon et al., 2014).
Obesity and cancer cachexia represent divergent states of nutritional and metabolic imbalance (Petruzelli and Wagner, 2016; Tsoli et al., 2015) and alterations in fat and energy metabolism have distinct consequences depending on the health conditions of these individuals. For example, increased lipid mobilization and energy expenditure is favourable in obesity, while it is deleterious in cancer (Petruzelli and Wagner, 2016). Even obesity and cachexia are opposite states, their relationship to cancer is not exactly antagonistic as there is an extensive overlap in the signalling pathways and molecular components involved (Tsoli and Robertson, 2013; Chen, 2011; Ungefroren et al., 2015). One such group of metabolic components are the FAs, which likely play a crucial role in the pathogenesis of both health conditions and cancer (Tsoli and Robertson, 2013; Chen, 2011; Ungefroren et al., 2015).

2. FOXO3 and FOXM1

Forkhead box (FOX) proteins belong to a superfamily of transcription factors that are responsible for the spatio-temporal regulation of a wide range of transcriptional programmes during normal development (Myatt and Lam, 2008; Myatt and Lam, 2007). FOXO3 is a member of the FOXO subfamily of transcription factors (Gomes et al., 2013) that behave as tumour suppressors (Paik et al., 2007). This FOXO subfamily acts downstream of phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT) (Gomes et al., 2008), integrating diverse positive and negative proliferative signals with the transcriptional machinery to mediate gene expression. In addition, FOXO3 can also be regulated by the extracellular signal-related kinase (ERK)/mitogen-activated protein kinase (MAPK) and IκB kinase (IKK) signalling pathways (Gomes et al., 2008). Conversely, another Forkhead protein FOXM1 behaves as a classic potent oncogene (Myatt and Lam, 2007; Gomes et al., 2013). An increase in its expression or activity promotes three key features of cancer: cell transformation, tumour progression and resistance to cytotoxic agents (Myatt and Lam, 2007, 2008; Zona et al., 2014). Notably, FOXM1 is a transcriptional target repressed by FOXO proteins and thus a downstream effector of the PI3K-AKT-FOXO axis (Gomes et al., 2013). FOXM1 and FOXO3 also antagonise the transcriptional activity of each other by competing for the same binding sites on common target genes (Gomes et al., 2013; Lam et al., 2013). The PI3K-AKT pathway plays an essential role in the signal transduction events, and is frequently overactivated in human cancers (Arcaro and Guerreiro, 2007). This signalling cascade is also affected in other disease states such as insulin resistance and type 2 diabetes mellitus (Valverde et al., 2005), which are incidentally associated with elevated levels of FFAs. In agreement, FFAs can activate receptors in the cell plasma membrane which in turn leads to the activation of the PI3K-AKT (Hara et al., 2014 and Hara et al., 2013). Collectively, these observations propose a potential intimate link between FA, the FOXO3-FOXM1 axis and cancer.

3. Fatty acids in cancer

3.1. Circulating free fatty acids

The fact that free fatty acid (FFA) concentrations are elevated in cancer patients suggests that FFAs may contribute to the development of cancer (Hsu et al., 2007). The diversity in FA structure (chain length, degree of unsaturation and position and stereoisomeric configuration of the double bonds) affect their metabolic fate (DeLany et al., 2000; Moussavi et al., 2008), different types of FAs presents β-oxidation and deposition rate differences (Moussavi et al., 2008). It was demonstrated that polysaturated fatty acids (PUFA), but not monounsaturated fatty acids (MUFA) or saturated fatty acid (SFA) suppress the expression of genes involved in lipogenic transcription and are better activators of PPAR-γ (Moussavi et al., 2008). Furthermore, unsaturated FAs have higher oxidation rates than does long-chain SFAs and the length of the carbon chain of SFAs is inversely correlated with the oxidation rate (Moussavi et al., 2008; McDonald et al., 1980). Indeed, β-oxidation is higher with an increase in polyunsaturated/saturated ratio intake and this ratio affects the utilization of FAs in the diet (Moussavi et al., 2008).

It is also well known that short-chain FAs and medium-chain FAs are preferentially oxidized compared to long-chain fatty acids (LCFA) (DeLany et al., 2000), because of this, short-chain FAs and medium-chain FAs contribute to a loss of adipose tissue in humans (St-Onge et al., 2003). In addition, some studies have clearly shown the importance of long-chain PUFAs and their nutritional value for human health and they are associated with cancer prevention (Abedi and Sahari, 2014).

There are a multitude of ways in which FAs can promote cancer progression. Firstly, they serve as building blocks for newly-synthesized membrane phospholipids. Secondly, they are a source of energy for cell proliferation through the β-oxidation pathway. Finally, they are used for the biosynthesis of pro-tumorigenic lipid-signalling molecules such as phosphatidylinositol-4,5-biphosphate (PIP2) that are involved in generating a secondary messenger molecule, the diacylglycerol (DG) that is formed by the action of PI3K – its accumulation activates the downstream oncogenic effector AKT to stimulate cell proliferation and survival as well as other cancer hallmarks (Zaidi et al., 2014). It is important to note that while FFAs can themselves have carcinogenic potentials, this capacity is further exacerbated by hyperinsulinemia, which is also stimulated by elevated levels of FFAs (Hsu et al., 2007). In agreement, studies in tumour-bearing animals showed an increase in lipolysis and therefore an increase in the FFA release into plasma due to the hydrolysis of adipose tissue TAGs (Sakurai and Klein, 1998). Consistently, proteins that have been identified as facilitating the uptake of FAs into cells, and those involved in FA transport have also been implicated in cancer progression (Balaban et al., 2015; Guaita-Esteruelas et al., 2016). Further in support of this idea is the link between dietary FFAs and breast cancer (Hsu et al., 2007). Accordingly, n-6 PUFAs have been found to have a strong tumour-enhancing function, whereas SFAs have a relatively weaker tumour-promoting effect. On the other hand, the n-3 PUFAs exhibit weak cancer protective functions, whereas MUFA do not have any discernible effects on cancer development (Fay et al., 1997). Notably, the n-3 PUFA docosahexaenoic acid (DHA) has both anti-inflammatory and anti-cancer properties. In colon cancer cells, DHA treatment leads to FOXO3 nuclear translocation and activation, allowing the transcriptional repression of the expression of oncogene miR-21 (Fluckiger et al., 2016). Conversely, incubation with the omega-3 FA eicosapentaeenoic acid (EPA), but not DHA, causes an increase in FOXO3 phosphorylation and hence inactivation in murine C2C12 myotubes (Kamolrat and Gray, 2013). In addition, in human colon cancer cells, the expression of the potent oncogene FOXM1 is increased in presence of the short chain FA butyrate, which is a product of colonic fermentation of dietary fibres (Serpa et al., 2010).

