

# A new link between diabetes and cancer: enhanced WNT/ $\beta$ -catenin signaling by high glucose

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## Abstract

Extensive epidemiological studies suggest that the diabetic population is at higher risk of site-specific cancers. The diabetes–cancer link has been hypothesized to rely on various hormonal (insulin, IGF1, adipokines), immunological (inflammation), or metabolic (hyperglycemia) characteristics of the disease and even on certain treatments. Inflammation may have an important but incompletely understood role. As a growth factor, insulin directly, or indirectly through IGF1, has been considered the major link between diabetes and cancer, while high glucose has been considered as a subordinate cause. Here we discuss the evidence that supports a role for insulin/IGF1 in general in cancer, and the mechanism by which hyperglycemia may enhance the appearance, growth and survival of diabetes-associated cancers. High glucose triggers several direct and indirect mechanisms that cooperate to promote cancer cell proliferation, migration, invasion and immunological escape. In particular, high glucose enhancement of WNT/ $\beta$ -catenin signaling in cancer cells promotes proliferation, survival and senescence bypass, and represents a previously unrecognized direct mechanism linking diabetes-associated hyperglycemia to cancer. Increased glucose uptake is a hallmark of tumor cells and may ensure enhanced WNT signaling for continuous proliferation. Mechanistically, high glucose unbalances acetylation through increased p300 acetyl transferase and decreased sirtuin 1 deacetylase activity, leading to  $\beta$ -catenin acetylation at lysine K354, a requirement for nuclear accumulation and transcriptional activation of WNT-target genes. The impact of high glucose on  $\beta$ -catenin illustrates the remodeling of cancer-associated signaling pathways by metabolites. Metabolic remodeling of cancer-associated signaling will receive much research attention in the coming years. Future epidemiological studies may be guided and complemented by the identification of these metabolic interplays. Together, these studies should lead to the development of new preventive strategies for diabetes-associated cancers.

## Key Words

- ▶ WNT
- ▶  $\beta$ -catenin
- ▶ insulin
- ▶ diabetes
- ▶ glucose-dependent insulinotropic peptide
- ▶ incretin
- ▶ transcription
- ▶ signaling
- ▶ cancer

*Journal of Molecular Endocrinology* (2014) 52, R51–R66

## Introduction

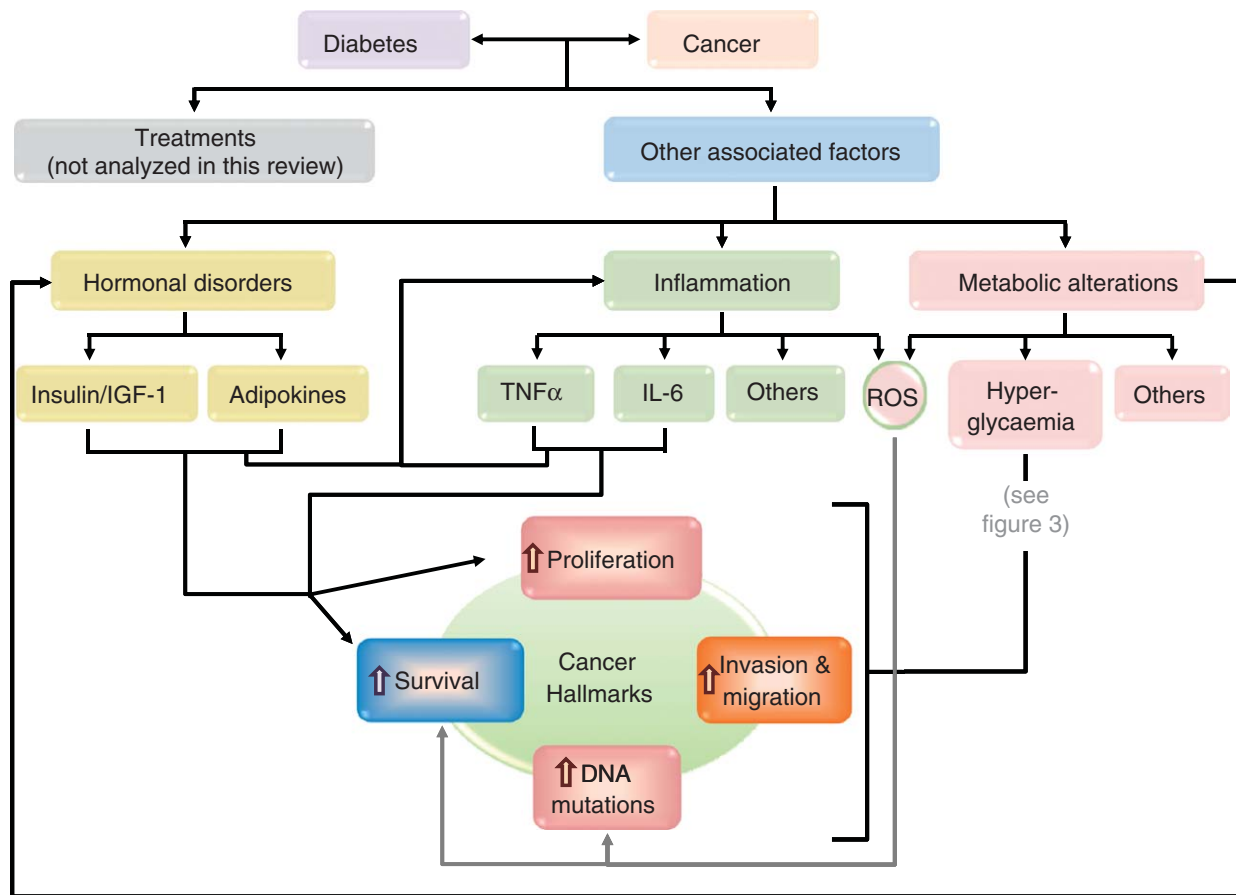
Extensive epidemiological studies have revealed that the diabetic population is at higher risk of suffering cancers of the liver, pancreas, endometrium, colon and others

(Shikata *et al.* 2013). Increased cancer risk in the diabetic population may be attributed to treatment for diabetes, to hormonal disorders, to the status of chronic inflammation

and to metabolic alterations underlying the diseases (summarized in Fig. 1). Moreover, diabetes may also develop following tumor establishment in certain pancreatic and liver cancers that progress very rapidly (Li *et al.* 2012; Fig. 1, please note the double headed arrow representing the bidirectionality of the link). As, to our knowledge, there are very few studies that analyze this point separately, we do not explore it in this review. The impact of antidiabetic treatments on cancer risk is discussed elsewhere (Bowker *et al.* 2006, Jonasson *et al.* 2009, Dowling *et al.* 2012, Bosetti *et al.* 2013).

