REVIEW

Metabolic reprogramming in type 2 diabetes and the development of breast cancer

Sheree D Martin and Sean L McGee

Metabolic Reprogramming Laboratory, Metabolic Research Unit, School of Medicine and Centre for Molecular and Medical Research, Deakin University, Geelong, Australia

Correspondence should be addressed to S L McGee: sean.mcgee@deakin.edu.au

Abstract

A wealth of epidemiological data has found that patients with type 2 diabetes have a greater risk of developing breast cancer. The molecular mechanisms underpinning this relationship are yet to be elucidated; however, this review examines the available evidence suggesting that the metabolic abnormalities observed in type 2 diabetes can predispose to the development of breast cancer. Alterations in substrate availability and the hormonal milieu, particularly hyperinsulinemia, not only create a favorable metabolic environment for tumorigenesis, but also induce metabolic reprogramming events that are required for the transformation of breast cancer cells. In addition, the dysfunction and hypoxia of adipose tissue surrounding the breast cancer niche is another putative link that will be discussed. Finally, the mechanisms by which breast cancer cells evade checkpoints associated with nutrient overload will be examined. Experimentally validating these potential links will be important for prediction and treatment of breast cancer in patients with type 2 diabetes.

Key Words

- ▶ type 2 diabetes
- ▶ breast cancer
- ▶ cancer metabolism
- ▶ hyperinsulinemia
- ▶ acetylation

Journal of Endocrinology
(2018) **237**, R35–R46

Introduction

Chronic diseases driven by nutrient excess, or energy overconsumption, are emerging as one of the greatest threats to human health in the 21st century. The resulting obesity is driving a chronic disease epidemic that includes type 2 diabetes, cardiovascular disease and cancer (Eyre *et al.* 2004). While common molecular mechanisms are only just beginning to emerge, there has been a wealth of epidemiological data describing the overlap between many of the diseases. Among this disease cluster, numerous epidemiological studies have shown that patients with type 2 diabetes are at a greater risk of developing breast cancer (Xue & Michels 2007). The incidence of type 2 diabetes has been steadily increasing for decades and currently affects approximately 10% of the population in most developed nations (Zimmet *et al.* 2016). In addition, many developing nations are quickly converging on equivalent incidence

rates as calorie-dense and inexpensive foods are becoming more readily available (Zimmet *et al.* 2016). Similarly, the rates of breast cancer have been increasing over this same period (Devesa *et al.* 1995). Interestingly, the link between type 2 diabetes and breast cancer appears to be most evident in post-menopausal women and remains evident when controlling for the confounding effects of obesity (Xue & Michels 2007). This suggests important interactions between key hormones and metabolic alterations in type 2 diabetes that predispose to the development of breast cancer. Numerous studies have examined the mechanistic underpinnings of this epidemiological link. A unifying theme developing from this research is that alterations in whole body and cellular metabolism that occur in type 2 diabetes provide a favorable metabolic environment and the pathogenic stimuli for the development of breast cancer.

This review will describe the major metabolic alterations in type 2 diabetes and provide an overview of how changes in cellular metabolism are harnessed by cancer cells to drive aberrant growth and proliferation. We will specifically examine the mechanisms by which type 2 diabetes might promote the development of breast cancer, with an emphasis on the role of hyperinsulinemia in this process. Finally, we will speculate on putative mechanisms by which breast cancer cells evade checkpoints typically engaged in high nutrient environments, such as those seen in type 2 diabetes, so that proliferation and survival are not compromised.

Metabolic alterations in type 2 diabetes

The diagnosis of type 2 diabetes is made on clinical criteria such as fasting hyperglycemia and glucose intolerance following ingestion of a glucose bolus (Bansal 2015). However, the pathogenesis of type 2 diabetes manifests for years before symptoms become apparent in patients. The development of the disease is typically driven by resistance to the actions of insulin in key metabolic tissues, such as the liver, skeletal muscle and adipose tissue, which has numerous deleterious effects on systemic metabolism (Samuel & Shulman 2012). With respect to glucose metabolism, insulin resistance impairs the suppression of hepatic glucose output by failing to adequately inhibit glycogenolysis. Simultaneously, glucose uptake and disposal by skeletal muscle and adipose tissue is impaired. Therefore, insulin resistance in these tissues has a net effect of inducing systemic hyperglycemia (Samuel & Shulman 2012). However, insulin also has important roles in regulating the metabolism of substrates beyond glucose. For example, insulin increases fatty acid uptake and storage in most insulin-responsive tissues (Goldberg *et al.* 2009). Furthermore, insulin enhances amino acid uptake and drives protein synthesis (Bonadonna *et al.* 1993). There is an emerging debate as to whether the insulin resistance observed in type 2 diabetes affects all insulin responsive processes or whether it is specific for the effects of insulin on carbohydrate metabolism (Brown & Goldstein 2008, Konner & Bruning 2012). For example, there is evidence in type 2 diabetes that the ability of insulin to promote hepatic lipogenesis is maintained, despite impairments in insulin-stimulated glycogen synthesis (Shimomura *et al.* 2000). The nature of this selective insulin resistance across all key metabolic tissues in patients has yet to be completely resolved. Nonetheless, insulin resistance results in systemic hyperglycemia, elevated circulating free fatty acids and

dyslipidemia. Therefore, the insulin resistance that ultimately drives the development of type 2 diabetes results in profound metabolic alterations that underpin many of the complications that develop because of the disease.

To overcome peripheral insulin resistance, pancreatic beta cells secrete additional insulin in an attempt to maintain euglycemia. This hyper-secretion of insulin places stress on beta cells that over time results in β -cell failure and death (Prentki & Nolan 2006). However, extended periods of insulin hyper-secretion also have important metabolic consequences. In the absence of impaired insulin action on lipid metabolism, as is thought to occur in selective insulin resistance, elevated insulin secretion can result in enhanced fatty acid uptake, lipogenesis and accumulation of lipid in metabolic tissues such as skeletal muscle and the liver (Ertunc & Hotamisligil 2016). This 'lipotoxicity' is thought to promote a chronic low-grade inflammatory state that can further impair normal metabolic processes (Ertunc & Hotamisligil 2016). Similarly, adipose tissue markedly expands under conditions of nutrient excess, which impairs its normal function. For example, the adipose vascular system is severely challenged by the rapid expansion in adipose tissue mass and can fail to adequately remodel, resulting in adipose tissue hypoxia (Ye *et al.* 2007). The lipid storage capacity of individual adipocytes can also be challenged, which similar to lipotoxicity in other tissues, initiates a cellular inflammatory response and in some cases, results in impaired cell viability and cell death (Guilherme *et al.* 2008). This initiates macrophage infiltration, further contributing to the inflammatory status of the surrounding adipose tissue (Guilherme *et al.* 2008). These challenges to normal adipocyte function also result in altered release of signaling molecules, termed adipokines, which can act in an autocrine, paracrine and endocrine fashion, increasing adipocyte lipolysis and inhibiting insulin action (Guilherme *et al.* 2008). Although insulin resistance is a major factor in the development of type 2 diabetes, the resulting metabolic milieu alters many other hormones and signaling molecules that can have important metabolic consequences. These include elevated glucagon (Brown *et al.* 2008), leptin resistance (Wauters *et al.* 2003) and elevated sympathetic tone (Huggett *et al.* 2003), to name just a few. These changes in circulating hormones and substrate availability can have potent effects on cellular metabolic reprogramming. Furthermore, systemic hyperglycemia, excessive circulating fatty acids and dyslipidemia, which are characteristic of type 2 diabetes can in itself also create a favorable metabolic environment for the development of certain cancers.

The following section will provide a broad overview of the major metabolic alterations observed in cancer cells before specifically examining the metabolic reprogramming events that occur in type 2 diabetes that might predispose to the development of breast cancer, with a view to provide biological mechanisms that potentially explain the epidemiological overlap between these diseases.

Metabolic reprogramming in cancer

Metabolic reprogramming is fundamental for the development, rapid proliferation and survival of cancer cells (DeBerardinis & Chandel 2016). Central to tumorigenesis is uncontrolled proliferation, which necessitates an increased production of macromolecules that contribute to biomass to support the generation of new cells. This includes new proteins, lipids for membrane synthesis and nucleotides for DNA and RNA synthesis (Hanahan & Weinberg 2011). Metabolism must also be reprogrammed to support the energetic needs of these biosynthetic processes. Furthermore, metabolic reprogramming is necessary to allow cancer cells to overcome growth inhibition checkpoints and apoptotic signaling as well as fueling invasion and metastasis (DeBerardinis & Chandel 2016).