Long-chain FAs travel in the circulation either as FFAs bound to albumin or as TAGs contained in very low-density lipoproteins and chylomicrons. These circulating TAGs are hydrolysed by lipoprotein lipase to FFAs and then taken up into cells (Balaban et al., 2015). Several proteins such as CD36/FAT and fatty acid-binding proteins (FABPs) have been identified to facilitate the uptake of FFAs into cells. Consistent with the idea that FFAs have a role in cancer, those FA-transport proteins have also been implicated in promoting cancer progression (Balaban et al., 2015; Guaita-Esteruelas et al., 2016). The long-chain monounsaturated FFA oleate has been shown to be able to stimulate the proliferation of human breast cancer cells,
with PI3K having a role in this process (Hsu et al., 2007; Hardy et al., 2005). Of note, FABP4 is an adipose tissue-secreted adipokine involved in the regulation of energy metabolism (Furuhashi et al., 2014), and plays an important role in FA uptake by cells (Wu et al., 2014). A recent study demonstrated that exogenous FABP4 can positively regulate cancer cell proliferation through the activation of PI3K-AKT and MAPK-ERK pathways in breast cancer cells (Guaita-Esteruelas et al., 2016). Intriguingly, FOXM1 expression is also up-regulated by FABP4 in these breast cancer cells, probably through activation of AKT and thereby repression of FOXO3 (Guaita-Esteruelas et al., 2016). In addition, BMS3089403, a well-known bifenpyral azole inhibitor for FABP4, is able to activate adenosine monophosphate-activated-activated protein kinase (AMPK) signalling pathway which has a negative role in cell proliferation (Lin et al., 2012).

AMPK is an evolutionary conserved heterotrimeric serine/threonine kinase in eukaryotes, which is a known cellular metabolic sensor that plays an important role in the control of energy homeostasis in response to external stresses (Carling, 2005; Shackelford and Shaw, 2009). Upon increased level of intracellular AMP/ATP ratio, AMPK responds by diverting cellular metabolism towards energy producing catabolic reactions while suppressing biosynthesis and proliferation (Hardie, 2014; Bullot et al., 2012). Recent studies have revealed that activation of AMPK is able to stimulate cell death through modulation of apoptosis and/or autophagy in numerous human cancers (Shackelford and Shaw, 2009; Kuhajda, 2008; Yu et al., 2009). On the other hand, this is significant as recent studies have documented that pharmacological activation of AMPK is able to block cell growth in a number of human cancers through activation of FOXO3. For example, it has been demonstrated that AMPK can retard cervical cancer cell growth through inhibition of FOXM1 function via the AMPK-AKT-FOXO3 signalling cascade (Yung et al., 2013). In addition, AMPK can also phosphorylate FOXO3 in the nucleus, and the AMPK-phosphorylated FOXO3 can in turn transcriptionally repress SKP2 expression. This repression then leads to increased levels of the SKP2 target CARM1 protein, which can cooperate with another transcription factor EB (TFEB) to increase the expression of autophagy-related and lysosomal genes (Shin et al., 2016). Furthermore, AMPK can also induce SIRT1-mediated deacetylation and inactivation of FOXO3 by decreasing cellular NAD⁺ levels, as NAD⁺ is a co-factor for Sirtuins (Canto et al., 2009) (Fig. 1). AMPK has been shown as a master regulator of apoptosis playing a major role in apoptosis initiation through transcriptional activation of Bim (Bodur et al., 2016).

3.2. Fatty acid synthesis and β-Oxidation

In humans as well as other mammals, two sources of FAs are involved in lipid metabolism, the exogenously-derived (dietary) FAs and the endogenously-synthesized FAs. The biosynthesis of the latter endogenous FAs is catalysed by fatty acid synthase (FASN). Accordingly, FASN synthesizes long-chain FAs by using acetyl-coenzyme A (CoA) as a primer, malonyl-CoA as a two-carbon donor, and NADPH as a reducing agent. The predominant product of FASN is the 16-carbon FA, palmitate. In normal well-nourished donor, and NADPH as a reducing agent. The predominant product of FASN is the 16-carbon FA, palmitate. In normal well-nourished donor, and NADPH as a reducing agent. The predominant product of FASN is the 16-carbon FA, palmitate. In normal well-nourished donor, and NADPH as a reducing agent. The predominant product of FASN is the 16-carbon FA, palmitate. In normal well-nourished donor, and NADPH as a reducing agent. The predominant product of FASN is the 16-carbon FA, palmitate. 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These TAGs, when necessary, generate energy through β-oxidation, which is a cyclical series of reactions that result in the shortening of FAs by two carbons per cycle, and generate also in each round NADH, FADH₂ and acetyl CoA (Carrañedo et al., 2013). Notably, despite having adequate nutritional supply in cancer cells, almost all FAs are derived from de novo synthesis (Baron et al., 2004). Concurrently, almost all cancer cells show an increased capability for FA de novo synthesis to satisfy the requirement for rapid cell multiplication (Gong and Liang, 2014). Although the link between de novo synthesis of FAs to the well-known tumour-associated increase in glycolysis is often reflected by a coordinated rise in lipogenic and glycolytic enzyme activities, the implications of increased lipogenesis for cancer cell biology did not become a focus of interest until recently. This is when the oncogenic antigen-S19 (OA-S19), a molecule found in tumour cells from breast cancer patients and linked with a markedly poorer prognosis, was unambiguously identified as FASN (Kuhajda et al., 1994; Witters et al., 1994). These findings suggest that FASN overexpression promotes cancer initiation and progression by conferring a powerful growth advantage and as such, cancer cells are selected for on the basis of increased FASN-catalysed de novo FA biogenesis. FA β-oxidation is a multi-phase process by which FAs are imported into cells and broken down by to produce energy (Lopaschuk et al., 2010). It plays an important role in various aspects of cancer development and progression (Tirado-Velez et al., 2012;Rodriguez-Enriquez et al., 2015;Park et al., 2016; Padanad et al., 2016). The β-oxidation enzymes, the trifunctional proteins: hydroxacyl-CoA dehydrogenase, 3-ketoacyl-CoA thioesterase and enoyl-CoA hydratase, are positively correlated with tumour cell density, and the inhibition of this pathway can reduce energy production and cellular proliferation in these cells (Lin et al., 2016). Circulating FAs are taken up into the cells by transporters, including fatty acid translocase (CD36/FAT), tissue specific fatty acid transport proteins (FATP), and FABPs, located on the cell surface (Lopaschuk et al., 2010). After entering the cell, a CoA group is added to the FA by fatty acyl-CoA synthase (FACS) to form a long-chain acyl-CoA. Carnitine palmitoyltransferase 1 (CPT1) is a long-chain FA transport protein rate-limiting for β-oxidation and it converts the long-chain acyl-CoA to long-chain acylcarnitine, thus allowing the modified FA to be transported across the inner mitochondrial membrane by carnitine translocase (CAT), which exchanges long-chain acylcarnitines for carnitine (Eaton et al., 2001; Qu et al., 2016). The inner mitochondrial membrane located CPT2 then reverts the long-chain acylcarnitine back to long-chain acyl-CoA for it to be fed into the FA β-oxidation pathway, which results in the production of one acetyl-CoA from each cycle of FA β-oxidation. This acetyl-CoA then enters the mitochondrial tricarboxylic acid cycle (TCA) cycle to generate energy. The NADH and FADH₂ produced by both FA β-oxidation and the TCA cycle are also used by the electron transport chain to produce ATP as an energy source (Eaton et al., 2001; Qu et al., 2016).