The major hormonal disorders in diabetes are unbalanced adipokine secretion, reviewed in Khandekar *et al.* (2011), and most important hyperinsulinemia and the

associated increase in insulin-like growth factor 1 (IGF1) signaling. Hyperinsulinemia may arise in type 1 diabetes (T1D) from exogenous injection due to treatment, and in type 2 diabetes (T2D) it develops early in the disease as a physiological response to lower the increasingly high glucose levels in the blood. The mechanisms whereby hyperinsulinemia could link diabetes and cancer have been extensively reviewed, and are thought to be mediated mainly by increased bioavailability of IGF1 (Novosyadlyy & LeRoith 2010, Djioque *et al.* 2013). However, recent epidemiological studies demonstrate that circulating IGF1 levels do not correlate with tumor progression and report no relationship between IGF1 or IGF-binding protein levels and cancer risk (Kaplan *et al.* 2012).



**Figure 1**

Links between diabetes and cancer. Diabetes and cancer are linked by a double headed arrow because the frequency of certain cancers is increased in the diabetic population and conversely certain cancer patients develop diabetes (see the text). The diagram shows a summary of mechanisms that may contribute to increased cancer risk in the diabetic population, that is i) some treatments which are not discussed in this review; ii) hormonal disorders such as increased circulating levels of insulin (endogenous or exogenous), and subsequent increase in insulin-like growth factor 1 (IGF1) signaling. Altered balances of some adipokines may also contribute to an

inflammatory state and increased proliferation; iii) chronic inflammation characterized by increased circulating levels of tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), interleukin 6 (IL6), and others which have been described to underlie the diabetic state; iv) metabolic disturbances are represented mainly by hyperglycemia and accumulation of reactive oxygen species (ROS), both of which may induce secretion of proinflammatory cytokines and hormonal disorders, such as increased insulin secretion, and therefore both lead to increased proliferation and mutations. The effects of hyperglycemia are detailed in Fig. 3. For other details, see the text.

Another aspect of the pathophysiology of diabetes and cancer is a shared status of chronic inflammatory signaling leading to insulin resistance (Grivennikov *et al.* 2010, Hummasti & Hotamisligil 2010, Nakagawa & Maeda 2012). Inflammatory cytokines signal through the mitogen-associated protein kinase: MAPK or JAK/STAT pathways, and contribute to cancer biology through increased proliferation, survival, accumulation of mutations (Hoffmann & Baltimore 2006, Parameswaran & Patial 2010), and suppression of host antitumor immunity (Yu *et al.* 2009). However, although it seems clear that inflammatory cytokines play an important role in tumor growth and invasion, the inflammatory response may also have antitumor activity (Allavena & Mantovani 2012, Haabeth *et al.* 2012). More studies are needed to clarify the contribution of the inflammatory response.

Diabetes-associated metabolic alterations such as increased circulating levels of lipids and sugar represent another link with cancer. Lipid metabolism and signaling might play an important, though still incompletely understood, role in cancer which has been recently covered by Natter & Kohlwein (2013). The analysis of the influence of lipids on diabetes-associated cancers is beyond the scope of this review. Hyperglycemia is the best characterized metabolic alteration in all types of diabetes, and we discuss in this review the evidence and molecular mechanisms that may associate hyperglycemia with cancer (Giovannucci *et al.* 2010, Wang *et al.* 2013). Hyperglycemia links diabetes and cancer indirectly through the induction of increased circulating levels of growth factors (insulin/IGF1) and inflammatory cytokines, but hyperglycemia also acts directly upon tumor cells. Among the direct actions on cancer cells, a relatively unexplored aspect is the influence of high glucose levels on cancer signaling. In this context, high glucose has been shown to be essential for WNT/ $\beta$ -catenin signaling, a key cancer-associated pathway (Anagnostou & Shepherd 2008, Chocarro-Calvo *et al.* 2013). As such, amplified WNT/ $\beta$ -catenin signaling represents a previously unrecognized link that may contribute to the higher frequencies of cancer in the diabetic population. Other examples of metabolic remodeling of cancer-related signaling are illustrated by enhanced MAPK and AKT cancer-related signaling through increased production of reactive oxygen species (ROS) via increased oxidative phosphorylation (OXPHOS) (Ray *et al.* 2012).

Mutations toward constitutive oncogene activation or loss of tumor suppressors have been viewed as initiating steps in cancer promotion (Hsu & Sabatini 2008, Jones & Thompson 2009), while metabolic changes have been

considered as an adaptation or a consequence of such mutations. As such, a number of oncogenes including *RAS* and *MYC* have been shown to alter the expression of many genes encoding metabolic enzymes critical for glycolysis, OXPHOS, etc. (Pylayeva-Gupta *et al.* 2011). Although this is undisputable, metabolic stress may also drive the acquisition of mutations for cancer promotion (Martinez-Outschoorn *et al.* 2013). Metabolic stress may be caused by excess nutrients (Wellen & Thompson 2010) – like hyperglycemia – in cells that are able to take them up but are incapable of storing them (the vast majority of our cells). In this respect, circulating levels of insulin or IGF1 will allow glucose uptake without the need for mutations. In this review, we provide an overview of the mechanisms that may link hyperglycemia to cancer with a special focus on those related to remodeling cancer-associated cell signaling.

### Hyperglycemia may feed cancer cells: the sweet kiss of death

Over the last century, cancer patients have been reported to exhibit signs of early glucose intolerance and insulin insensitivity, most likely as a result of an acute phase inflammatory response induced by the tumor (Marat *et al.* 1999, Klement & Kammerer 2011). On the other hand, enhanced glucose uptake is a well-known metabolic hallmark of cancer cells. Hyperglycemia could therefore ensure a high glucose supply for cancer cells favoring anabolic cancer metabolism to fuel tumor growth and thereby explain the increased cancer risk associated with diabetes. Thus the relationship between hyperglycemia and cancer appears bidirectional: cancer can cause hyperglycemia, and hyperglycemia may facilitate cancer appearance and growth.

Increased glucose flux and metabolism, maintained by angiogenesis, promotes cell cycle progression, excessive proliferation, and anti-apoptotic signaling in cancer cells. *In vitro*, in tumor cell lines from several organs (breast, colon, others), diabetogenic glucose concentrations alter the expression of genes that promote cell proliferation, migration, and adhesion (Masur *et al.* 2011). *In vivo*, in tumor-bearing animals, blood glucose levels strongly correlate with tumor growth. Certain experimental cancers behave more aggressively when animals overeat, and less aggressively when animals are calorically restricted (Algire *et al.* 2008, Kalaany & Sabatini 2009, Park *et al.* 2010), providing evidence that diet may influence neoplasia (Pollak 2009). Indeed, animals fed a calorie-restricted diet

show a strong reduction in plasma glucose levels and prolonged survival (Santisteban *et al.* 1985).

In humans, high sugar intake and elevated blood glucose levels are associated with increased cancer risk, with hyperglycemia being a predictor of poor survival (Krone & Ely 2005, Derr *et al.* 2009). In large cohort studies, hyperglycemia is positively correlated to an increased risk of developing cancers associated with the gastrointestinal tract (Jee *et al.* 2005, Stattin *et al.* 2007, Ikeda *et al.* 2009). A diet which repeatedly elevates blood glucose levels due to a high glycemic load has been suggested to provide additional growth stimuli for neoplastic cells (Mulholland *et al.* 2008, Masur *et al.* 2011).