Increased aerobic glycolysis irrespective of oxygen availability, also known as the 'Warburg effect', is a common adaption in cancer cells (Warburg 1956). Warburg also hypothesized that this increase in glycolysis was a consequence of impairments in oxidative respiration. However, it is now accepted that mitochondrial function is intact in most cancer cells and remains the major source of ATP for the cancer cells (Weinberg *et al.* 2010, Fan *et al.* 2013, Martinez-Reyes *et al.* 2016). However, beyond its role in energy production, increased glycolysis can supply metabolite intermediates for metabolic pathways that diverge from glycolysis, which are involved in the synthesis of the macromolecules necessary for proliferation (Locasale *et al.* 2011). The product of the first step in glycolysis, glucose-6-phosphate (G6P), can also enter the pentose phosphate pathway. The oxidative branch of this pathway generates two NADPH molecules, which provide the reductive power required for the generation of new fatty acids through *de novo* lipogenesis (Patra & Hay 2014). As will be discussed later, this NADPH also has important implications for cellular redox balance. The non-oxidative arm of the pentose phosphate pathway

generates ribose-5-phosphate, which is used to produce new nucleotides for DNA and RNA synthesis (Patra & Hay 2014). Similarly, dihydroxyacetone phosphate, an intermediate metabolite of glycolysis, can be reduced to form glycerol-3-phosphate by the enzyme glycerol-3-phosphate dehydrogenase, which can be used to provide glycerol for the synthesis of new glyceride lipids that are essential components of membrane lipids and for the storage of fatty acids such as triglycerides (Santos & Schulze 2012). The biosynthetic functions associated with glycolysis contribute to the elevated flux of this pathway in many cancer cells (Christofk *et al.* 2008, Hitosugi *et al.* 2012, Slavov *et al.* 2014).

A consequence of efflux of intermediates out of the glycolytic pathway and increased lactate production is that glucose flux into the TCA cycle is reduced in a number of cancers (Koukourakis *et al.* 2005, McFate *et al.* 2008). However, glutamine is an important substrate for anaplerosis of the TCA cycle, via its conversion to glutamate and then α -ketoglutarate (Owen *et al.* 2002). The uptake of glutamine and subsequent conversion to glutamate is also required for the production of nonessential amino acids and for the synthesis of glutathione for the glutathione system that buffers reactive oxygen species (Jin *et al.* 2015). It is also used to supply carbon and nitrogen for biosynthesis reactions in protein and nucleotide synthesis as well as playing a potential role in the uptake of essential amino acids (Vander Heiden *et al.* 2011). Another key metabolic feature of cancer cells is an increased rate of fatty acid synthesis through *de novo* lipogenesis, which plays an important role in maintaining their rapid proliferation (Daniels *et al.* 2014, Lin *et al.* 2016). Fatty acids are synthesized from cytosolic acetyl-CoA and NADPH, typically derived from glucose metabolism and to a lesser extent amino acid metabolism and play an essential role in the formation of new lipid membranes (Santos & Schulze 2012). Furthermore, fatty acids can have important roles in controlling cancer cell signaling through lipidation reactions (Liu *et al.* 2010). Newly synthesized fatty acids can also be stored as triglycerides for later use, and it is emerging that certain cancer cells can rely heavily on fatty acid oxidation for ATP generation (Pike *et al.* 2011). Cancer cells synthesize fatty acids even when exogenous fatty acids are available, and this often involves transcriptional reprogramming of this pathway (Zaidi *et al.* 2013). As well as *de novo* synthesis, fatty acids can be taken up from the extracellular environment for use in these same processes, which appears to become more prominent

in situations of nutrient deprivation (DeBerardinis & Chandel 2016).

The metabolic reprogramming of cancer cells is a highly dynamic process, which allows these cells to rapidly adapt to changes in substrate availability and their changing tumor microenvironment (Vander Heiden & DeBerardinis 2017). Indeed, in the face of oxygen or nutrient deprivation, cancer cells reprogram metabolism such that viability and growth are minimally impacted (DeBerardinis & Chandel 2016). Furthermore, recent evidence shows that cancer cells are able to signal to adjacent cells and induce autophagy in order to obtain adequate nutrient supply (Martinez-Outschoorn *et al.* 2011a). While these metabolic adaptive responses can be linked to the ability of cancer cells to gain resistance to certain therapies, identification of specific metabolic vulnerabilities is also viewed as a potential way of identifying new opportunities for cancer treatments (Luengo *et al.* 2017). Nonetheless, it is clear that metabolic reprogramming is essential for cancer development.

Linking metabolic reprogramming events in type 2 diabetes to breast cancer

There are numerous epidemiological studies describing a link between type 2 diabetes and breast cancer. These studies suggest that in patients with type 2 diabetes, the risk of developing breast cancer is 1.1–2.15 times greater than that in healthy subjects (Muck *et al.* 1975, Talamini *et al.* 1997, Resta *et al.* 2004, Lipscombe *et al.* 2006). The following section will describe cellular metabolic reprogramming events that potentially link type 2 diabetes and breast cancer and are summarized in Fig. 1. The prevailing consensus within the field is that while these metabolic reprogramming events might not be the initiating stimulus for breast cancer cell transformation in isolation, they create the metabolic phenotype that is required for high proliferative rates and resistance to cell death and are therefore essential for the transformation process (Vander Heiden & DeBerardinis 2017). This review will discuss how the metabolic milieu in type 2 diabetes

Figure 1

Putative metabolic reprogramming mechanisms in type 2 diabetes and breast cancer. The insulin resistance and systemic inflammation associated with type 2 diabetes induces hyperglycemia, dyslipidemia and alters circulating amino acids, increasing glucose, fatty acid and glutamine availability for utilization by breast cancer cells. The hyperinsulinemia that attempts to overcome insulin resistance can reprogram breast cancer metabolism in a number of ways. Insulin increases flux through glycolysis and the pentose phosphate pathway, which is not only linked to energy production, but also biosynthetic processes such as synthesis of lipids for membranes and nucleotides, which provide the biomass for cell proliferation. Insulin also increases the uptake of glutamine and fatty acids to be used to generate energy or biomass, as well as the synthesis of new fatty acids. Adipose tissue hypoxia can reprogram breast cancer glucose metabolism to favor glycolysis and also increase lactate availability, which can be oxidized by breast cancer cells.

creates a favorable environment and microenvironment to support these same functions. In this context, a key consideration is that adipocytes are the predominant cell type in the niche in which breast cancer cells develop and metabolic dysfunction of adipocytes in type 2 diabetes can affect the metabolism and function of surrounding cells (Hoy *et al.* 2017). Extensive genetic studies have identified that breast cancer is a heterogeneous disease, made up of many distinct subtypes and classifications that in reality likely reflect distinct cancers (Dai *et al.* 2015). An overview of the major breast cancer classifications is beyond the scope of this review (please refer to Malhotra *et al.* 2010, Dai *et al.* 2015 for comprehensive reviews on this topic); however, it should be noted that distinct metabolic phenotypes have been observed in different breast cancer subtypes (Ogrodzinski *et al.* 2017). Therefore, it is intuitive that the mechanism(s) by which type 2 diabetes might influence the development of breast cancer will differ markedly for different breast cancers. Similarly, distinct metabolic heterogeneity exists within different regions of a tumor, which depends on substrate and oxygen availability and penetration into the tumor and is in-turn highly dynamic (Hensley *et al.* 2016). Therefore, a single tumor might, over time, engage a number of the putative mechanisms that will be discussed in the following sections. For the purposes of this review, we will emphasize how alterations in metabolism of the major macronutrient substrates that occur in type 2 diabetes can influence primary breast cancer cell and tumor biology. Although it is recognized that metabolic reprogramming also plays a critical role in breast cancer cell migration and metastasis, this will not be a major focus of this review.