3.3. FOXO3-FOXM1 in fatty acid synthesis and β-oxidation

It has been demonstrated that the CPT1 knock-down in breast cancer cells is related to the up-regulation of pro-apoptotic genes (e.g. BAD, CASP9, COL18A1) and down-regulation of invasion and metastasis related-genes (e.g. TIMP-1, PDGF-A, SERPINB2) (Pucci et al., 2016), suggesting a role for CPT1 in cancer cell survival, invasion and metastasis. In the first step of β-oxidation, different acyl-CoA oxidases generate H₂O₂ which increases the cellular oxidative stress levels (Dansen et al., 2004). FOXO3 has been shown to participate in the detoxification of H₂O₂ generated from β-oxidation and thus protects cells from oxidative stress. Similarly, the levels of catalases involved in the detoxification of H₂O₂ derived from peroxisomal β-oxidation of FAs in mice are also positively regulated by FOXO3 activation (Nemoto and Finkel, 2002). In addition, FOXO3 also plays a key role in regulating the production of ketone bodies from the acetyl CoA derived from β-oxidation of FAs (Nadal et al., 2002) (Fig. 2). Furthermore, FOXO3 transcription factors

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have also been implicated in the regulation of FA metabolism, and it is known that FOXO3 upregulates sterol carrier proteins (SCP)X and SCP2 through transcription initiation at the level of gene promoter.

While the in vivo function of SCP2 remains unclear, SCPx is the thiolase involved in the breakdown of branched-chain FAs (Dansen et al., 2004).

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Of particular importance and relevance is a recent study of the nematode *Caenorhabditis elegans*, which provides the strongest and most convincing evidence that the FOXO3-FOXO1 axis play a central role in FA and related energy metabolism. It reveals that DAF-16, the *C. elegans* homologue of FOXO3, cooperates with another transcription factor Tcr-1/TCERG1 to enhance the expression of gene networks involved in lipid synthesis and breakdown to promote longevity (Amrit et al., 2016). The genes coordinately regulated by DAF-16/FOXO3 and Tcr-1/TCERG1, include those regulating de novo FA synthesis, desaturation and elongation as well as TAG production (e.g. *pod-1, mlcd-1, fasn-1, mbo-2, dgt-2, acc-22, fat-5, fat-6, fat-7, argl-1, acs-17, cpt-2, acdh-9, ech-7, ech-1.2, acox-1, acaa-2 etc*) (Table 1). For example, the DAF-16/FOXO3 regulated *C. elegans* gene *fasn-1* encodes FASN, the major regulatory enzyme that mediates the de novo synthesis of SFAs. Another DAF-16/FOXO3 target *acs-22* (FATP4) is the membrane transporter essential for absorption of dietary lipids (Herrmann et al., 2001). Pod-2 (ACACA) is the alpha subunit of a central enzyme involved in FA biosynthesis by catalyzing the conversion of acetyl-CoA to malonyl-CoA (Keenan et al., 2015), while MLCD-1 (MLYCD) mediates the reverse reaction (Lopaschuk et al., 2010). Malonyl-CoA is both a substrate for FASN and an inhibitor of β-oxidation, so MLCD acts as an important enzyme in the balance between lipogenesis and lipolysis (Zhou et al., 2009), furthermore MLYCD inhibition suppresses human breast cancer cell proliferation (Zhou et al., 2009; Balaban et al., 2015). *Acs-*2 and *Acs-*17 are acyl-CoA synthases (FACSs) that convert FA into fatty acyl-CoA in order for it to enter the mitochondria and to be β-oxidized (Lopaschuk et al., 2010). Cpt-2 (CPT2) converts the long-chain acylcarnitine back to acyl-CoA for the modified FA to enter the FA β-oxidation pathway in the mitochondria. Ech-7 (ECHS1) and Ech-1 (HADHA) are enzymes that catalyze and second and the last three steps of mitochondrial β-oxidation of long chain FAs, respectively (Janssen et al., 1997; Orii et al., 1997).

### 3.4. ER stress

FFAs are highly related with endoplasmic reticulum (ER) stress (Cunha et al., 2012). ER stress contributes to the development and progression of many diseases, including cancer (Ozcan and Tabas, 2012). Perturbations in ER function initiate the unfolded protein response (UPR) which activated by 3 ER transmembrane molecules: PKR–like ER kinase (PERK), inositol-requiring kinase-1 (IRE1), and activating transcription factor (ATF) 6 (Cunha et al., 2012; Ozcan and Tabas, 2012). The prime function of the UPR is to restore ER homeostasis by reducing protein load and increasing ER folding capacity and misfolded protein degradation. Attenuation of protein translation is executed by PERK through phosphorylation of the eukaryotic translation initiation factor 2α (eIF2α), which induces the UPR effector CHOP (C/EBPα-homologous protein). In pathologic settings, prolonged CHOP expression triggers apoptosis (Zhang et al., 2014).

It has been demonstrated that the SFA palmitate can induce ER stress (Cunha et al., 2012). The synthesis of palmitase is catalyzed by FASN that is highly expressed in cancer cells (Baron et al., 2004; Zhou et al., 2003) and is known to induce toxicity and cell death in various cell types, including cancer cells (Rojas et al., 2014). Administered palmitate is rapidly incorporated into lipid depot of the ER and impairs the ER structure and integrity, thereby inducing ER stress (Rojas et al., 2014; Bomradaradee et al., 2006). The palmitate-induced ER stress can in turn cause FOXO3 activation and thereby the gene expression of death protein 5 (DPS) and Puma in the pancreatic β-cells (Cunha et al., 2012). Experiments in murine C2C12 myotubes have demonstrated that palmitate increases protein degradation via suppression of AKT-FOXO3 signalling and DHA protects against the detrimental effects of palmitate by re-establishing the AKT-mediated inhibition of FOXO3 (Woodworth-Hobbs et al., 2014) (Fig. 2). It was also demonstrated that activated FOXO3, similarly to DAF-16, protects ER function and maintains secretory protein metabolism independently of the IRE1 UPR pathway in mammalian cells (Safra et al., 2014).

### 4. Adipokines

In mammals, excess energy is stored primarily as TAGs, which are mobilized when energy demands arise (Nakamura et al., 2014). FAs are the main components of adipose tissue (Drevon, 2005) that are stored as TAGs (Carracedo et al., 2013). In fact, one of the main functions of adipose tissue is the storage of TAGs and their subsequent release (Gustafson and Smith, 2015). Recently, adipose tissue has come into focus as an endocrine organ that secretes adipokines (Ungefroren et al., 2015; Drevon, 2005; Roni et al., 2006; Stern et al., 2016). Adipokines function as classic circulating hormones to communicate with other organs, including brain, liver, muscle, the immune system, and adipose tissue itself (Kwon and Pessin, 2013) regulating important biological processes in target organs and may exert specific effects on a variety of biological processes (Fasshauer and Bluher, 2015) being important for development many diseases such as cancer (Ungefroren et al., 2015; Drevon, 2005).