Increased demands for glucose by cancer cells and the positive correlation between cancer risk and hyperglycemia, as in T1D and T2D, may not be a coincidence. Thus, hyperglycemia should not be neglected as a potential underlying factor facilitating cancer growth and/or establishment.

### Hyperglycemia vs hyperinsulinemia as a cancer–diabetes link

Although impaired glucose tolerance, without diabetes, is associated with increased cancer risk (Dankner *et al.* 2007), hyperglycemia inexorably induces increased insulin secretion unless there is a defect in insulin production or secretion. Hyperinsulinemia develops early in T2D patients in response to hyperglycemia and may also be present in T1D patients after exogenous injection of insulin. As insulin acts as a growth factor, hyperglycemia has been classically considered as a subordinate and hyperinsulinemia as the primary causative factors for cancer (Giovannucci 2001). Early attempts to clarify this point showed that tumor growth was retarded in animals with T1D (Heuson & Legros 1972), suggesting that tumor growth relies on insulin and not on high glucose. However, the autoimmune nature of T1D may complicate the interpretation of this result, because the immune system plays a pivotal role in cancer cell surveillance (Allavena & Mantovani 2012, Haabeth *et al.* 2012). *In vitro* studies also showed that adding insulin to the medium containing high glucose promoted the sequential activation of PI3K, AKT, and mTOR leading to the increased anabolic activity in cancer cells and subsequent 20–40% enhanced proliferation rates (Klement & Kammerer 2011, Ward & Thompson 2012). However, in these experiments, the effects of hyperinsulinemia and hyperglycemia could not be disentangled as both were present and the tissue culture medium contained high levels of glucose.

*In vitro*, activation of the receptors for insulin or IGF1 (IR and IGF1R respectively) increases proliferation and blocks apoptosis. This, together with the observation that cancer cells over express IRs and IGF1Rs supports the idea that insulin and IGF1 are important drivers of cancer cell growth. However these receptors appear to be over expressed in most solid and hematopoietic tumors and are not specifically increased in those cancers associated with diabetes (Belfiore *et al.* 2009, Gallagher & LeRoith 2011). Furthermore, targeting IGF1R with different inhibitors has been helpful only in small subsets of patients, reviewed in Chen & Sharon (2013), although the failure of the treatment could be attributed in some cases to constitutive activation of the pathway. On the other hand, increased circulating levels of insulin or IGF1 have been reported in prostate cancer (Hellawell *et al.* 2002, Rowlands *et al.* 2012). Nevertheless, prostate cancer is less frequent in the diabetic than in the nondiabetic population (Kasper & Giovannucci 2006). Moreover, some authors have reported decreased tumor growth after insulin treatment in diabetic animals (Fisher *et al.* 1995) or the successful treatment of some patients with metastatic tumors by an insulin-induced hypoglycemic coma (Koroljow 1962). Some authors even propose that insulin may help in antitumoral treatment by increasing membrane permeability to other drugs (Lasalvia-Prisco *et al.* 2004).

In contrast, high glycemic index or high glycemic load does correlate with the site-specific cancers associated with diabetes (Gnagnarella *et al.* 2008, Mulholland *et al.* 2009). Cancer cells upregulate glucose transporters (GLUTs) independently of insulin (Pollak 2008, Szablewski 2013), although insulin may further increase the exhibition of glucose transporter GLUT1 and glucose uptake with it in some cells (Cifuentes *et al.* 2011). The importance of high glucose for cancer growth and survival is supported by results obtained after glucose starvation. Malignant cells *in vitro* quickly lose ATP when starved of glucose (Demetrakopoulos *et al.* 1978, Priebe *et al.* 2011). Glucose starved cells commit apoptosis after toxic accumulation of ROS that results from a positive feedback loop including increased tyrosine kinase signaling (Graham *et al.* 2012). In animals bearing tumors (Zhou *et al.* 2007), and in human patients (Seyfried *et al.* 2009), lowering blood glucose with ketogenic diets to force mitochondrial use of ketones as energy sources restricts the amount of glucose available to cancer cells and improves or prolongs survival. Moreover, treatment with metformin, which decreases hepatic gluconeogenesis and reduces glucose release to the blood, improves cancer outcome (El-Mir *et al.* 2000, Dowling *et al.* 2012).

However, metformin also has direct actions on cancer cells, some of them through induction of the metabolic sensor AMPK (Dowling *et al.* 2012, Hardie 2013).

Better-controlled experiments might help evaluate the relative importance of insulin and glucose. For example, tumor appearance and growth may be tested in animals with hyperglycemia induced in the absence of hyperinsulinemia or inflammation. In this respect, it is interesting to highlight that association of T1D with the diabetes-specific cancers is stronger than in T2D, even though hyperinsulinemia may play a more prominent role in T2D (García-Jiménez *et al.*, manuscript in preparation). Nevertheless, if exogenous administration of insulin in T1D is associated with cancers, it should be considered among the cancers associated with treatments for diabetes which appear to be even more site-restricted, for example to the bladder, kidney, and breast, but not to gastrointestinal tumors which are more strongly linked to T1D.

### Hyperglycemia contributes to the abnormal glucose metabolism in cancer cells

Cancer cells originate from noncancer cells and exhibit very distinctive metabolic hallmarks (Hanahan & Weinberg 2011). Senescence and apoptosis bypass coupled to higher proliferation rates and migratory capacity must be fed. Enhanced angiogenesis in response to factors secreted by the tumor drives the genesis of new blood vessels that increase the supply of energetic substrates and building blocks needed to make new cells. Proliferative and resting cells differ more in their demands for anabolic substrates than in their ATP requirements (Locasale & Cantley 2011, Chocarro-Calvo *et al.* 2013). However, the anabolic urge of tumor cells drives them to adapt with profound metabolic changes, among which the most remarkable is the switch from OXPHOS toward aerobic glycolysis, known since 1956 as the 'Warburg effect' after its discoverer, the Nobel prize-winner Otto Warburg. Glycolysis maximizes the production of building blocks at the cost of diminished energy production compared with OXPHOS. Through glycolysis, cancer cells convert each mole of glucose into 2 mol pyruvate obtaining 2 mol ATP. Via OXPHOS, 36 mol ATP are obtained from each mole of glucose. The advantage of glycolytic metabolism is the production of glycolytic intermediaries that can be used in anabolic pathways that allow synthesis of proteins, nucleic acids, and lipids needed for proliferation. Although the Warburg effect was initially observed in rapidly proliferating cancer cells, normal liver cells and highly proliferative T lymphocytes also exhibit increased