Glucose metabolism

The hyperglycemia that occurs in type 2 diabetes can have a profound effect on cancer cell biology by providing greater glucose availability to drive cancer proliferation and by inducing metabolic reprogramming that favors a transformed phenotype. Although glucose uptake and disposal in most major metabolic tissues are an insulin-dependent process, glucose uptake and disposal in cancer cells, including breast cancer cells (Yang *et al.* 2007), are largely insulin independent. Insulin-mediated glucose uptake into skeletal muscle and adipose tissue is facilitated by the glucose transporter GLUT4, which following activation of the canonical insulin signaling pathway, translocates from intracellular sites to the plasma membrane, where it can participate in glucose transport (Stockli *et al.* 2011). In contrast, GLUT1 is overexpressed in

most breast cancer types (Macheda *et al.* 2005), although there is evidence of breast cancer classification-specific expression of different GLUTs (Hussein *et al.* 2011). The localization of GLUT1 at the plasma membrane is relatively constitutive and is critical for breast cancer function. From studies of the MMTV-NIC mouse mammary tumor model crossed with GLUT1 deficient mice, it appears that GLUT1 is particularly important for the initiation of tumorigenesis (Wellberg *et al.* 2016), as well as maintaining normal tumor growth (Young *et al.* 2011). Importantly, GLUT1 is a high-affinity glucose transporter, with a K_m of 1–2 mM (Gulve *et al.* 1994). This means that at the systemic glucose concentrations typically observed in type 2 diabetes patients, the GLUT1 transporter is highly active and glucose transport is non-limiting under these conditions. Indeed, glucose availability represented by high fasting blood glucose is an independent risk factor for death in breast cancer patients (Minicozzi *et al.* 2013). The diabetic environment increases GLUT1 expression levels in a number of tissues (Gaither *et al.* 1999), which appears to be independent of systemic glucose levels (Simmons *et al.* 1993b), but could be related to higher insulin and insulin-like growth factor 1 (IGF1) levels (Simmons *et al.* 1993a).

High levels of glucose transport in breast cancer cells are also coupled to elevated rates of both glycolysis and flux through the pentose phosphate pathway (Yang *et al.* 2016). In addition to elevated glucose availability, other metabolic alterations in type 2 diabetes can promote flux through these pathways. Insulin is a well-characterized activator of glycolysis by promoting the dephosphorylation and activation of phosphofructokinase, which is thought to be mediated by activation of protein phosphatase 2A by G6P and activation of other protein phosphatases by Akt (Wu *et al.* 2005). Hyperinsulinemia due to insulin resistance in type 2 diabetes is associated with elevated rates of glycolysis in tissues where glucose transport is insulin independent (Guo *et al.* 2012). Importantly, hyperglycemia and hyperinsulinemia have synergistic effects on breast cancer cell growth through Akt and phospholipase C-dependent mechanisms (Tomas *et al.* 2012). While the accumulation of G6P activates G6P dehydrogenase (G6PDH), the rate-limiting enzyme of the pentose phosphate pathway, G6PDH expression and activity are elevated in type 2 diabetes in a number of tissues, including adipose tissue (Park *et al.* 2005) and skeletal muscle (Lee-Young *et al.* 2016). Insulin is a key regulator of G6PDH gene expression through an mTORC1-dependent mechanism (Wagle *et al.* 1998) and the hyperinsulinemia that occurs during the

development of type 2 diabetes could enhance pentose phosphate pathway flux in breast cancer cells through this signaling pathway.

While there are numerous mechanisms linking hyperglycemia and hyperinsulinemia to the regulation of glucose metabolism in breast cancer, type 2 diabetes can also reprogram cellular metabolism that could be equally important. The degree to which breast cancer cells rely on non-oxidative glucose utilization is, in part, dependent on cell hypoxia and the expression of the hypoxia-inducible factor-1 α (HIF-1 α) (Robey *et al.* 2005). This transcription factor enhances the expression of gene programs involved in glycolysis and angiogenesis (Robey *et al.* 2005). Like many cancer cells, HIF-1 α is increased in breast cancer and is linked to its progression and patient prognosis (Rausch *et al.* 2017). Adipose tissue hypoxia in obesity and type 2 diabetes is a well-characterized phenomenon that occurs as this tissue rapidly expands (Ye *et al.* 2007) and could provide the stimulus for HIF-1 α transcriptional reprogramming of glucose metabolism in breast epithelial cells toward that of a transformed cell type. In addition to being a key regulator of the transcriptional program controlling glycolysis, HIF-1 α also enhances the expression of the pyruvate dehydrogenase kinases (Kim *et al.* 2006), which inhibit the activity of pyruvate dehydrogenase complex and flux of pyruvate into the mitochondrial TCA cycle. Inhibiting this reaction and pyruvate oxidation ensures that high rates of glycolysis can be maintained through the reduction of pyruvate to lactate, which regenerates NAD⁺ for use in glycolysis. Interestingly, 17 β -estradiol (E2), the circulating levels of which are frequently reduced in type 2 diabetes and its receptor is lost in estrogen receptor (ER)-negative breast cancers, can oppose this reprogramming in glucose metabolism (O'Mahony *et al.* 2012) and could be one mechanism that explains the relationship between type 2 diabetes and breast cancer in post-menopausal women.

Amino acid metabolism

Similar to a number of other tumor types, basal triple-negative breast cancer (TNBC) is highly dependent on glutamine oxidation (van Geldermalsen *et al.* 2015). In particular, culture of these cells in glutamine-free media inhibited the proliferation of HCC1806 cells, but not ER-positive MCF-7 cells. The ER-selective nature of this phenotype could be related to the loss of transcriptional control of oxidative metabolism by E2, resulting in greater anaplerosis from glutamine. Plasma-free glutamine levels are elevated in type 2 diabetes (Zhou *et al.* 2013),

suggesting that increased glutamine availability in the diabetic state could be important for this phenotype. Interestingly, plasma glutamine levels are also increased in breast cancer patients (Bi & Henry 2017), and it has been suggested that the chronic low-grade inflammation that is common to both disease states is important for this increase in glutamine availability (Poschke *et al.* 2013). Furthermore, knockdown of the ASCT2 glutamine transporter inhibited the proliferation of HCC1806 breast cancer cells *in vitro* and in xenograft studies *in vivo* (van Geldermalsen *et al.* 2015). ASCT2 expression is sensitive to insulin through activation of SGK1, SGK3 and Akt, which increase ASCT2 abundance at the plasma membrane (Palmada *et al.* 2005). Whether hyperinsulinemia in type 2 diabetes regulates ASCT2 through these mechanisms in TNBC cells remains to be determined. Although glutamine has obvious roles in anaplerosis and biomass synthesis, it also appears to be essential for breast cancer cells to oxidize lactate, which can be used as an oxidative fuel source when glucose availability is compromised (Park *et al.* 2016). In this context, glutamine is used to synthesize glutathione, which buffers the reactive oxygen species generated through oxidative metabolism of substrates such as lactate. As mentioned previously, hypoxia is prevalent in adipose tissue in obesity and by extension most patients with type 2 diabetes, suggesting that lactate derived from surrounding hypoxic adipocytes could be an important fuel source for breast cancer cells in these patients (Martinez-Outschoorn *et al.* 2011b).

Lipid metabolism

The synthesis of fatty acids and other lipids is essential for membrane biosynthesis that is an integral part of cell proliferation. Lipogenesis from substrates such as glucose and amino acids is a feature of numerous different cancer cells. Gene expression analyses reveals wide-spread reprogramming of fatty acid metabolism pathways in different breast cancer classifications. In ER-positive breast cancer cells, there is upregulation of genes involved in both the synthesis and utilization of fatty acids, while in ER-negative breast cancer cells, genes involved in uptake and storage are increased and genes involved in their oxidation are reduced (Monaco 2017). Interestingly, a gene expression signature for cell transformation contains a number of genes involved in fatty acid metabolism and metabolic diseases such as type 2 diabetes more broadly (Hirsch *et al.* 2010), possibly suggesting a common pathogenesis via transcriptional reprogramming. Indeed, a reduction in gene pathways involved in oxidative

metabolism is observed in the skeletal muscle of patients with type 2 diabetes (Mootha *et al.* 2003, Patti *et al.* 2003).