Some adipokines, such as TNF-α or IL-6, increase circulating FFA (from adipose tissue) and also reduce adiponectin (APN) secretion (Roni et al., 2006). On the other hand, FAs interact with nuclear receptor proteins that bind to certain regulatory domains of DNA and thereby alter transcription of the target genes, such as the peroxisome proliferator-activated receptor (PPAR)-γ (Drevon, 2005). PPAR-γ is a nuclear receptor transcription factor which plays a key role in the regulation of adipocytes differentiation and adipokines production and secretion (e.g. APN) and is also involved in lung, pancreatic, thyroid or colorectal cancer development (Polvani et al., 2016; Taylor et al., 2016; Friedrich et al., 2016; Chuang et al., 2016). Dietary FAs are able to regulate adipose tissue secretory function as well (Styrieki and Mutch, 2011), altering the secretion of APN, leptin, TNF-α and IL-6 (Drevon, 2005; Styrieki and Mutch, 2011). It was demonstrated that arachidonic acid increases IL-6 levels as palmitate that also increases TNF-α levels, meanwhile the APN levels are decreased by palmitate and linoleic acid (Drevon, 2005; Styrieki and Mutch, 2011). Conversely, DHA and EPA increase APN levels and decrease leptin levels, EPA also prevents increase of TNF-α (Drevon, 2005; Styrieki and Mutch, 2011).

These adipokines are all produced and secreted by adipocytes and promote various aspects of growth, development, and metastasis in cancer (Deng et al., 2016). APN and leptin are two highly expressed adipokines that have opposing effects. APN has predominantly anti-inflammatory effects and has decreased blood levels of APN in obesity, whereas leptin has multiple pro-inflammatory effects and its blood levels are increased in obesity (Deng et al., 2016; Chen, 2011). APN inhibits IL-6 secretion and lowers the levels of TNF-α (Chen, 2011; Ungefroren et al., 2015) and leptin stimulates production of IL-6 and TNF-α (Deng et al., 2016). IL-6 and TNF-α blood levels are also increased in obesity (Deng et al., 2016). Furthermore, increased cancer incidence and poor prognosis are associated with increased blood levels of IL-6, TNF-α and leptin; and decreased blood levels of APN (Chen, 2011). (Fig. 3 A).

APN and leptin exert almost diametrically opposing effects on tumour development, and increased APN/leptin ratio is associated with decreased cancer risk (Deng et al., 2016). APN has beneficial effects by decreasing the levels of many risk factors, it stimulates apoptosis and controls proliferation, adhesion, invasion, and colony formation in cancer cells. TNF-α is a pro-inflammatory cytokine produced by immune cells that have infiltrated cancer tissues. TNF-α stimulates cancer cell proliferation, inhibits apoptosis, and induces malignant transformation. IL-6 is a cytokine produced by immune cells and cancer cells that promotes cancer cell proliferation, survival, and metastasis. IL-6 also inhibits immune cell function, promoting cancer progression. Therefore, the decreased levels of TNF-α and IL-6 and increased levels of APN in cancer tissues indicate that these adipokines play important roles in the development and progression of cancer.
formation and regulates various signalling pathways such as AMPK and Jak/STAT (Chen, 2011, Ungefroren et al., 2015; Kim et al., 2016). On the other hand, elevated levels of leptin are discussed as a factor driving cancer development and progression, because leptin is known to be mitogenic, proinflammatory, antiapoptotic, and proangiogenic (Ungefroren et al., 2015). It is able to activate some oncogenic signalling pathways such as MAPK, NF-κB, and PI3K/akt (Ungefroren et al., 2015). APN levels have been studied in several types of cancer such as breast, endometrial or colon cancers (Ungefroren et al., 2015) meanwhile it is known that leptin can promote several cancers including prostate, colorectal, thyroid, renal, pancreatic, endometrial and oesophageal cancers (Chen, 2011).

IL-6 is known to promote carcinogenesis and has been strongly implicated in the development and growth of a variety of cancers (Deng et al., 2016; Chen, 2011). Plasma levels of IL-6 correlate with disease aggressiveness and poor prognosis (Deng et al., 2016). IL-6 has been shown to activate other signal pathways to increase carcinogenesis and metastasis such as MAPK and PI3K/akt pathway (Chen, 2011) and Jak/STAT pathway promoting cancer cell proliferation, survival and angiogenesis (Deng et al., 2016). TNF-α is associated with cellular transformation, proliferation, invasion, angiogenesis, and metastasis (Deng et al., 2016) and it is able to highly activate STAT3 pathway (Chen, 2011) and to inactivate APN pathway (Sente et al., 2016).

FOXO3 is also an important downstream target of APN. APN increases the expression of FOXO3 in liver cancer cells, preventing LPS-induced ROS production and NADPH oxidase activity (Shrestha and Park, 2016), and also stimulates the FOXO3 dephosphorylation and its nuclear translocation and thereby, activation in keratinocytes (Jin et al., 2016). In agreement, it has been shown that the anti-proliferative effects of APN in cancer cells occur through the AMPK-FOXO3 pathway (Kim et al., 2016; Shrestha et al., 2016; Nepal and Park, 2013). APN promotes autophagy in macrophages by suppressing the AKT-mediated phosphorylation of FOXO3 (Li et al., 2015), while leptin treatment activates the autophagic process via the p38-FOXO3 axis, playing a critical role in restricting tumour growth (Nepal et al., 2015). Moreover, leptin administration