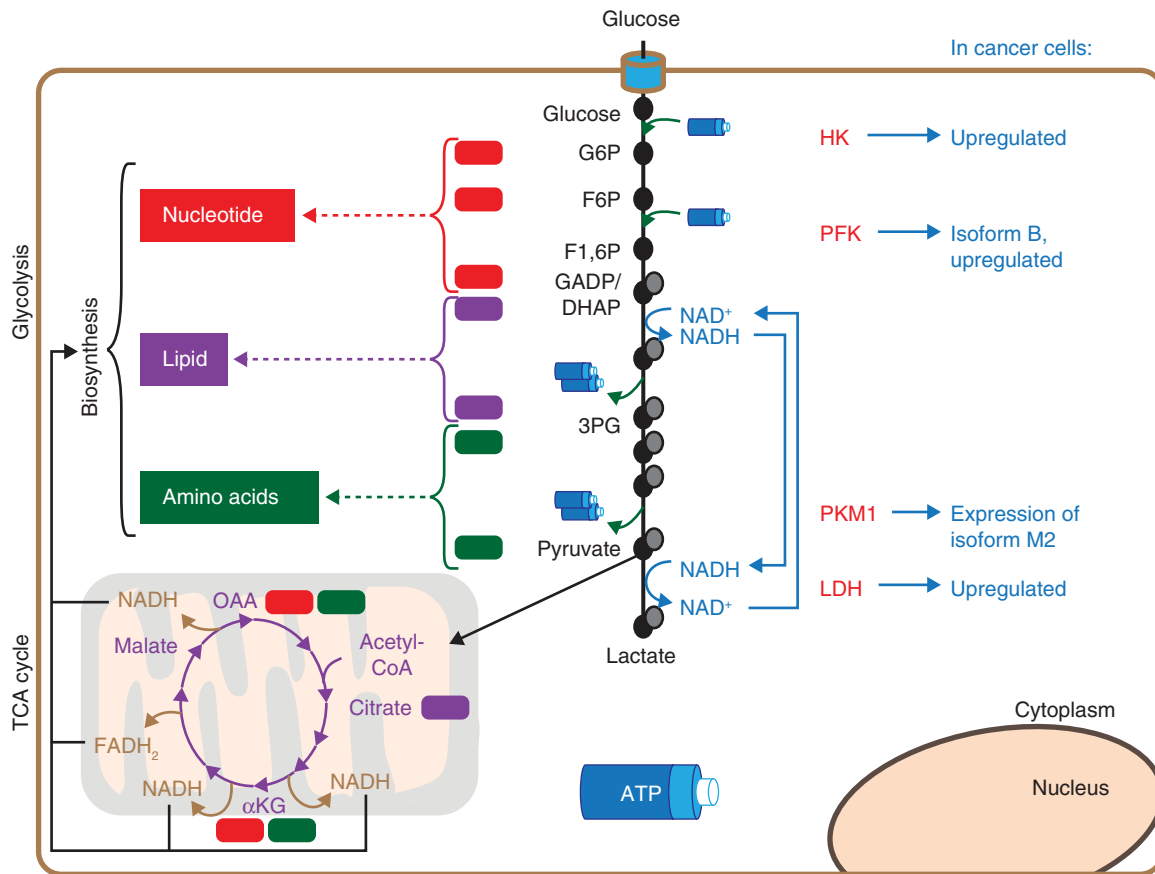
glycolysis as a mechanism to maximize the accumulation of anabolic intermediaries required to sustain proliferation (Lunt & Vander Heiden 2011, MacIver *et al.* 2013).

An increase in glucose availability that is not contested by storage or the Warburg effect will generally speed up the metabolism, including OXPHOS. This leads to an increase in ROS production, through the mitochondrial respiratory complexes (Balaban *et al.* 2005) that results in increased DNA damage and cell death (Wellen & Thompson 2010). Cancer cells increase their glucose uptake and utilization but keep a reduced OXPHOS rate. Increasing glycolysis flux allows enhanced uptake of carbon sources and accumulation of anabolic intermediaries. Decreasing OXPHOS flux declines ROS production which leads to increased cell survival and contributes to sustain pluripotency. Potential mechanisms to decrease ROS in cancer cells and maintain pluripotency are discussed in the next section on 'mechanisms for hyperglycemia increased cancer'. Nevertheless, cancer cells do not completely switch off OXPHOS. The enzymatic machinery is only less efficient due to differential expression of specific enzymatic variants (Balaban *et al.* 2005).

The apparent paradox that a cancer cell with high energy demands switches toward glycolysis may be interpreted as the adaptation of tumor cells to supply the anabolic intermediates required for rapid proliferation. Therefore, the poor energetic pay off of glycolysis needs to be compensated by a high glucose supply from angiogenesis-derived new blood vessels, high glucose uptake through the upregulation of GLUTs, and increased glycolytic flux through changes in critical enzymes (summarized in Fig. 2).

To keep pace with the increased demand for energy and anabolic intermediates, glucose uptake is enhanced in cancer cells independently of insulin. This is exploited in clinical practice to detect residual tumor activity after surgery through [<sup>18</sup>F]fluorodeoxyglucose positron emission tomography (FDG-PeT).

GLUTs, and especially GLUT1 whose expression is insulin-independent, are upregulated in many cancer cells (Tennant *et al.* 2009). GLUTs expression is upregulated by oncogenes such as RAS, hypoxia (via increased activity of the hypoxia inducible factor transcription regulator, HIF1 $\alpha$ ), accumulation of ROS, and other factors characteristic of tumor cells (Cushman & Wardzala 1980, Suzuki & Kono 1980). Additionally, HIF1 $\alpha$  cooperates with activated AKT, downstream of PI3K signaling, to enhance the expression of critical glycolytic enzymes (see Fig. 2) such as hexokinase (HK), phospho fructo kinase isoform B (PFKB) (Deprez *et al.* 1997, Majewski *et al.* 2004) and lactate