However, recent functional studies have found that specific breast cancer cells are highly efficient at utilizing free fatty acids released from adipocytes, for both incorporation into biomass and for oxidation to provide ATP (Balaban *et al.* 2017). This effect was consistent for both the luminal ER-positive MCF7 cell line and the basal ER-negative MDA-MB-231 cell line and was linked to enhanced cellular proliferation rates (Balaban *et al.* 2017). As this effect was consistent irrespective of ER status, it seems unlikely that the ability of breast cancer cells to oxidize fatty acids is linked to the known transcriptional effects of E2 on oxidative metabolic pathways. Consistent with this idea, fatty acids from adipocytes were found to increase mitochondrial oxidative capacity in these same breast cancer cells (Balaban *et al.* 2017). This highlights an example where substrate availability influences the metabolic phenotype of cancer cells and is another potential mechanism linking type 2 diabetes with the predisposition to breast cancer. Perhaps most intriguingly, it was shown that breast cancer cells were able to stimulate the release of fatty acids from adipocytes in a co-culture system (Balaban *et al.* 2017). While the mechanisms remain unknown, these data highlight that similar to other cancer cells, breast cancer cells can signal to cells in the surrounding niche to sequester nutrients that promotes their accelerated proliferation. The metabolic alterations that occur in type 2 diabetes could further promote fatty acid utilization by breast cancer cells. Indeed, insulin-resistant adipocytes fail to suppress lipolysis, increasing free fatty acid efflux from adipose tissue (Guilherme *et al.* 2008). Furthermore, greater sympathetic tone and adipokine secretion, as is observed in type 2 diabetes, both have similar effects in promoting greater lipolysis (Guilherme *et al.* 2008). Supporting these suppositions, it has been shown that knockdown of the key lipolytic machinery in adipocytes, the hormone-sensitive lipase (HSL) and adipose tissue triglyceride lipase (ATGL), resulted in reduced MDA-MB-231 proliferation and migration in conditioned media experiments (Balaban *et al.* 2017).

How do breast cancer cells protect cell viability in high nutrient environments?

A key feature of cancer cells is that they are able to avoid metabolic checkpoints through the reprogramming of their metabolism, such that proliferation and survival are

not impacted by situations of low energy balance (Vander Heiden & DeBerardinis 2017). However, with states of nutrient excess becoming more common in modern society, it is also clear that mechanisms exist to protect cell viability in the face of persistent nutrient excess that exceeds cellular energetic demand. Indeed, one can argue that the development of insulin resistance in response to nutrient excess is a defense mechanism to protect cell viability from nutrient overload (Connor *et al.* 2015). While cancer cells have a high energetic demand due to their high proliferation rates, it is clear that cancer cells have also developed a number of mechanisms to thrive in high nutrient environments where nutrient supply outstrips energetic demand, as occurs in type 2 diabetes.

High nutrient environments are also highly oxidized environments through free radicals that are generated during substrate oxidation processes and the uncoupling of substrate supply with energetic demand (Houstis *et al.* 2006, Anderson *et al.* 2009). Indeed, type 2 diabetes is characterized as a disease that challenges normal redox homeostasis (Houstis *et al.* 2006, Anderson *et al.* 2009, Hoehn *et al.* 2009). However, the reprogramming of cancer cell metabolism assists in combating oxidative stress through enhanced flux through the pentose phosphate pathway, which generates NADPH that is used to recycle the glutathione and thioredoxin antioxidant systems (Patra & Hay 2014). This reprogramming of metabolism toward greater NADPH production has important implications for breast cancer, with a recent study showing that NADPH production through these mechanisms is essential for the epithelial-mesenchymal transition (EMT) and stemness of basal-like breast cancer cells (Dong *et al.* 2013). These findings also imply that metabolic reprogramming is sufficient to induce breast cancer cell transformation. As type 2 diabetes can result in metabolic reprogramming that favors greater flux through the pentose phosphate pathway in a number of tissues (Park *et al.* 2005, Lee-Young *et al.* 2016), these findings also present another potential mechanistic link describing the predisposition to breast cancer in these patients.

Protein acetylation is also emerging as an important mechanism linking nutrient sensing with cell function. Acetylation involves the addition of an acetyl group to either the α -amino group of the N-terminus of proteins or the ϵ -amino group of lysine residues within proteins (Drazic *et al.* 2016). Lysine acetylation is a reversible reaction catalyzed by lysine acetyltransferases and deacetylases; however, all acetylation reactions are sensitive to the availability of acetyl-CoA, the metabolite

that is used as the acetyl group donor in these reactions (Drazic *et al.* 2016). Therefore, global acetylation levels are highly responsive to cellular nutrient levels and flux through oxidative metabolic pathways (Drazic *et al.* 2016). Similar to the fatty acid synthesis pathway, cytosolic and nuclear acetyl-CoA is generated from citrate that is exported from the mitochondria and converted back to acetyl-CoA via the actions of ATP-citrate lyase (ACL) (Pietrocola *et al.* 2015). Lysine acetylation was initially characterized as a key post-translational modification regulating histone proteins and gene expression. However, recent proteomic studies show that a vast number of proteins are acetylated, which can control enzyme activity, localization and protein interactions (Drazic *et al.* 2016). Interestingly, nutrient sensitive acetylation of metabolic enzymes appears to be a key regulatory mechanism controlling metabolic pathway flux and substrate utilization (Wang *et al.* 2010, Zhao *et al.* 2010). For example, glucose-mediated acetylation of glycolytic enzymes in the liver promotes glycolytic flux, while their deacetylation is linked to gluconeogenesis (Zhao *et al.* 2010, Bond *et al.* 2017). It appears that cancer cells harness protein acetylation to regulate metabolism (Hu *et al.* 2017) as well as to enhance the activity of signaling pathways mediating cell growth (Chocarro-Calvo *et al.* 2013). For example, breast cancer metastasis is dependent on elevated acetyl-CoA levels that result in Smad2 acetylation and EMT (Rios Garcia *et al.* 2017). The acetylation of metabolic enzymes is also increased in type 2 diabetes (Kosanm *et al.* 2014) and insulin is a key driver of cytosolic and nuclear acetyl-CoA production by activating ACL via phosphorylation by Akt (Berwick *et al.* 2002). What is unclear, however, is how the selective nature of protein acetylation is regulated in cancer cells. For example, the p53 tumor suppressor gene, which is a key transcriptional regulator of cell cycle arrest and apoptosis, is also activated by acetylation at numerous lysine residues (Brooks & Gu 2011). A number of lysine deacetylases are increased in breast cancer (Lapierre *et al.* 2016, Cao *et al.* 2017, Guerriero *et al.* 2017, Huang *et al.* 2017) and their substrate selectivity could play a key role in controlling acetylation patterns to ensure breast cancer progression. Similarly, acetyl-CoA availability has been shown to link N-acetylation with apoptosis responses (Yi *et al.* 2011). As the N-acetylation reaction is thought to be non-reversible (Drazic *et al.* 2016), the mechanisms by which cancer cells are able to escape this metabolic control of apoptosis remains to be determined, but could involve modulation of the NAT enzymes that catalyze N-acetylation.

Conclusions

Alterations in metabolism that occur in type 2 diabetes potentially describe the epidemiological link with breast cancer. Changes in substrate availability and the hormonal milieu, particularly hyperinsulinemia, which are observed in type 2 diabetes create a favorable metabolic environment for the development of breast cancer. Similarly, adipose tissue dysfunction can also drive metabolic reprogramming events that favor cellular transformation. Many of the alterations in glucose, lipid and amino acid metabolism observed in breast cancer can be induced by aspects of type 2 diabetes. A challenge for the field moving forward will be to mechanistically link metabolic aspects of type 2 diabetes with metabolic aspects of breast cancer. Meeting this substantial challenge will allow better prediction of breast cancer development and will also provide opportunities for personalized medicine to combat this deadly disease.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

The authors' work related to this article is supported by grants from the National Health and Medical Research Council (NHMRC) of Australia (APP1127059), the National Breast Cancer Foundation (IN-15-061) and the Centre for Molecular and Medical Research, Deakin University.

Author contribution statement

Both authors contributed equally to the writing of this manuscript and the generation of the figure.

Acknowledgements

The authors wish to thank Dr Kirsten Howlett (Institute for Physical Activity and Nutrition, Deakin University) for critical reading of this manuscript.