| Table 1 | List of human homologues and orthologues of lipid-metabolic genes identified as DAF-16 and/or TCER-1 targets through RNA-Seq by Amrit et al. (2016) and their potential functions in lipid metabolism. |
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| C. elegans genes regulated by DAF-16/FOXO3 | Human Orthologues (from WormBase) (Stein et al., 2001) | Lipid & Energy Metabolism Function |
| pod-2 | Acetyl-CoA carboxylase alpha (ACACA) | The major regulatory enzyme of FA biosynthesis, catalyzes the conversion of acetyl-CoA to malonyl-CoA (Keenan et al., 2015). |
| mlcd-1 | Malonyl-CoA decarboxylase (MlyCD) | An enzyme that produces acetyl-CoA from malonyl-CoA (Landriscina et al., 1971). |
| fasn-1 | Fatty acid synthase (FASN) | The major regulatory enzyme that mediates the de novo synthesis of SFAs (Chirala et al., 2003). |
| mbo-2 | Diacylglycerol O-acetyltransferase 1 (DGAT1) | One of 2 enzymes that catalyze the final step in TAG synthesis in which diacylglycerol is covalently bound to long chain fatty acyl-CoAs (TACG synthesis (Schuber et al., 2013). |
| dgat-2 | Fatty acid transport protein 4 (FATP4) | The transporter responsible for very long chain FA biosynthesis (Herrmann et al., 2001). |
| YS3G8B.1, K0781.4 | Monacylglycerol O-acetyltransferase 1/2 (MOGAT1/2) | Enzymes involved in TAG synthesis, transferring acyl groups other than aminoacyl groups (Stone et al., 2004). |
| fat-5, fat-6, fat-7 | Stearoyl-CoA desaturase 1/5 (SCD1/5) | Integral membrane proteins of the endoplasmic reticulum (ER) that catalyzes the formation of MUFAs from SFAs, a key regulator of energy metabolism (Wang et al., 2005). |
| lipl-1, lipl-2, lipl-5 | Members of the Lipases family (LIPF) | Proteins involved in lipid (cholesterol ester) storage; lipl-1 is predicted to have hydrolase activity, acting on ester bonds (Redonnet-Vernhet et al., 1997). |
| atgl-1 | Patatin-like phospholipase domain containing (PNPLA) family protein | Proteins involved in lipid storage (Kienesberger et al., 2009). |
| acs-17 | Acyl-CoA synthetase long-chain family member 3/4 (ACSL3/4) | Long chain acyl-CoA synthetases, responsible for channelling long chain fatty acids (LCFAs) into oxidation (Durgan et al., 2006). |
| cpt-2 | Carnitine palmitoyltransferase II | Transporter protein catalyzes an acyl-group transfer between added CoA and carnitine (Yates and Garland, 1970). |
| acdh-9 | Acyl-CoA dehydrogenase family, member 8 (ACAD8) | Enzyme catalyzes the ω-β-dehydrogenation of acyl-CoA esters catalyze the dehydrogenation of acyl-CoA derivatives in the metabolism of FAs or branch chained amino acid (Nguyen et al., 2002) (Telford et al., 1999). |
| ech-7 | Short-chain enoyl-CoA hydratase (ECHS1) | Enzyme functions in the second step of the mitochondrial β-oxidation pathway. It catalyzes the hydration of 2-trans-enoyl-coenzyme A (CoA) intermediates to 1,3-dihydroxy-acyl-CoAs (Jansen et al., 1997). |
| ech-1,2 | Hydroxyacyl-CoA Dehydrogenase/3-Ketoacyl-CoA Thiolase/Enoyl-CoA Hydratase, Alpha Subunit (HADHA), The trifunctional protein that catalyzes the last three steps of mitochondrial β-oxidation of LCFAs (Orii et al., 1997). |
| acax-1 | Peroxisomal straight-chain acyl-CoA oxidase 1 (ACOX1) | The enzyme catalyzes the first, rate-limiting step in peroxisomal β-oxidation of medium to very long straight chain Fas (Morais et al., 2007). |
| F08AR.2, F08AR.3, F08AR.4, C48B4.1 | Peroxisomal acyl-coenzyme A oxidase 2 (ACOX2) | The key regulatory enzyme of the β-oxidation pathway 2 for side chain oxidation of cholesterol (Yeh et al., 2006; Lazra et al., 2015). |
| acao-2 | Acyl-CoA acyltransferase (ACAA2) | The enzyme catalyzes the hydration of 2-trans-enoyl-coenzyme A (CoA) esters to 1,3-dihydroxyacyl-CoAs (Jansen et al., 1997). |
| hacd-1 | HADHA: Hydroxyacyl-coenzyme A dehydrogenase | An enzyme involved in β-oxidation (Makamura et al., 2014). |
| fat-2 | FAT atypical cadherin 2 (FAT2) | A delta-12 fatty acyl desaturase (Katoh and Katoh, 2006). |
| ac-2 | Acyl-CoA synthetase family member | An enzyme function in the mitochondrial matrix to catalyze the oxidation of 3-hydroxyacyl-CoAs as part of the beta-oxidation pathway. Its enzymatic activity is highest with medium-chain-length fatty acids (Yang et al., 2005) |
| elo-1, elo-2 | PUFA elongases, such as ELOVI | Microsomal enzymes involved in very long chain FA elongation during increased β-oxidation (Oh et al., 1997; Jakobsson et al., 2005). |
| acdh-11 | Acyl-CoA dehydrogenase family member | Very long-chain specific acyl-CoA dehydrogenase (Ma et al., 2015). |
| lps-10, lps-14 | Lipase related protein | Proteins predicted to have hydrolase and lipid storage activity (Stein et al., 2001). |
also increases FOXO3 expression and the expression of genes related with autophagy (Nepal et al., 2015). However, it has also been documented that leptin administration inactivates FOXO3 in muscle cells (Sainz et al., 2009). This leptin-mediated FOXO3 inhibition might be tissue or condition-specific, as FOXM1, the downstream target and antagonist of FOXO3, and its targets are up-regulated in leptin-deficient mice (Davis et al., 2010) (Fig. 3B).

The levels of another key adipokine IL-6 are also regulated by FOXO3. IL-6 is increased after Foxo3 silencing or Sirt1-mediated FOXO3 inhibition (Wang et al., 2011 and Wang et al., 2013), suggesting that FOXO3 represses IL-6 expression. Moreover, IL-6 signalling pathway inhibition has been shown to be related to FOXO3 activation, up-regulating the pro-apoptotic FOXO3 target protein Bim in myeloma cancer cells (Shen et al., 2013; Essafi et al., 2005). In a positive feedback mechanism, IL-6 treatment also increases the expression of FOXM1 in pancreatic cancer cells (Xu et al., 2016). Conversely, experiments in macrophages from Foxm1−/− mice and FOXM1-deficient primary amnion cells showed increased levels of IL-6 (Lim et al., 2014; Balli et al., 2012). Another adipokine TNF-α decreases the expression of FOXO3 at the transcript level (Sente et al., 2016) and increases FOXM1 expression to promote cell proliferation and the resistance to apoptosis (Xia et al., 2012) (Fig. 3B).

5. Insulin signalling

High levels of FFAs in the circulation are involved in the pathogenesis of insulin resistance (Guilherme et al., 2008), which can in turn lead to compensatory hyperinsulinaemia (Wilcox, 2005). Insulin resistance with compensatory hyperinsulinaemia has been implicated in the aetiology of certain cancers, including colon, endometrial, possibly pancreatic and renal-cell cancers and breast cancer (Hsu et al., 2007; Wilcox, 2005). Hyperinsulinaemia is also linked to the more rapid and aggressive growth of several cancers, such as colorectal cancer, pancreatic carcinoma, liver cancer, postmenopausal breast cancer, and endometrial cancer (Ungefroren et al., 2015). This indirect effect of hyperinsulinaemia on carcinogenesis is mediated by the action of insulin (Ungefroren et al., 2015), which is known to signal through the PI3K-AKT axis and its downstream transcription network (Dormond et al., 2007; Wang et al., 2012; Gerber et al., 1998). Insulin triggers an intracellular pathway mediated by PI3K-AKT, allowing phosphorylation of FOXO factors which leads to its nuclear exclusion and, thereby suppression of FOXO-dependent transcription of target genes (Martins et al., 2016). In addition, AKT-dependent phosphorylation is also required as a prerequisite for ubiquitin-mediated degradation of FOXO3 (Ponugoti et al., 2012). On the other hand, FOXM1 stimulates β-cell extension and proliferation, and in doing so, enhances insulin secretion (Davis et al., 2010; Golson et al., 2015). Foxm1 mRNA levels positively correlated with fasting plasma insulin and C-peptide (Davis et al., 2010). As well as this, studies evaluating insulin secretion, as reflected by C-peptide levels, have identified a correlation between high plasma insulin concentrations and poor clinical outcome and survival in prostate cancer and insulin levels could be a predictive factor for higher colorectal neoplasia susceptibility (Ma et al., 2008; Chen et al., 2013).

Likewise, elevated plasma levels of insulin can interfere with the therapeutic effect of cytotoxic drugs. This is due to the ability of insulin to activate PI3K-AKT signalling, which can in turn induce anti-apoptosis and chemoresistance in tumour cells (Ungefroren et al., 2015). FOXO3 and FOXM1 have antagonistic functions in the regulation of their target genes and this axis can modulate chemotherapy resistance (Zhao and Lam, 2012; Bella et al., 2014). FOXM1 has also been demonstrated to play a crucial role in cancer chemotherapeutic drug resistance (Myatt and Lam, 2007; Zona et al., 2014; Zhao and Lam, 2012; Bella et al., 2014; Chen et al., 2010). Insulin-like growth factor (IGF)-1 also up-regulates the expression and activity of Foxm1 (Murillo-Cuesta et al., 2011; Aburto et al., 2012; Sanchez-Calderon et al., 2010 and Loddo

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et al., 2014), suggestion a positive feed forward circuit involving IGF-1, insulin, AKT and the FOXO3-FOXM1 axis. Consistently, in breast cancer cells, it has been demonstrated that therapeutic combinations that target IGF-1 receptor may reduce the invasive potential of cancer cells that are resistant to trastuzumab through mechanisms that depend in part on FOXM1 (Sanabria-Figueroa et al., 2015).