**Figure 2**

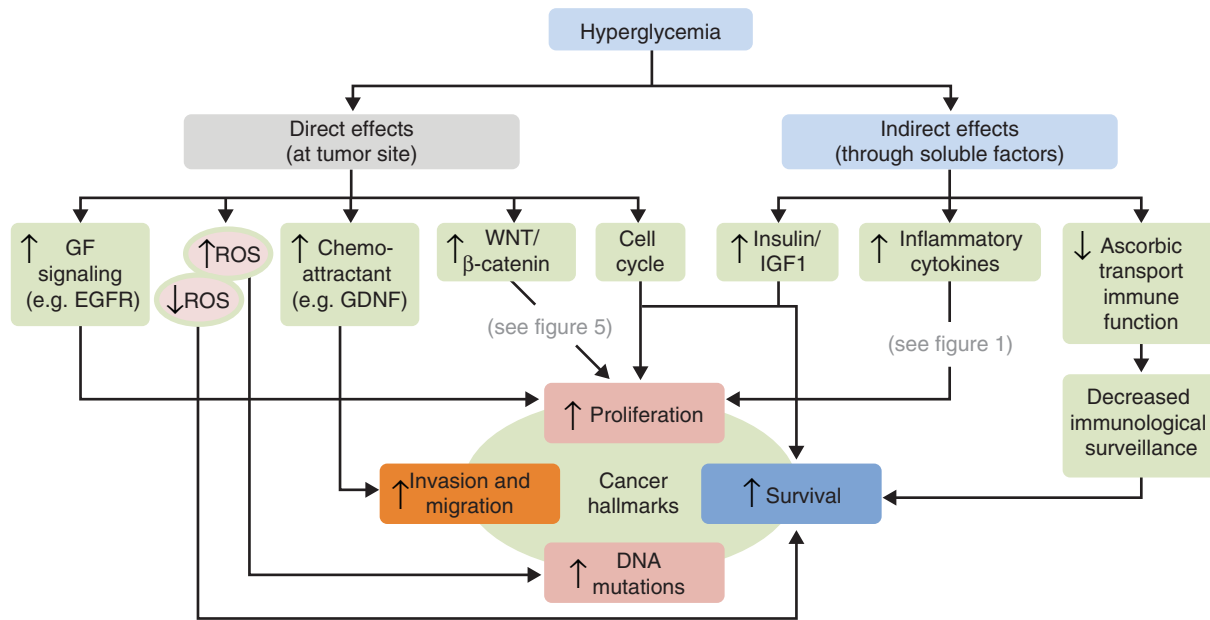
Glucose-addiction and recycling of glucose into macromolecules to feed proliferation. Of the metabolic adaptations of cancer cells the most remarkable are the increased glycolytic and decreased oxidative phosphorylation (OXPHOS) rates. Although other substrates such as glutamine provide a source of nitrogen and carbon, glucose is the main carbon source and as such uptake of glucose is enhanced by several adaptations. When glucose enters glycolysis, it renders ATP (blue cylinders), redox power (NADH), and, most important for highly proliferating cells, anabolic intermediaries (black dots) ready to use as precursors to synthesize nucleotides (red boxes), amino acids (green boxes), and lipids (purple boxes), which are the building blocks for nucleic acids, proteins, and membranes during proliferation. Increased glycolytic flux is necessary to

dehydrogenase (LDH). LDH reduces pyruvate to lactate and regenerates  $\text{NAD}^+$ . Lactate fuels hepatic gluconeogenesis and  $\text{NAD}^+$  regeneration is critical for continued flux through glycolysis as well as for the deacetylase activity of sirtuins that are critically involved in cancer and longevity. Other glycolytic steps differ in cancer cells due to differential expression of enzyme isoforms. For example, the M2 isoform of pyruvate kinase (PKM2) expressed in cancer cells facilitates diversion of glycolytic intermediates into biosynthetic pathways in contrast with the isoform PKM1, expressed in noncancer cells (Hamanaka & Chandel 2012).

fulfill the increasing demands of proliferating cancer cells which adapt through upregulation of several critical enzymes such as hexokinase (HK), phospho fructo kinase isoform B (PFKB), and lactate dehydrogenase (LDH) which regenerates the  $\text{NAD}^+$  to be used in the next glycolysis cycle and through the expression of characteristic isoform of others like pyruvate kinase, isoform M2 (PKM2) that facilitates the use of glycolytic intermediates in various anabolic pathways. For other details, see the text. AA, amino acid;  $\alpha\text{KG}$ ,  $\alpha$ -ketoglutarate; DHAP, dihydroxyacetone phosphate; F1,6P, fructose-1,6-biphosphate; F6P, fructose-6-phosphate; G6P, glucose-6-phosphate; GADP, glyceraldehyde-3-phosphate; OAA, oxaloacetate; 3PG, 3-phosphoglycerate.

### Effects of hyperglycemia at the level of the organism and their impact on cancer development

Hyperglycemia may increase cancer through several cooperative mechanisms, summarized in Fig. 3. We have divided the effects of hyperglycemia on cancer as 'direct' when the effect is exerted directly on tumor cells and 'indirect' when the action takes place at other organs that will later on influence tumor cells. Indirect mechanisms include the induction of i) increased circulating levels of insulin and bioavailability of IGF1, ii) increased secretion

**Figure 3**

The many mechanisms by which hyperglycemia may feed cancer cells. Hyperglycemia may have direct effects on the tumor site, or indirect effects through soluble factors. Direct effects promote: i) increased growth factor signaling (GF) and accelerated cell cycle. ii) An initial accumulation of ROS enhances mutagenesis and leads to the secondary selection of clones with diminished ROS production to ensure survival. Alternatively, some cancer cells also export ROS to neighboring cells to ensure their own survival (see the main text). iii) The upregulation of chemo-attractants for invasion, such as glial cell line-derived neurotrophic factor (GDNF). iv) An increase in the WNT/ $\beta$ -catenin signaling pathway which favors proliferation,

of inflammatory cytokines and adipokines, and iii) decreased immune surveillance.

First, high plasma glucose concentrations induce insulin secretion and elevate the levels of circulating insulin and free IGF1 (Rajaram *et al.* 1997), two potent anti-apoptotic growth factors for most cancer cells (Pollak 2008). In addition, insulin also stimulates the release of the proinflammatory cytokine interleukin 6 (IL6) from human adipocytes (LaPensee *et al.* 2008).

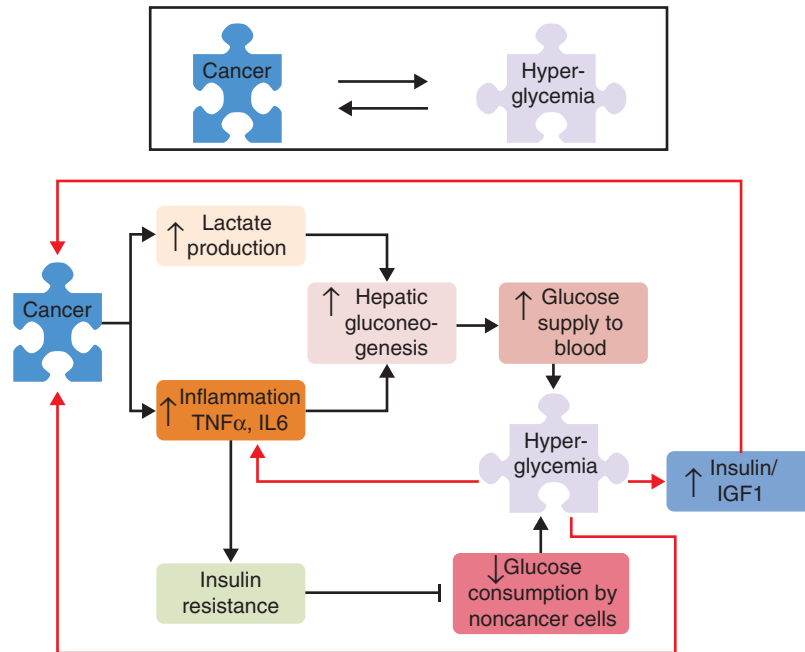
Second, high plasma glucose *in vitro* and *in vivo* activates monocytes and macrophages to produce the inflammatory cytokines tumor necrosis factor alpha (TNF $\alpha$ ) and IL6 (Devaraj *et al.* 2005, Gonzalez *et al.* 2012). Interestingly, circulating TNF $\alpha$  and IL6 levels are also increased through a tumor-induced acute phase inflammatory response (McCall *et al.* 1992) and trigger insulin resistance in cancer patients (Makino *et al.* 1998). Additionally, the inflammatory process leads to increased gluconeogenesis in the liver of cancer patients, which is further enhanced by lactate secreted from the tumor (Waterhouse *et al.* 1979; Fig. 4). Hepatic gluconeogenesis

antisenescence and invasion. The mechanisms used for high glucose to enhance this pathway are summarized in Fig. 5. Indirect effects of hyperglycemia on cancer cells are mediated through i) increased levels of insulin/IGF1 and/or ii) inflammatory cytokines as well as iii) a diminished immunological surveillance. The reduced immune response is achieved through the reduction in ascorbic acid transport in critical immune cells that diminishes their phagocytic and proliferation capabilities. Both direct and indirect effects converge on cancer hallmarks (increased proliferation, survival, invasion, and migration and accumulation of mutations in the DNA). For other details, see the main text.