References

- Anderson EJ, Lustig ME, Boyle KE, Woodlief TL, Kane DA, Lin CT, Price JW 3rd, Kang L, Rabinovitch PS, Szeto HH, *et al.* 2009 Mitochondrial H₂O₂ emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans. *Journal of Clinical Investigation* **119** 573–581. (<https://doi.org/10.1172/JCI37048>)
- Balaban S, Shearer RF, Lee LS, van Geldermalsen M, Schreuder M, Shtein HC, Cairns R, Thomas KC, Fazakerley DJ, Grewal T, *et al.* 2017 Adipocyte lipolysis links obesity to breast cancer growth: adipocyte-derived fatty acids drive breast cancer cell proliferation and migration. *Cancer and Metabolism* **5** 1. (<https://doi.org/10.1186/s40170-016-0163-7>)

- Bansal N 2015 Prediabetes diagnosis and treatment: a review. *World Journal of Diabetes* **6** 296–303. (<https://doi.org/10.4239/wjcd.v6.i2.296>)
- Berwick DC, Hers I, Heesom KJ, Moule SK & Tavare JM 2002 The identification of ATP-citrate lyase as a protein kinase B (Akt) substrate in primary adipocytes. *Journal of Biological Chemistry* **277** 33895–33900. (<https://doi.org/10.1074/jbc.M204681200>)
- Bi X & Henry CJ 2017 Plasma-free amino acid profiles are predictors of cancer and diabetes development. *Nutrition and Diabetes* **7** e249. (<https://doi.org/10.1038/nutd.2016.55>)
- Bonadonna RC, Saccomani MP, Cobelli C & DeFronzo RA 1993 Effect of insulin on system A amino acid transport in human skeletal muscle. *Journal of Clinical Investigation* **91** 514–521. (<https://doi.org/10.1172/JCI116230>)
- Bond ST, Howlett KF, Kowalski GM, Mason S, Connor T, Cooper A, Streltsov V, Bruce CR, Walder KR & McGee SL 2017 Lysine post-translational modification of glyceraldehyde-3-phosphate dehydrogenase regulates hepatic and systemic metabolism. *FASEB Journal* **31** 2592–2602. (<https://doi.org/10.1096/fj.201601215R>)
- Brooks CL & Gu W 2011 The impact of acetylation and deacetylation on the p53 pathway. *Protein and Cell* **2** 456–462. (<https://doi.org/10.1007/s13238-011-1063-9>)
- Brown MS & Goldstein JL 2008 Selective versus total insulin resistance: a pathogenic paradox. *Cell Metabolism* **7** 95–96. (<https://doi.org/10.1016/j.cmet.2007.12.009>)
- Brown RJ, Sinaï N & Rother KI 2008 Too much glucagon, too little insulin: time course of pancreatic islet dysfunction in new-onset type 1 diabetes. *Diabetes Care* **31** 1403–1404. (<https://doi.org/10.2337/dc08-0575>)
- Cao C, Vasilatos SN, Bhargava R, Fine JL, Oesterreich S, Davidson NE & Huang Y 2017 Functional interaction of histone deacetylase 5 (HDAC5) and lysine-specific demethylase 1 (LSD1) promotes breast cancer progression. *Oncogene* **36** 133–145. (<https://doi.org/10.1038/onc.2016.186>)
- Chocarro-Calvo A, Garcia-Martinez JM, Ardila-Gonzalez S, De la Vieja A & Garcia-Jimenez C 2013 Glucose-induced beta-catenin acetylation enhances Wnt signaling in cancer. *Molecular Cell* **49** 474–486. (<https://doi.org/10.1016/j.molcel.2012.11.022>)
- Christofk HR, Vander Heiden MG, Wu N, Asara JM & Cantley LC 2008 Pyruvate kinase M2 is a phosphotyrosine-binding protein. *Nature* **452** 181–186. (<https://doi.org/10.1038/nature06667>)
- Connor T, Martin SD, Howlett KF & McGee SL 2015 Metabolic remodelling in obesity and type 2 diabetes: pathological or protective mechanisms in response to nutrient excess? *Clinical and Experimental Pharmacology and Physiology* **42** 109–115. (<https://doi.org/10.1111/1440-1681.12315>)
- Dai X, Li T, Bai Z, Yang Y, Liu X, Zhan J & Shi B 2015 Breast cancer intrinsic subtype classification, clinical use and future trends. *American Journal of Cancer Research* **5** 2929–2943.
- Daniels VW, Smans K, Royaux I, Chypre M, Swinnen JV & Zaidi N 2014 Cancer cells differentially activate and thrive on de novo lipid synthesis pathways in a low-lipid environment. *PLoS ONE* **9** e106913. (<https://doi.org/10.1371/journal.pone.0106913>)
- DeBerardinis RJ & Chandel NS 2016 Fundamentals of cancer metabolism. *Science Advances* **2** e1600200. (<https://doi.org/10.1126/sciadv.1600200>)
- Devesa SS, Blot WJ, Stone BJ, Miller BA, Tarone RE & Fraumeni JF Jr 1995 Recent cancer trends in the United States. *Journal of the National Cancer Institute* **87** 175–182. (<https://doi.org/10.1093/jnci/87.3.175>)
- Dong C, Yuan T, Wu Y, Wang Y, Fan TW, Miriyala S, Lin Y, Yao J, Shi J, Kang T, et al. 2013 Loss of FBP1 by Snail-mediated repression provides metabolic advantages in basal-like breast cancer. *Cancer Cell* **23** 316–331. (<https://doi.org/10.1016/j.ccr.2013.01.022>)
- Drazic A, Myklebust LM, Ree R & Arnesen T 2016 The world of protein acetylation. *Biochimica et Biophysica Acta* **1864** 1372–1401. (<https://doi.org/10.1016/j.bbapap.2016.06.007>)
- Ertunc ME & Hotamisligil GS 2016 Lipid signaling and lipotoxicity in metaflammation: indications for metabolic disease pathogenesis and treatment. *Journal of Lipid Research* **57** 2099–2114. (<https://doi.org/10.1194/jlr.R066514>)
- Eyre H, Kahn R, Robertson RM, Clark NG, Doyle C, Hong Y, Gansler T, Glynn T, Smith RA, Taubert K, et al. 2004 Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. *Circulation* **109** 3244–3255. (<https://doi.org/10.1161/01.CIR.0000133321.00456.00>)
- Fan J, Kamphorst JJ, Mathew R, Chung MK, White E, Shlomi T & Rabinowitz JD 2013 Glutamine-driven oxidative phosphorylation is a major ATP source in transformed mammalian cells in both normoxia and hypoxia. *Molecular Systems Biology* **9** 712. (<https://doi.org/10.1038/msb.2013.65>)
- Gaither K, Quraishi AN & Illsley NP 1999 Diabetes alters the expression and activity of the human placental GLUT1 glucose transporter. *Journal of Clinical Endocrinology and Metabolism* **84** 695–701.
- Goldberg IJ, Eckel RH & Abumrad NA 2009 Regulation of fatty acid uptake into tissues: lipoprotein lipase- and CD36-mediated pathways. *Journal of Lipid Research* **50** (Supplement) S86–S90. (<https://doi.org/10.1194/jlr.R800085-JLR200>)
- Guerriero JL, Sotayo A, Ponichtera HE, Castrillon JA, Pourzia AL, Schad S, Johnson SF, Carrasco RD, Lazo S, Bronson RT, et al. 2017 Class IIa HDAC inhibition reduces breast tumours and metastases through anti-tumour macrophages. *Nature* **543** 428–432. (<https://doi.org/10.1038/nature21409>)
- Guilherme A, Virbasius JV, Puri V & Czech MP 2008 Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. *Nature Reviews Molecular Cell Biology* **9** 367–377. (<https://doi.org/10.1038/nrm2391>)
- Gulve EA, Ren JM, Marshall BA, Gao J, Hansen PA, Holloszy JO & Mueckler M 1994 Glucose transport activity in skeletal muscles from transgenic mice overexpressing GLUT1. Increased basal transport is associated with a defective response to diverse stimuli that activate GLUT4. *Journal of Biological Chemistry* **269** 18366–18370.
- Guo X, Li H, Xu H, Woo S, Dong H, Hu F, Lange AJ & Wu C 2012 Glycolysis in the control of blood glucose homeostasis. *Acta Pharmaceutica Sinica B* **2** 10.
- Hanahan D & Weinberg RA 2011 Hallmarks of cancer: the next generation. *Cell* **144** 646–674. (<https://doi.org/10.1016/j.cell.2011.02.013>)
- Hensley CT, Faubert B, Yuan Q, Lev-Cohain N, Jin E, Kim J, Jiang L, Ko B, Skelton R, Loudat L, et al. 2016 Metabolic heterogeneity in human lung tumors. *Cell* **164** 681–694. (<https://doi.org/10.1016/j.cell.2015.12.034>)
- Hirsch HA, Iliopoulos D, Joshi A, Zhang Y, Jaeger SA, Bulysk M, Tschlis PN, Shirley Liu X & Struhl K 2010 A transcriptional signature and common gene networks link cancer with lipid metabolism and diverse human diseases. *Cancer Cell* **17** 348–361. (<https://doi.org/10.1016/j.ccr.2010.01.022>)
- Hitosugi T, Zhou L, Elf S, Fan J, Kang HB, Seo JH, Shan C, Dai Q, Zhang L, Xie J, et al. 2012 Phosphoglycerate mutase 1 coordinates glycolysis and biosynthesis to promote tumor growth. *Cancer Cell* **22** 585–600. (<https://doi.org/10.1016/j.ccr.2012.09.020>)
- Hoehn KL, Salmon AB, Hohnen-Behrens C, Turner N, Hoy AJ, Maghzal GJ, Stocker R, Van Remmen H, Kraegen EW, Cooney GJ, et al. 2009 Insulin resistance is a cellular antioxidant defense mechanism. *PNAS* **106** 17787–17792. (<https://doi.org/10.1073/pnas.0902380106>)
- Houstis N, Rosen ED & Lander ES 2006 Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature* **440** 944–948. (<https://doi.org/10.1038/nature04634>)
- Hoy AJ, Balaban S & Saunders DN 2017 Adipocyte-tumor cell metabolic crosstalk in breast cancer. *Trends in Molecular Medicine* **23** 381–392. (<https://doi.org/10.1016/j.molmed.2017.02.009>)
- Hu H, Zhu W, Qin J, Chen M, Gong L, Li L, Liu X, Tao Y, Yin H, Zhou H, et al. 2017 Acetylation of PGK1 promotes liver cancer cell proliferation and tumorigenesis. *Hepatology* **65** 515–528. (<https://doi.org/10.1002/hep.28887>)