6. Conclusions and future directions

The relationship between FAs and cancer has been intensively explored in recent years and these studies have vastly increased our knowledge about this link. It is now clear that FA metabolism has a key role in the initiation, progression and drug resistance of cancer. Nevertheless, the molecular mechanism by which FA metabolism regulates cancer development is only beginning to unfold. Accumulating evidence has suggested a role for the FOXO3-FOXM1 signalling axis in linking FA metabolism to cancer initiation, progression and drug resistance. In consequence, targeting the FA metabolism-FOXO3-FOXM1 signalling network could be of therapeutic interest. A promising area for future exploration will be the use of existing or novel lipid metabolism drugs to treat cancer. To date, many drugs associated with obesity such as lipid-lowering (statins) or antidiabetic drugs (metformin) have been used in cancer treatment with good effects (Brown, 2007; De Queiroz et al., 2015; Wolfe et al., 2015), whereas metformin is also able to inhibit the expression of FOXM1 (Wang et al., 2014). Collectively, these observations advocate further that targeting lipid metabolism in conjunction with the FOXO3-FOXM1 axis maybe a viable strategy for tackling cancer development, progression and drug resistance. In consequence, a better understanding of the FOXO3-FOXM1 axis and its relationship with FA metabolism and cancer could provide insights into improved cancer treatments and for overcoming drug resistance. Furthermore, these FAs can potentially be important and less invasive markers for early cancer diagnosis and prognosis, for designing personalised therapeutic regimes, and for monitoring treatments.

Conflict of interest statement

The authors declare that they have no competing interests.

Disclosure statement

The authors have nothing to disclose.

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References

Abedi, E., Sahari, M.A., 2014. Long-chain polyunsaturated fatty acid sources and evaluation of their nutritional and functional properties. Food Sci. Nutr. 2, 443–463.

Aburto, M.R., Magarinus, M., Leon, Y., Varela-Nieto, I., Sanchez-Calderon, H., 2012. AKT signaling mediates IGF-I survival actions on otc neural progenitors. PLoS One 7, e30790.

Amir, F.R., Steenkiste, E.M., Ratnapan, R., Chen, S.W., McClendon, T.B., Kostka, D., Yanowitz, J., Olsen, C.P., Ghazi, A., 2016. DAF-16 and TCER-1 facilitate adaptation to germline loss by restoring lipid homeostasis and repressing reproductive physiology in C. elegans. PLoS Genet. 12, e1006378.

Acaro, A., Guerreiro, A.S., 2007. The phosphoinositide 3-kinase pathway in human cancer: genetic alterations and therapeutic implications. Curr. Genomics 8, 271–286.

Balaban, S., Lee, L.S., Schreuder, M., Hoy, A.J., 2015. Obesity and cancer progression: is there a role of fatty acid metabolism? Biomed. Res. Int. 2015, 274585.

Balli, D., Ren, X., Chou, F.S., Cross, E., Zhang, Y., Kalinchencov, V.V., Kalin, T.V., 2012. FOXm1 transcription factor is required for macrophage migration during lung inflammation and tumor formation. Oncogene 31, 3875–3885.

Baron, A., Migita, T., Dang, C., Loda, M., 2004. Fatty acid synthase: a metabolic oncogene in prostate cancer? J. Cell Biochem. 91, 47–53.

Bella, L., Zona, S., Nestal de Moraes, G., Lam, E.W., 2014. FOXM1: a key oncofetal transcription factor in health and disease. Semin. Cancer Biol. 29, 32–49.

Bodur, C., Karakas, B., Timucin, A.C., Teiz, T., Basaga, H., 2016. AMP-activated protein kinase alpha2 3-bromopyruvate-induced energy depletion to apoptosis via activation of FOXO3a and upregulation of proapoptotic Bcl-2 proteins. Mol. Carcinog. 55, 1584–1597.

Borradaile, N.M., Han, X., Hark, J.D., Gale, S.E., Ors, D.S., Schaffer, J.E., 2016. Disruption of endoplasmic reticulum structure and integrity in lipotic cell death. J. Lipid Res. 47, 2775–2788.

Brown, A.J., 2007. Cholesterol, Status and Cancer, pp. 135–141.

Bultot, L., Guigas, B., Von Wilmowsk-Moellendorff, A., Maisin, L., Vertommen, D., Hussain, N., Beuillens, M., Guinovart, J.J., Foret, M., Viollet, B., Bakamto, K., Hua, Q., Takeda, M., NA, 2012. AMP-Activated protein kinase phosphorylates and inactivates glycogen synthase. Biochem. J. 443, 193–203.

Calle, E.E., Kaaks, R., 2004. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat. Rev. Cancer 4, 579–591.

Castaño, C., Gerhart-Hines, Z., Feige, J.N., Lagouge, M., Ngoieira, E., Milne, J.C., Elliott, P.J., Puiscever, P., Auwero, K., 2009. AMPK regulates energy expenditure by modulating NAD+ metabolism and SIRT1 activity. Nature 458, 1056–1060.

Carling, D., 2005. AMP-activated protein kinase: balancing the scales. Biochimie 87, 81–97.

Carracedo, A., Cantley, L.C., Ponder, P.F., 2013. Cancer metabolism: fatty acid oxidation in the limelight. Nat. Rev. Cancer 13, 227–232.

Chen, J., 2011. Multiple Signal Pathways in Obesity-associated Cancer, pp. 201-2070.

Chen, J., Gomes, A.R., Monteiro, L.J., Xiong, S.Y., Wu, L.H., Ng, T.T., Karadedou, C.T., Millour, J., Ip, Y.C., Cheung, Y.N., Sunters, A., Chan, K.Y., Lam, E.W., Khoo, R.S., 2010. Constitutively nuclear FOXO3a localization predicts poor survival and correlates with Akt phosphorylation in breast cancer. PLoS One 5, e12293.

Chen, L., Li, P., Wang, R., Li, P., Luo, L., Yang, B., Wang, H., Chen, M., 2013. Circulating C-peptide level is a predictive factor for colorectal neoplasia: evidence from the meta-analysis of prospective studies. Cancer Causes Control 24, 1837–1847.

Chirala, S.S., Chang, H., Matzuk, M., Abu-Ebeigha, L., Luo, J., Mahon, K., Finegold, M., 2015. FOXM1: a key oncofetal transcription factor in health and disease. Semin. Cancer Biol. 29, 32–49.

Chirala, S.S., Chang, H., Matzuk, M., Abu-Ebeigha, L., Luo, J., Mahon, K., Finegold, M., 2015. FOXM1: a key oncofetal transcription factor in health and disease. Semin. Cancer Biol. 29, 32–49.