increases circulating glucose levels and, consistently, removal of the tumor improves glucose clearance (Permert *et al.* 1993, Yoshikawa *et al.* 1994). In summary, high glucose and inflammation feed each other as high glucose triggers inflammation while inflammation induces insulin resistance and hepatic gluconeogenesis, both leading to increased glycemia in a positive feedback loop.

Third, high glucose alters immune function because glucose competitively impairs the transport of ascorbic acid into immune cells (Krone & Ely 2005). As ascorbic acid is needed for effective phagocytosis, mitosis and for proper function of lymphocytes, the immune response to malignant cells diminishes with hyperglycemia. It stands to reason that all these mechanisms may act synergistically.

Thus, at the level of the organism not only does hyperglycemia enhance tumor growth through several non exclusive mechanisms, but there are also a number of mechanisms by which the tumor induces metabolic adaptations in other organs to favor hyperglycemia. The supply of high glucose to the 'parasite' cancer cells is thus increased. These bidirectional relationships are summarized in Fig. 4.

**Figure 4**

Cancer cells ensure high glucose supply through enhanced hyperglycemia and hyperglycemia favors tumor growth: the strategy of a parasite. Hyperglycemia favors tumor growth at the organism level – as depicted in 'indirect mechanisms' in Fig. 3 – by increased secretion of the growth factors, insulin and IGF1, reduced immune surveillance, and increased circulating inflammatory cytokines. This causes insulin resistance that diminishes glucose consumption (by noncancer cells) and increased hepatic gluconeogenesis. Reduced uptake from the blood and increased supply

from the liver contribute to hyperglycemia. Cancer supports and enhances hyperglycemia in various ways: i) the metabolic switch in cancer cells drives increased glycolytic flux and lactate production. Lactate induces gluconeogenesis at the liver contributing to hyperglycemia. ii) Tumor growth also induces an acute inflammatory response with increased production of inflammatory cytokines  $TNF\alpha$  and IL6, known to cause insulin resistance and induce hepatic gluconeogenesis. Both of these processes contribute to hyperglycemia.

### Mechanisms for hyperglycemia increased cancer risk: direct effects on cancer cells

The direct effects of high glucose on tumor cells include i) increased proliferation, ii) induced mutations, iii) augmented invasion and migration and iv) rewiring of cancer-associated signaling pathways.

First, high glucose accelerates the cell cycle through changes in the expression of critical genes such as *E2F* and cyclins A and E (Masur *et al.* 2011). Proliferation is also induced through increased expression of epidermal growth factor (EGF) and enhanced EGF receptor signaling in pancreatic cancer cells (Li *et al.* 2011).

Second, high glucose induces mutations through upregulated oxidative stress-responsive genes (like thioredoxin-interacting protein) that in turn increase the levels of ROS (Turturro *et al.* 2007). ROS facilitate mutations and cell death through increased DNA damage, impaired repair, accumulation of advanced glycation end products (Sindhu *et al.* 2004) and, as reported in diabetic individuals, through the overproduction of superoxide by

the mitochondrial electron transport chain (Brownlee 2001). Unrestricted glucose availability may accelerate the metabolic rate and lead to increased oxygen consumption and ROS generation in a first phase. High ROS will cause mutations first at the mitochondrial DNA (where ROS are produced through OXPHOS) and then in nuclear encoded genes, see Wellen & Thompson (2010). As most mitochondrial DNA encode for proteins, there will be a high probability that enzymes for OXPHOS will be altered leading to a subsequent decrease in ROS generation. From the generated mutants, those that allow for efficient diversion of captured glucose toward anabolism will be rapidly selected. These include those mutants that render constitutive activation of the AKT signaling pathway and independence of insulin for glucose uptake. Reduction in ROS production will ensure survival and pluripotency of those clones. That is, a switch from high to low ROS production in cancer cells may develop temporarily. Alternatively, ROS produced by cancer cells may be exported to neighboring cells, enabling cancer cells to survive by keeping a low oxidative potential as reported by



Martinez-Outschoorn *et al.* (2013), who used oncogene-transformed cancer cells cocultured with fibroblasts and demonstrated that oxidative stress imposed by oncogene activated cancer cells induces metabolic reprogramming toward glycolysis in surrounding fibroblasts, which in turn exported lactate toward cancer cells. Fibroblasts were nesting and protecting the oncogenic cancer cells in a very interesting model of metabolic symbiosis, where the tumor behaves as a parasite (Martinez-Outschoorn *et al.* 2013). Further research on metabolic interrelationships between cancer and neighboring cells is needed.

Third, high glucose induces invasiveness and migration. Masur *et al.* (2011) demonstrated that diabetogenic glucose concentrations decrease E-cadherin and increase protein kinase C $\alpha$  signaling leading to increased cell motility. E-cadherin maintains cell–cell adhesion and plays a pivotal role in epithelial–mesenchymal transition (EMT), a multifaceted developmental program critical for the acquisition of migration and invasion capabilities and for the maintenance of stem cells. EMT might be activated transiently and to different degrees by carcinoma cells during metastasis, reviewed in Hanahan & Weinberg (2011). Acquisition of EMT phenotype and expression of cancer stem markers were induced in basal luminal breast carcinoma by high glucose consumption which reduced ROS production (Dong *et al.* 2013) allowing survival. Dong *et al.* first observed that high glucose induced epigenetic silencing of a critical gluconeogenesis enzyme through the EMT-related transcriptional repressor Snail. Lack of this gluconeogenic enzyme on its own increased glycolysis and the NADPH produced via pentose phosphate pathway (ensuring anabolic intermediates for proliferation) and reduced OXPHOS. Both reduced OXPHOS and increased NADPH (used by enzymes that detoxify H<sub>2</sub>O<sub>2</sub>) contributed to lower ROS production, and correlated with expression of cancer stem cell markers dependent on  $\beta$ -catenin/transcription factor 4 (TCF4) activation, see also comment by Schieber & Chandel (2013).

In addition to the previous direct effects of high glucose on migration, several diffusible mediators of high glucose also increase migration in the pancreatic cells. For example, high glucose induces the expression of urokinase plasminogen activator. This enhances invasive and migratory activities (Li *et al.* 2011) and also upregulates chemo-attractant glial cell line-derived neurotrophic factor (GDNF) expression and its interaction with the RET tyrosine kinase receptor, a critical step for tumor progression, migration, and invasion (Liu *et al.* 2011).