- Huang WT, Tsai YH, Chen SH, Kuo CW, Kuo YL, Lee KT, Chen WC, Wu PC, Chuang CY, Cheng SM, *et al.* 2017 HDAC2 and HDAC5 up-regulations modulate survivin and miR-125a-5p expressions and promote hormone therapy resistance in estrogen receptor positive breast cancer cells. *Frontiers in Pharmacology* **8** 902. (<https://doi.org/10.3389/fphar.2017.00902>)
- Huggett RJ, Scott EM, Gilbey SG, Stoker JB, Mackintosh AF & Mary DA 2003 Impact of type 2 diabetes mellitus on sympathetic neural mechanisms in hypertension. *Circulation* **108** 3097–3101. (<https://doi.org/10.1161/01.CIR.0000103123.66264.FE>)
- Hussein YR, Bandyopadhyay S, Semaan A, Ahmed Q, Albashiti B, Jazaerly T, Nahleh Z & Ali-Fehmi R 2011 Glut-1 expression correlates with basal-like breast cancer. *Translational Oncology* **4** 321–327. (<https://doi.org/10.1593/tlo.11256>)
- Jin L, Li D, Alesi GN, Fan J, Kang HB, Lu Z, Boggan TJ, Jin P, Yi H, Wright ER, *et al.* 2015 Glutamate dehydrogenase 1 signals through antioxidant glutathione peroxidase 1 to regulate redox homeostasis and tumor growth. *Cancer Cell* **27** 257–270. (<https://doi.org/10.1016/j.ccell.2014.12.006>)
- Kim JW, Tchernyshyov I, Semenza GL & Dang CV 2006 HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia. *Cell Metabolism* **3** 177–185. (<https://doi.org/10.1016/j.cmet.2006.02.002>)
- Konner AC & Bruning JC 2012 Selective insulin and leptin resistance in metabolic disorders. *Cell Metabolism* **16** 144–152. (<https://doi.org/10.1016/j.cmet.2012.07.004>)
- Kosanam H, Thai K, Zhang Y, Advani A, Connelly KA, Diamandis EP & Gilbert RE 2014 Diabetes induces lysine acetylation of intermediary metabolism enzymes in the kidney. *Diabetes* **63** 2432–2439. (<https://doi.org/10.2337/db12-1770>)
- Koukourakis MI, Giatromanolaki A, Sivridis E, Gatter KC, Harris AL & Tumor and Angiogenesis Research Group 2005 Pyruvate dehydrogenase and pyruvate dehydrogenase kinase expression in non small cell lung cancer and tumor-associated stroma. *Neoplasia* **7** 1–6. (<https://doi.org/10.1593/neo.04373>)
- Lapierre M, Linares A, Dalvai M, Duraffourd C, Bonnet S, Boulahtouf A, Rodriguez C, Jalaguier S, Assou S, Orsetti B, *et al.* 2016 Histone deacetylase 9 regulates breast cancer cell proliferation and the response to histone deacetylase inhibitors. *Oncotarget* **7** 19693–19708. (<https://doi.org/10.18632/oncotarget.7564>)
- Lee-Young RS, Hoffman NJ, Murphy KT, Henstridge DC, Samocha-Bonet D, Siebel AL, Iliades P, Zivanovic B, Hong YH, Colgan TD, *et al.* 2016 Glucose-6-phosphate dehydrogenase contributes to the regulation of glucose uptake in skeletal muscle. *Molecular Metabolism* **5** 1083–1091. (<https://doi.org/10.1016/j.molmet.2016.09.002>)
- Lin HP, Cheng ZL, He RY, Song L, Tian MX, Zhou LS, Groh BS, Liu WR, Ji MB, Ding C, *et al.* 2016 Destabilization of fatty acid synthase by acetylation inhibits de novo lipogenesis and tumor cell growth. *Cancer Research* **76** 6924–6936. (<https://doi.org/10.1158/0008-5472.CAN-16-1597>)
- Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR & Hux JE 2006 Increased prevalence of prior breast cancer in women with newly diagnosed diabetes. *Breast Cancer Research and Treatment* **98** 303–309. (<https://doi.org/10.1007/s10549-006-9166-3>)
- Liu M, Sjogren AK, Karlsson C, Ibrahim MX, Andersson KM, Olofsson FJ, Wahlstrom AM, Dalin M, Yu H, Chen Z, *et al.* 2010 Targeting the protein prenyltransferases efficiently reduces tumor development in mice with K-RAS-induced lung cancer. *PNAS* **107** 6471–6476. (<https://doi.org/10.1073/pnas.0908396107>)
- Locasale JW, Grassian AR, Melman T, Lyssiotis CA, Mattaini KR, Bass AJ, Heffron G, Metallo CM, Muranen T, Sharfi H, *et al.* 2011 Phosphoglycerate dehydrogenase diverts glycolytic flux and contributes to oncogenesis. *Nature Genetics* **43** 869–874. (<https://doi.org/10.1038/ng.890>)
- Luengo A, Gui DY & Vander Heiden MG 2017 Targeting metabolism for cancer therapy. *Cell Chemical Biology* **24** 1161–1180. (<https://doi.org/10.1016/j.chembiol.2017.08.028>)
- Macheda ML, Rogers S & Best JD 2005 Molecular and cellular regulation of glucose transporter (GLUT) proteins in cancer. *Journal of Cellular Physiology* **202** 654–662. (<https://doi.org/10.1002/jcp.20166>)
- Malhotra GK, Zhao X, Band H & Band V 2010 Histological, molecular and functional subtypes of breast cancers. *Cancer Biology and Therapy* **10** 955–960. (<https://doi.org/10.4161/cbt.10.10.13879>)
- Martinez-Outschoorn UE, Pavlides S, Howell A, Pestell RG, Tanowitz HB, Sotgia F & Lisanti MP 2011a Stromal-epithelial metabolic coupling in cancer: integrating autophagy and metabolism in the tumor microenvironment. *International Journal of Biochemistry and Cell Biology* **43** 1045–1051. (<https://doi.org/10.1016/j.biocel.2011.01.023>)
- Martinez-Outschoorn UE, Prisco M, Ertel A, Tsigos A, Lin Z, Pavlides S, Wang C, Flomenberg N, Knudsen ES, Howell A, *et al.* 2011b Ketones and lactate increase cancer cell 'stemness,' driving recurrence, metastasis and poor clinical outcome in breast cancer: achieving personalized medicine via Metabolo-Genomics. *Cell Cycle* **10** 1271–1286. (<https://doi.org/10.4161/cc.10.8.15330>)
- Martinez-Reyes I, Diebold LP, Kong H, Schieber M, Huang H, Hensley CT, Mehta MM, Wang T, Santos JH, Woychik R, *et al.* 2016 TCA cycle and mitochondrial membrane potential are necessary for diverse biological functions. *Molecular Cell* **61** 199–209. (<https://doi.org/10.1016/j.molcel.2015.12.002>)
- McFate T, Mohyeldin A, Lu H, Thakar J, Henriques J, Halim ND, Wu H, Schell MJ, Tsang TM, Teahan O, *et al.* 2008 Pyruvate dehydrogenase complex activity controls metabolic and malignant phenotype in cancer cells. *Journal of Biological Chemistry* **283** 22700–22708. (<https://doi.org/10.1074/jbc.M801765200>)
- Minicozzi P, Berrino F, Sebastiani F, Falcini F, Vattiato R, Cioccoloni E, Calagreti G, Fusco M, Vitale MF, Tumino R, *et al.* 2013 High fasting blood glucose and obesity significantly and independently increase risk of breast cancer death in hormone receptor-positive disease. *European Journal of Cancer* **49** 3881–3888. (<https://doi.org/10.1016/j.ejca.2013.08.004>)
- Monaco ME 2017 Fatty acid metabolism in breast cancer subtypes. *Oncotarget* **8** 29487–29500. (<https://doi.org/10.18632/oncotarget.15494>)
- Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, Lehar J, Puigserver P, Carlsson E, Ridderstrale M, Laurila E, *et al.* 2003 PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. *Nature Genetics* **34** 267–273. (<https://doi.org/10.1038/ng1180>)
- Muck BR, Trotnow S & Hommel G 1975 Cancer of the breast, diabetes and pathological glucose tolerance. *Archiv Fur Gynakologie* **220** 73–81. (<https://doi.org/10.1007/BF00673150>)
- O'Mahony F, Razandi M, Pedram A, Harvey BJ & Levin ER 2012 Estrogen modulates metabolic pathway adaptation to available glucose in breast cancer cells. *Molecular Endocrinology* **26** 2058–2070. (<https://doi.org/10.1210/me.2012-1191>)
- Ogrodzinski MP, Bernard JJ & Lunt SY 2017 Deciphering metabolic rewiring in breast cancer subtypes. *Translational Research* **189** 105–122. (<https://doi.org/10.1016/j.trsl.2017.07.004>)
- Owen OE, Kalhan SC & Hanson RW 2002 The key role of anaplerosis and cataplerosis for citric acid cycle function. *Journal of Biological Chemistry* **277** 30409–30412. (<https://doi.org/10.1074/jbc.R200006200>)
- Palmada M, Speil A, Jeyaraj S, Bohmer C & Lang F 2005 The serine/threonine kinases SGK1, 3 and PKB stimulate the amino acid transporter ASCT2. *Biochemical and Biophysical Research Communications* **331** 272–277. (<https://doi.org/10.1016/j.bbrc.2005.03.159>)
- Park J, Rho HK, Kim KH, Choe SS, Lee YS & Kim JB 2005 Overexpression of glucose-6-phosphate dehydrogenase is associated with lipid dysregulation and insulin resistance in obesity. *Molecular and Cellular Biology* **25** 5146–5157. (<https://doi.org/10.1128/MCB.25.12.5146-5157.2005>)