Dormond, O., Madsen, J.C., Briscoe, D.M., 2007. The effects of mTOR-Akt interactions on anti-apoptotic signaling in vascular endothelial cells. J. Biol. Chem. 282, 23667–23679.

Drevon, C.A., 2005. Fatty acids and expression of adipokines. Biochim. Biophys. Acta 1740, 287–292.

Durian, D.J., Smith, J.K., Horie, M.A., Egbejimi, O., Cuihbert, K.D., Zaha, V.G., Dyck, J.R., Abel, E.D., Young, M.E., 2006. Distinct transcriptional regulation of...
long-chain acyl-CoA synthetase isoforms and cytosolic thioesterase 1 in the rodent heart by fatty acids and insulin. Am. J. Physiol. Heart Circ. Physiol. 290, 1228–1235, 2006.

Eaton, S., Bartlett, K., Quaintance, V., Raber, J., Noack, K., 2016. Carnitine palmitoyl transferase I and the control of beta-oxidation in heart mitochondria. Biochem. Biophys. Res. Com- mun. 472, 1052–1058.

Eaton, S., Barlow, R.W., Hassen, Y.A., Soeiro, I., Mufti, G.J., Thomas, N.S., Myatt, S.S., Lam, E.W.F., 2007. The emerging roles of forkhead box (Fox) proteins in vertebrates and developmental and nutritional regulation in mammals. Annu. Rev. Physiol. 69, 45–74.

Eaton, S., Bartlett, K., Raber, J., Noack, K., 2016. Carnitine palmitoyl transferase I and the control of beta-oxidation in heart mitochondria. Biochem. Biophys. Res. Com- mun. 472, 1052–1058.

Eaton, S., Bartlett, K., Quaintance, V., Raber, J., Noack, K., 2016. Carnitine palmitoyl transferase I and the control of beta-oxidation in heart mitochondria. Biochem. Biophys. Res. Com- mun. 472, 1052–1058.

Eaton, S., Bartlett, K., Quaintance, V., Raber, J., Noack, K., 2016. Carnitine palmitoyl transferase I and the control of beta-oxidation in heart mitochondria. Biochem. Biophys. Res. Com- mun. 472, 1052–1058.

Eaton, S., Bartlett, K., Quaintance, V., Raber, J., Noack, K., 2016. Carnitine palmitoyl transferase I and the control of beta-oxidation in heart mitochondria. Biochem. Biophys. Res. Com- mun. 472, 1052–1058.
enhances intestinal fatty acid oxidation and reduces energy intake in rats. J Lipid Res. 54, 1369–1384.

Seite, G., van Berendonk, J. M., Fransen, E., Vriots, C. J., Hoymans, V. Y. 2016. Tu-
mer necrosis factor-alpha impairs adiponectin signaling, mitochondrial biogenesis, and myogenesis in primary human myotubes cultures. Am. J. Physiol. Heart Circ. Physiol. 310, H1164–H1175.

Serpak, S., Polido, F., Carvalho, T., Torre, C., Gonçalves, L.C., Casalou, L., Lamosa, P., Rodrigues, M., Zhu, Z., Lam, E.W.F., Dias, S. 2010. Butyrate-rich colonic micro-
environment is a relevant selection factor for metabolically adapted tumor cells. J. Biol. Chem. 285, 39211–39223.

Shadeford, D.B., Shaw, R.K., 2015. The LKB1-AMPK pathway: metabolism and growth control in tumour suppression. Nat. Rev. Cancer 9, 563–575.

Shen, J.K., Du, H.P., Ma, Q., Yang, M., Wang, Y.G., Jin, J. 2013. 4-Chlorobenzoyl-
berbamine, a novel berbamine derivative, induces apoptosis in multiple myeloma cell lines. J. Cell. Physiol. 228, 2157–2166.

Shin, H.J., Kim, H., Oh, S., Lee, J.G., Kee, M., Ko, H.J., Kweon, M.N., Won, K.J., Baek, S.H., 2016. AMPK-SK2-CARM1 signalling cascade in transcriptional regulation of autophagy. Nature 534, 553–557.

Shrestha, A.R., Parhi, A. 2016. Global adiponectin attenuates LPS-induced reactive oxygen species production in HepG2 cells via FoxO3A and HO-1 signaling. Life Sci. 148, 71–79.

Shrestha, A., Nepal, S., Chang, J.H., Kim, S.H., Jeong, G.S., Jeong, C.H., Park, G.H., Jung, S., Lim, J., Cho, E., Lee, S., Park, P.H. 2016. Critical role of AMPK/ FoxO3A Axis in global adiponectin-induced cell cycle arrest and apoptosis in cancer cells. J. Cell. Physiol. 231, 2575–2585.

St-Onge, M.P., Bourque, C., Jones, P.I., Ross, R., Parsons, W.E., 2003. Medium- versus long-chain triglycerides for 27 days increases fat oxidation and energy expe-
diture without resulting in changes in body composition in overweight women. Horm. Metab. Res. 35, 213–216.

Stein, L., Sternberg, P., Durbin, R., Thierry-Mieg, J., Spieth, J., 2001. WormBase: network access to the genome and biology of Caenorhabditis elegans. Nucleic Acids Res. 29, 82–86.

Stern, J.H., Rutkowski, J.M., Scheer, P.E., 2016. Adiponectin, leptin, and fatty acids in the maintenance of metabolic homeostasis through adipose tissue crosstalk. Cell Metab. 23, 770–784.

Stone, S.J., Myers, H.M., Woods, S.M., Brown, K.E., Feingold, K.R., Elias, P.M., Farese Jr., J.L., 2004. Lipoprotein and skin barrier abnormalities in DAGAT2-
deficient mice. J. Biol. Chem. 279, 11767–11776.

Stryjecki, C., Mutch, D.M., 2011. Fatty acid gene interactions, adipokines and obesity. Eur. J. Clin. Nutr. 65, 285–297.

Tavazzi, E., Melo, M., Camusso-Spiegler, J.M., Soares, P., Sobrinho-Simoes, M., 2016. ENDORCINE TUMOURS: genetic predictors of thyroid cancer outcome. Eur. Endocrinol. 174, R117–R126.

Telford, E.A., Moynihan, L.M., Markham, A.F., Lench, N.J., 1999. Isolation and char-
acterisation of a cDNA encoding the precursor for a novel member of the acyl-
coA dehydrogenase family. Biochem. Biophys. Acta 1446, 371–376.

Tirado-Velez, J.M., Jomauy, I., Saez-Benito, A., Cozar-Castellano, I., Perdomo, G., 2012. Inhibition of fatty acid metabolism reduces human myeloma cells pro-
liferation. PLoS One 7, e46484.

Tisoli, M., Robertson, G., 2013. Cancer Cachexia: Malignant Inflammation, Tumor-
nes, and Metabolic Mayhem. pp. 174–183.

Tisoli, M., Swarbrick, M.M., Robertson, G.R., 2015. Lipolysis and thermogenic differ-
cence of adipose tissue-cachexia. Semin. Cell Dev. Biol. http://dx.doi.org/10.1016/j.semcdb.2015.10.039.

Ungefroren, H., Gieseler, F., Lenger, H., 2015. Obesity and cancer. Horm. Mol. Biol. Clin. Investig. 21, 5–11.