Thus, cancer cell hallmarks concerning glucose metabolism may be consequences and also a cause of

transformation (Ward & Thompson 2012). Oncogenic mutations may dictate increased glucose uptake, which may itself dictate distinct phenotypes inside the tumor, allowing the coexistence of cancer stem and migratory cells as well as highly proliferative cells. Some tumors have been described as symbiotic associations of cells that secrete and cells that import lactate to be used as energy sources (Kennedy & Dewhirst 2009). The diversity of tumor cells may rely on metabolic differences and on the relationships between tumor cells and their surrounding cells. These are very promising research avenues that will advance our understanding of tumor pathophysiology and may empower therapeutic strategies.

Fourth, high glucose enhances cancer-associated WNT signaling (see below) by allowing nuclear retention and accumulation of transcriptionally active  $\beta$ -catenin independently of hyperinsulinemia, adipokines, or inflammation (Chocarro-Calvo *et al.* 2013).  $\beta$ -catenin is a potent transcriptional coactivator targeted to genes involved in proliferation (Niehrs & Acebron 2012, Anastas & Moon 2013) and senescence bypass (Larue *et al.* 2009) among others. Nuclear  $\beta$ -catenin is a well-known tumor marker of bad prognosis, and therefore the requirement for high glucose by WNT signaling to promote nuclear accumulation of  $\beta$ -catenin is likely to have a major impact on cancer biology.

### WNT signaling links hyperglycemia and diabetes to cancer

The WNTs comprise a large family of secreted cys-rich glycoprotein ligands that coordinate cell fate decision-making in a broad range of developmental and homeostatic contexts (Clevers & Nusse 2012). WNT proteins bind to their membrane receptors and activate a number of pathways, including planar cell polarity pathway, Ca<sup>2+</sup> signaling, and the canonical WNT/ $\beta$ -catenin pathway which is the best known and the most deeply involved in cancer. Functional WNT/ $\beta$ -catenin signaling is transiently activated to maintain stem cells in the intestinal crypts (Korinek *et al.* 1998). However, constitutive WNT signaling was believed to lead to nuclear accumulation of the WNT effector  $\beta$ -catenin (a well-known tumor marker) and promotion of aberrant cell growth, senescence bypass (Delmas *et al.* 2007), and cancer (Clevers 2006). Notably, aberrant WNT signaling is present in 40–90% gastrointestinal cancers (White *et al.* 2012), which are the specific cancer sites more tightly associated with diabetes.

WNT signaling is also tightly associated with diabetes. Indirect links are illustrated by WNT-regulated control of adipocyte differentiation and obesity (Lu *et al.* 2013),

a major risk factor for diabetes. Direct links are illustrated by the mutations reported in its effector, the transcription factor TCF7L2 (previously known as TCF4), which represent the strongest genetic link with diabetes in all ethnicities (Saxena *et al.* 2006, Lyssenko 2008). The role of the TCF7L2 intronic mutations associated with diabetes has remained elusive, but since their discovery, WNT/ $\beta$ -catenin signaling has been shown to increase the expression of incretin hormones (Garcia-Martinez *et al.* 2009) that are global regulators of metabolism and are required for normal glucose-dependent insulin secretion. As such, WNT-mediated induction of incretin production established a new link between WNT and diabetes. This has been reinforced by the findings that WNT also induces incretin receptor expression and signaling in the pancreas as well as insulin expression and secretion, reviewed in Garcia-Jimenez (2010). In other tissues, WNT induces the expression of the receptors for insulin and IGF1 (Singh *et al.* 2013). Recently, Savic *et al.* (2011) have demonstrated that the diabetes-associated TCF7L2 intronic mutations had a gain of expression effect and a role on glucose metabolism. Next, Boj *et al.* (2012) demonstrated that most of the genes controlled by TCF7L2 in the liver are metabolic regulators. In fact, the hepatic response to fasting critically relies on TCF7L2. Consistently, hepatic gluconeogenesis is diminished in animals whose TCF7L2 loci have been silenced. Reintroduction of the gene restores glucose production by the liver in concordance with the high blood glucose levels found during fasting in human carriers of the TCF7L2 mutation.

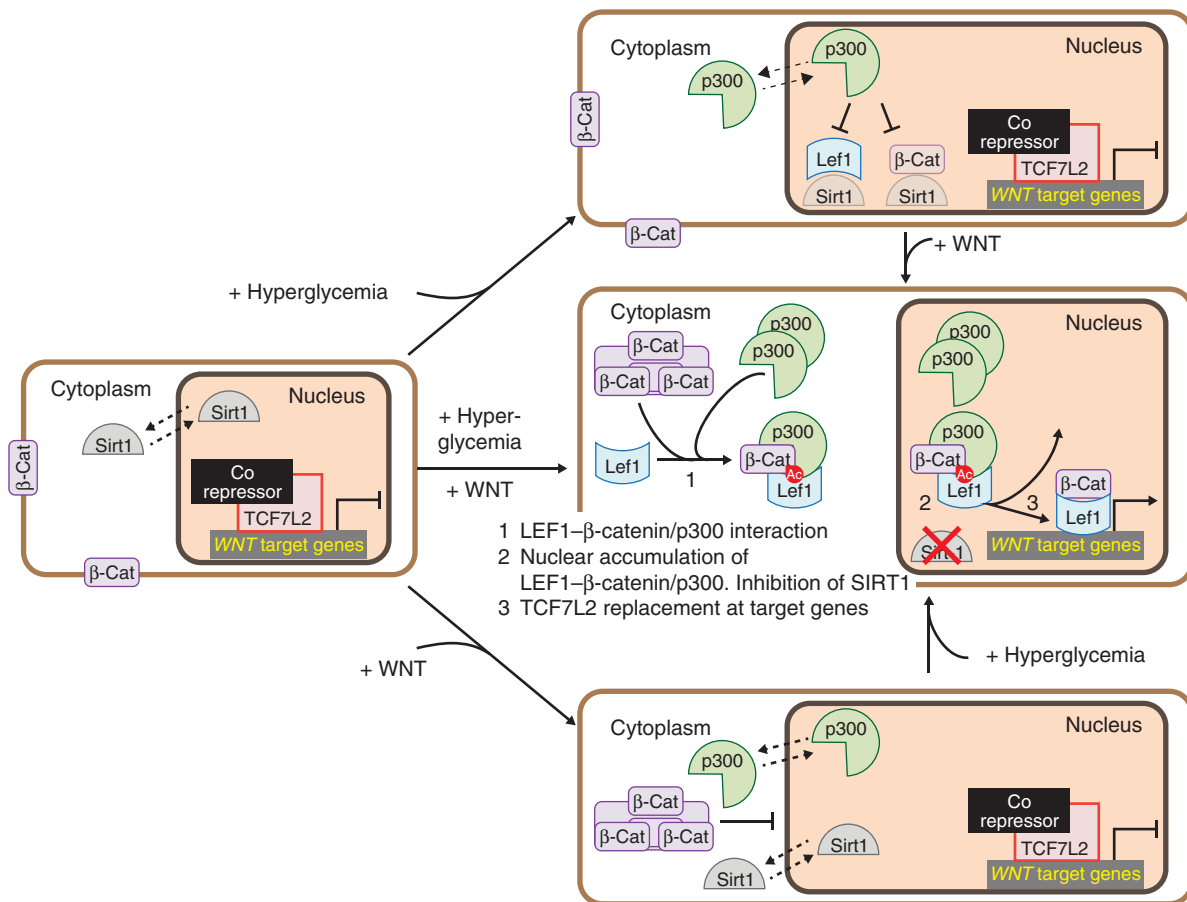
Thus, a growing number of genes involved in metabolism have to be added to the classical WNT/ $\beta$ -catenin targets that are mostly involved in proliferation and prosurvival (see below). This suggests that WNT may serve as a new factor that links enhanced cancer risk with metabolic diseases such as hyperglycemia, obesity, and diabetes. This link becomes especially relevant because TCF7L2 mutations associated with diabetes increase basal circulating glucose levels, and because WNT increases insulin production, secretion, and signaling through enhanced receptor expression.