- Park S, Chang CY, Safi R, Liu X, Baldi R, Jasper JS, Anderson GR, Liu T, Rathmell JC, Dewhirst MW, *et al.* 2016 ERRalpha-regulated lactate metabolism contributes to resistance to targeted therapies in breast cancer. *Cell Reports* **15** 323–335. (<https://doi.org/10.1016/j.celrep.2016.03.026>)
- Patra KC & Hay N 2014 The pentose phosphate pathway and cancer. *Trends in Biochemical Sciences* **39** 347–354. (<https://doi.org/10.1016/j.tibs.2014.06.005>)
- Patti ME, Butte AJ, Crunkhorn S, Cusi K, Berria R, Kashyap S, Miyazaki Y, Kohane I, Costello M, Saccone R, *et al.* 2003 Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential role of PGC1 and NRF1. *PNAS* **100** 8466–8471. (<https://doi.org/10.1073/pnas.1032913100>)
- Pietrocola F, Galluzzi L, Bravo-San Pedro JM, Madeo F & Kroemer G 2015 Acetyl coenzyme A: a central metabolite and second messenger. *Cell Metabolism* **21** 805–821. (<https://doi.org/10.1016/j.cmet.2015.05.014>)
- Pike LS, Smift AL, Croteau NJ, Ferrick DA & Wu M 2011 Inhibition of fatty acid oxidation by etomoxir impairs NADPH production and increases reactive oxygen species resulting in ATP depletion and cell death in human glioblastoma cells. *Biochimica et Biophysica Acta* **1807** 726–734. (<https://doi.org/10.1016/j.bbabi.2010.10.022>)
- Poschke I, Mao Y, Kiessling R & de Boniface J 2013 Tumor-dependent increase of serum amino acid levels in breast cancer patients has diagnostic potential and correlates with molecular tumor subtypes. *Journal of Translational Medicine* **11** 290. (<https://doi.org/10.1186/1479-5876-11-290>)
- Prentki M & Nolan CJ 2006 Islet beta cell failure in type 2 diabetes. *Journal of Clinical Investigation* **116** 1802–1812. (<https://doi.org/10.1172/JCI29103>)
- Rausch LK, Netzer NC, Hoegel J & Pramsohler S 2017 The linkage between breast cancer, hypoxia, and adipose tissue. *Frontiers in Oncology* **7** 211. (<https://doi.org/10.3389/fonc.2017.00211>)
- Resta F, Triggiani V, Sabba C, Licchelli B, Ghiyasaldin S, Liso A, Schittulli F, Quaranta M, Paradiso A, Tafaro E, *et al.* 2004 The impact of body mass index and type 2 diabetes on breast cancer: current therapeutic measures of prevention. *Current Drug Targets: Immune, Endocrine and Metabolic Disorders* **4** 327–333. (<https://doi.org/10.2174/1568008043339686>)
- Rios Garcia M, Steinbauer B, Srivastava K, Singhal M, Mattijssen F, Maida A, Christian S, Hess-Stumpff H, Augustin HG, Muller-Decker K, *et al.* 2017 Acetyl-CoA carboxylase 1-dependent protein acetylation controls breast cancer metastasis and recurrence. *Cell Metabolism* **26** 842.e845–855.e845. (<https://doi.org/10.1016/j.cmet.2017.09.018>)
- Robey IF, Lien AD, Welsh SJ, Baggett BK & Gillies RJ 2005 Hypoxia-inducible factor-1alpha and the glycolytic phenotype in tumors. *Neoplasia* **7** 324–330. (<https://doi.org/10.1593/neo.04430>)
- Samuel VT & Shulman GI 2012 Mechanisms for insulin resistance: common threads and missing links. *Cell* **148** 852–871. (<https://doi.org/10.1016/j.cell.2012.02.017>)
- Santos CR & Schulze A 2012 Lipid metabolism in cancer. *FEBS Journal* **279** 2610–2623. (<https://doi.org/10.1111/j.1742-4658.2012.08644.x>)
- Shimomura I, Matsuda M, Hammer RE, Bashmakov Y, Brown MS & Goldstein JL 2000 Decreased IRS-2 and increased SREBP-1c lead to mixed insulin resistance and sensitivity in livers of lipodystrophic and ob/ob mice. *Molecular Cell* **6** 77–86. ([https://doi.org/10.1016/S1097-2765\(05\)00010-9](https://doi.org/10.1016/S1097-2765(05)00010-9))
- Simmons RA, Flozak AS & Ogata ES 1993a The effect of insulin and insulin-like growth factor-I on glucose transport in normal and small for gestational age fetal rats. *Endocrinology* **133** 1361–1368. (<https://doi.org/10.1210/endo.133.3.8365373>)
- Simmons RA, Flozak AS & Ogata ES 1993b Glucose regulates glut 1 function and expression in fetal rat lung and muscle in vitro. *Endocrinology* **132** 2312–2318. (<https://doi.org/10.1210/endo.132.6.8504736>)
- Slavov N, Budnik BA, Schwab D, Airoldi EM & van Oudenaarden A 2014 Constant growth rate can be supported by decreasing energy flux and increasing aerobic glycolysis. *Cell Reports* **7** 705–714. (<https://doi.org/10.1016/j.celrep.2014.03.057>)
- Stockli J, Fazakerley DJ & James DE 2011 GLUT4 exocytosis. *Journal of Cell Science* **124** 4147–4159. (<https://doi.org/10.1242/jcs.097063>)
- Talamini R, Franceschi S, Favero A, Negri E, Parazzini F & La Vecchia C 1997 Selected medical conditions and risk of breast cancer. *British Journal of Cancer* **75** 1699–1703. (<https://doi.org/10.1038/bjc.1997.289>)
- Tomas NM, Masur K, Piecha JC, Niggemann B & Zanker KS 2012 Akt and phospholipase Cgamma are involved in the regulation of growth and migration of MDA-MB-468 breast cancer and SW480 colon cancer cells when cultured with diabetogenic levels of glucose and insulin. *BMC Research Notes* **5** 214. (<https://doi.org/10.1186/1756-0500-5-214>)
- van Geldermalsen M, Wang Q, Nagarajah R, Marshall AD, Thoeng A, Gao D, Ritchie W, Feng Y, Bailey CG, Deng N, *et al.* 2015 ASCT2/SLC1A5 controls glutamine uptake and tumour growth in triple-negative basal-like breast cancer. *Oncogene* **35** 3201–3208. (<https://doi.org/10.1038/onc.2015.381>)
- Vander Heiden MG & DeBerardinis RJ 2017 Understanding the intersections between metabolism and cancer biology. *Cell* **168** 657–669. (<https://doi.org/10.1016/j.cell.2016.12.039>)
- Vander Heiden MG, Lunt SY, Dayton TL, Fiske BP, Israelsen WJ, Mattaini KR, Vokes NI, Stephanopoulos G, Cantley LC, Metallo CM, *et al.* 2011 Metabolic pathway alterations that support cell proliferation. *Cold Spring Harbor Symposia on Quantitative Biology* **76** 325–334. (<https://doi.org/10.1101/sqb.2012.76.010900>)
- Wagle A, Jivraj S, Garlock GL & Stapleton SR 1998 Insulin regulation of glucose-6-phosphate dehydrogenase gene expression is rapamycin-sensitive and requires phosphatidylinositol 3-kinase. *Journal of Biological Chemistry* **273** 14968–14974. (<https://doi.org/10.1074/jbc.273.24.14968>)
- Wang Q, Zhang Y, Yang C, Xiong H, Lin Y, Yao J, Li H, Xie L, Zhao W, Yao Y, *et al.* 2010 Acetylation of metabolic enzymes coordinates carbon source utilization and metabolic flux. *Science* **327** 1004–1007. (<https://doi.org/10.1126/science.1179687>)
- Warburg O 1956 On respiratory impairment in cancer cells. *Science* **124** 269–270.
- Wauters M, Considine RV, Yudkin JS, Peiffer F, De Leeuw I & Van Gaal LF 2003 Leptin levels in type 2 diabetes: associations with measures of insulin resistance and insulin secretion. *Hormone and Metabolic Research* **35** 92–96. (<https://doi.org/10.1055/s-2003-39054>)
- Weinberg F, Hamanaka R, Wheaton WW, Weinberg S, Joseph J, Lopez M, Kalyanaraman B, Mutlu GM, Budinger GR & Chandel NS 2010 Mitochondrial metabolism and ROS generation are essential for Kras-mediated tumorigenicity. *PNAS* **107** 8788–8793. (<https://doi.org/10.1073/pnas.1003428107>)
- Wellberg EA, Johnson S, Finlay-Schultz J, Lewis AS, Terrell KL, Sartorius CA, Abel ED, Muller WJ & Anderson SM 2016 The glucose transporter GLUT1 is required for ErbB2-induced mammary tumorigenesis. *Breast Cancer Research* **18** 131. (<https://doi.org/10.1186/s13058-016-0795-0>)
- Wu C, Khan SA & Lange AJ 2005 Regulation of glycolysis-role of insulin. *Experimental Gerontology* **40** 894–899. (<https://doi.org/10.1016/j.exger.2005.08.002>)
- Xue F & Michels KB 2007 Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. *American Journal of Clinical Nutrition* **86** s823–s835. (<https://doi.org/10.1093/ajcn/86.3.823S>)
- Yang ZQ, Moffa AB, Haddad R, Streicher KL & Ethier SP 2007 Transforming properties of TC-1 in human breast cancer: interaction with FGFR2 and beta-catenin signaling pathways. *International Journal of Cancer* **121** 1265–1273. (<https://doi.org/10.1002/ijc.22831>)
- Yang DQ, Freund DM, Harris BR, Wang D, Cleary MP & Hegeman AD 2016 Measuring relative utilization of aerobic glycolysis in breast cancer cells by positional isotopic discrimination. *FEBS Letters* **590** 3179–3187. (<https://doi.org/10.1002/1873-3468.12360>)
- Ye J, Gao Z, Yin J & He Q 2007 Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. *American Journal of Physiology*:

