REVIEW

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

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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

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.
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 beta-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 eflux 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 (Kourourakis 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...
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 follows 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 actor-1 alpha (HIF-1α) (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-1α 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-1α 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-1α 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, 17β-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 reveal 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 (Houistsi et al. 2006, Anderson et al. 2009). Indeed, type 2 diabetes is characterized as a disease that challenges normal redox homeostasis (Houistsi 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

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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 García et al. 2017). The acetylation of metabolic enzymes is also increased in type 2 diabetes (Kosanam 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 (Lapiere 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.

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Author contribution statement

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