Valenzuela, D.A., Benito, M., Llovera, M., Lorente, M. 2005. The Brown Adipose Cell: A Model for Understanding the Molecular Mechanisms of Insulin Resistance, pp. 59–73.

Wang, J., Yu, L., Schmidt, R.E., Su, C., Huang, X., Gould, K., Cao, G., 2005. Charac-
terization of HSCDS, a human stearyl-CoA desaturase unique to pri-
mates. Biochem. Biophys. Res. Commun. 322, 735–742.

Wang, S.T., Chang, C.C., Yen, M.C., Tu, F.C., Chi, C.L., Peng, Y.T., Chen, D.Y., Lan, J.L., Lin, C.C., 2011. RNA interference-mediated silencing of FoxO3 antigen-
ates cells as a strategy for the enhancement of DNA vaccine potency. Gene Ther. 18, 372–383.

Wang, Y., Hua, S., Tian, W., Zhang, L., Zhao, J., Zhang, H., Wang, X., Yue, F., 2012. Mitogenic and anti-apoptotic effects of insulin in endometrial cancer are mediated by PI3K/AKT and MAPK-dependent. Gynecol. Oncol. 125, 734–741.

Wang, F.M., Sarmask, A., Hiruma, Y., Sun, Q., Sammutt, B., Widdle, J.J., Rodman, G.D., Galson, D.L., 2013. Measles virus nucleocapsid protein, a key mediator of the iNOS-IL-6 expression via down-regulation of signal transducer and activator of transcription-3. J. Virol. 87, 7338–7348.

Wang, Y., Yao, B., Wang, J.L., Zhang, M., Fu, S., Gao, H., Peng, R., Zhang, L., Tang, J., 2014. Increased FoxM1 expression is a target for suppression of ER in prostate cancer. Int. J. Oncol. 44, 1521–1527.

Wills, R.A., 2014. Adipocytes. Cold Spring Harb. Lab. Press.

Wolfe, A.R., Debeb, B.G., Lacerda, L., Larson, R., Bambhroliya, A., Huang, X., Bertucci, F., Finetti, P., Birnbaum, D., Van Laere, S., Diagaradjan, P., Fruhbeck, G., 2009. Leptin administration favors muscle mass accretion by stimulating muscle protein synthesis and inhibiting proteolysis. J. Clin. Endocrinol. Metab. 94, 3838–3843.

Wolfe, A.R., Debeb, B.G., Lacerda, L., Larson, R., Bambhroliya, A., Huang, X., Bertucci, F., Finetti, P., Birnbaum, D., Van Laere, S., Diagaradjan, P., Fruhbeck, G., 2009. Leptin administration favors muscle mass accretion by stimulating muscle protein synthesis and inhibiting proteolysis. J. Clin. Endocrinol. Metab. 94, 3838–3843.
Woodworth-Hobbs, M.E., Hudson, M.B., Rahnert, J.A., Zheng, B., Franch, H.A., Price, S.R., 2014. Docosahexaenoic acid prevents palmitate-induced activation of proteolytic systems in C2C12 myotubes. J. Nutr. Biochem. 25, 868–874.

World Health Organisation, 2014. Risk Factors, Overweight and Obesity, Global Health Observatory (GHO) Data (Accessed 24 July 2016), From: http://www.who.int/gho/ncd/risk_factors/overweight/en/.

Wu, L.E., Samocha-Bonet, D., Whitworth, P.T., Fazakerley, D.J., Turner, N., Biden, T.J., James, D.E., Cantley, J., 2014. Identification of fatty acid binding protein 4 as an adipokine that regulates insulin secretion during obesity. Mol. Metab. 3, 462–473.

Xia, L., Mo, P., Huang, W., Zhang, L., Wang, Y., Zhu, H., Tian, D., Liu, J., Chen, Z., Zhang, Y., Chen, Z., Hu, H., Fan, D., Nie, Y., Wu, K., 2012. The TNF-alpha/ROS/HIF-1-induced upregulation of FoxMi expression promotes HCC proliferation and resistance to apoptosis. Carcinogenesis 33, 2250–2259.

Xu, L., Kitade, H., Ni, Y., Ota, T., 2015. Roles of chemokines and chemokine receptors in obesity-associated insulin resistance and nonalcoholic fatty liver disease. Biomolecules 5, 1563–1579.

Xu, Q., Fu, R., Yin, G., Liu, X., Liu, Y., Xiang, M., 2016. Microarray-based gene expression profiling reveals genes and pathways involved in the oncogenic function of REG3A on pancreatic cancer cells. Gene 578, 263–273.

Yang, S.Y., He, X.Y., Schulz, H., 2005. 3-Hydroxyacyl-CoA dehydrogenase and short chain 3-hydroxyacyl-CoA dehydrogenase in human health and disease. FEBS J. 272, 4874–4883.

Yates, D.W., Garland, P.B., 1970. Carnitine palmitoyltransferase activities (EC 2.3.1.-) of rat liver mitochondria. Biochem. J. 119, 547–552.

Yeh, C.S., Wang, J.Y., Cheng, T.L., Juan, C.H., Wu, C.H., Lin, S.R., 2006. Fatty acid metabolism pathway play an important role in carcinogenesis of human colorectal cancers by Microarray-Bioinformatics analysis. Cancer Lett. 233, 297–308.

Yu, S.Y., Chan, D.W., Liu, V.W., Ngaan, H.Y., 2009. Inhibition of cervical cancer cell growth through activation of upstream kinases of AMP-activated protein kinase. Tumour Biol. 30, 80–85.

Yung, M.M.H., Chan, D.W., Liu, V.W.S., Yao, K.-M., Ngaan, H.Y.-S, 2013. Activation of AMPK inhibits cervical cancer cell growth through AKT/FOXO3a/FOXM1 signaling cascade. BMC cancer 13, 327–327.

Zaidi, N., Lupien, L., Kuenmerle, N.R., Kinlaw, W.B., Swinnen, J.V., Smans, K., 2014. Lipogenesis and lipolysis: the pathways exploited by the cancer cells to acquire fatty acids. Prog. Lipid Res. 52, 585–589.

Zhang, S.X., Sanders, E., Friesler, S.J., Wang, J.J., 2014. Endoplasmic reticulum stress and the unfolded protein responses in retinal degeneration. Exp. Eye Res. 125, 30–40.

Zhao, F., Lam, E.W.F., 2012. Role of the forkhead transcription factor FOXO-FOXM1 axis in cancer and drug resistance. Front. Med. China 6, 376–380.

Zhou, W., Simpson, P.J., McFadden, J.M., Townsend, C.A., Medghalchi, S.M., Vadlamudi, A., Finn, M.L., Ronnert, C.V., Kuhajda, F.P., 2003. Fatty Acid Synthase Inhibition Triggers Apoptosis during S Phase in Human Cancer Cells. Cancer Res. 62, 7330–7337.

Zhou, W., Tu, Y., Simpson, P.J., Kuhajda, F.P., 2009. Malonyl-CoA decarboxylase inhibition is selectively cytotoxic to human breast cancer cells. Oncogene 28, 2979–2987.

Zona, S., Bella, L., Burton, M.J., Nestal de Moraes, G., Lam, E.W.F., 2014. FOXM1: an Emerging Master Regulator of DNA Damage Response and Genotoxic Agent Resistance, pp. 1316–1322.