- Endocrinology and Metabolism* **293** E1118–E1128. (<https://doi.org/10.1152/ajpendo.00435.2007>)
- Yi CH, Pan H, Seebacher J, Jang IH, Hyberts SG, Heffron GJ, Vander Heiden MG, Yang R, Li F, Locasale JW, *et al.* 2011 Metabolic regulation of protein N-alpha-acetylation by Bcl-xL promotes cell survival. *Cell* **146** 607–620. (<https://doi.org/10.1016/j.cell.2011.06.050>)
- Young CD, Lewis AS, Rudolph MC, Ruehle MD, Jackman MR, Yun UJ, Ilkun O, Pereira R, Abel ED & Anderson SM 2011 Modulation of glucose transporter 1 (GLUT1) expression levels alters mouse mammary tumor cell growth in vitro and in vivo. *PLoS ONE* **6** e23205. (<https://doi.org/10.1371/journal.pone.0023205>)
- Zaidi N, Lupien L, Kuemmerle NB, Kinlaw WB, Swinnen JV & Smans K 2013 Lipogenesis and lipolysis: the pathways exploited by the cancer cells to acquire fatty acids. *Progress in Lipid Research* **52** 585–589. (<https://doi.org/10.1016/j.plipres.2013.08.005>)
- Zhao S, Xu W, Jiang W, Yu W, Lin Y, Zhang T, Yao J, Zhou L, Zeng Y, Li H, *et al.* 2010 Regulation of cellular metabolism by protein lysine acetylation. *Science* **327** 1000–1004. (<https://doi.org/10.1126/science.1179689>)
- Zhou Y, Qiu L, Xiao Q, Wang Y, Meng X, Xu R, Wang S & Na R 2013 Obesity and diabetes related plasma amino acid alterations. *Clinical Biochemistry* **46** 1447–1452. (<https://doi.org/10.1016/j.clinbiochem.2013.05.045>)
- Zimmet P, Alberti KG, Magliano DJ & Bennett PH 2016 Diabetes mellitus statistics on prevalence and mortality: facts and fallacies. *Nature Reviews Endocrinology* **12** 616–622. (<https://doi.org/10.1038/nrendo.2016.105>)

Received in final form 22 February 2018

Accepted 27 February 2018

Accepted Preprint published online 27 February 2018