Excellent and extensive reviews focused on WNT signaling have recently been published (Clevers & Nusse 2012, Anastas & Moon 2013), but here we will draw a very simple outline. In the 'canonical' WNT/ $\beta$ -catenin signaling pathway, WNT binds to frizzled and lipoprotein receptor-related protein LRP5/6 coreceptors. This leads to inactivation of glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ), a kinase that constitutively phosphorylates cytosolic  $\beta$ -catenin to trigger its degradation.

Traditionally, it was understood that the resulting pool of stabilized cytosolic  $\beta$ -catenin delocalized from the membrane and entered the nucleus. Once there, it was thought to bind as a potent coactivator to transcription factor members of the T cell factor/lymphoid enhancer factor (TCF/LEF) family such as TCF7L2 and LEF1, activating target genes which include those of critical factors for proliferation and prosurvival such as those encoding MYC and Cyclin D1. However, there is now new and solid evidence that demonstrates that WNT stimulation alone is not enough to promote nuclear accumulation of  $\beta$ -catenin, but that this process requires and depends on high glucose to increase its nuclear retention in a variety of human tumor-derived cell lines related to cancers associated with hyperglycemia and diabetes (Chocarro-Calvo *et al.* 2013). As nuclear accumulation of  $\beta$ -catenin is a well-known tumor marker of bad prognosis, constitutive WNT signaling in cancer on one side, and increased glucose uptake by tumor cells on the other, reveals a previously unrecognized requisite for WNT signaling in cancer, namely its amplification by high glucose (Chocarro-Calvo *et al.* 2013). The ability of high glucose to amplify WNT/ $\beta$ -catenin signaling provides a link between cancer and hyperglycemia which is independent of inflammation, hyperinsulinemia, or ROS induced mutations. As cancer cells are a well-characterized source of autocrine WNT signaling (Bafico *et al.* 2004), high glucose uptake may be critical to maintaining nuclear accumulation of  $\beta$ -catenin and subsequent tumor growth and progression, a notion reinforced by the strong dependence of tumor cells on glucose availability as highlighted above.

### High glucose enhances cancer-associated WNT signaling through targeted acetylation of $\beta$ -catenin

High glucose remodels cancer-associated WNT/ $\beta$ -catenin signaling to promote the formation and nuclear entry of a LEF1- $\beta$ -catenin complex which binds to promoters marked by poised TCF7L2, replacing it and leading to increased expression of WNT target genes (Chocarro-Calvo *et al.* 2013). The model depicted in Fig. 5 summarizes the findings that support this idea. In the absence of WNT and high glucose (left panel), WNT target genes are bound by TCF7L2 and a corepressor complex that silences their expression, while  $\beta$ -catenin remains associated with the cytoplasmic membrane. High glucose alone (up-right panel) does not increase or de-localize  $\beta$ -catenin, despite a small increase in p300 levels and WNT-target

**Figure 5**

High glucose enhances cancer-associated WNT/β-catenin signaling: a new link between hyperglycemia and cancer. In the absence of high glucose and WNT signals (left panel), *WNT* target genes remain silenced through targeted binding of TCF7L2-corepressor complexes, and β-catenin is located at specific plasma membrane sites. Stimulation with high glucose, WNT, or both, is depicted on the right panels. Upon exposure to high glucose (upper-right panel) there is a small accumulation of p300 in the nucleus and cytoplasm, but β-catenin remains at the membrane and WNT target genes remain silenced. If only WNT signals are present instead of high glucose (bottom-right panel), there is a small increase in p300 and

there is accumulation of cytosolic β-catenin, but nuclear accumulation does not occur and there is no induction of *WNT* target genes. Upon coincidence of both WNT and high glucose (mid-right panel), the expression of *WNT* target genes is induced by LEF1-β-catenin complexes that displace TCF7L2-corepressor complexes. Hyperglycemia acts on cytosolic β-catenin accumulated via WNT induction to promote three effects: (1) acetylation of β-catenin that favors formation of LEF1-β-catenin/p300 complex, (2) inhibition of SIRT1 activity required for nuclear accumulation of LEF1-β-catenin/p300, and (3) replacement TCF7L2 by LEF1-β-catenin complex inducing the transcriptional activity of target genes of *WNT*.

genes remain silenced. Stimulation by WNT proteins only (bottom-right panel) allows β-catenin release from the degradation complex and accumulation in the cytosol but not in the nucleus. Coincidence of both signals (right-mid panel) allows high glucose to cooperate with WNT by inducing acetylation of lysine residues in the armadillo repeats of β-catenin by p300 (whose levels are cooperatively upregulated by WNT and high glucose). This acetylation event is a requirement for LEF1-β-catenin complex formation, a step that facilitates β-catenin nuclear entry and specific DNA targeting by LEF1-β-catenin relying on the exhibition by LEF1 of classical

nuclear localization signal and specific DNA-binding domain (both absent in β-catenin). In this context, the interactions of β-catenin with TCF7L2 in breast cancer cells have been recently shown to rely on the oxidative state (Dong *et al.* 2013). High ROS production led to the accumulation of β-catenin-FOXA3 complexes in detriment of β-catenin-TCF7L2 complexes and using the antioxidant *N*-acetylcystein or lowering ROS production displaced β-catenin from FOXA3 toward TCF7L2. In gastrointestinal cancer cells high glucose enhances binding of β-catenin-TCF7L2 complexes to target genes but the presence of WNT signaling displaces TCF7L2 and favors

$\beta$ -catenin–LEF1 complexes (Chocarro-Calvo *et al.* 2013). It would be interesting to investigate, in individuals who are carriers of the mutation related to diabetes (that leads to increased expression of TCF7L2 and increased blood glucose), how  $\beta$ -catenin partnership evolves to adapt to metabolic challenges posed by high glucose and ROS. Also, as acetylation of both histone and non-histone proteins is regulated by nutrients (Wang *et al.* 2010, Zhao *et al.* 2010) it would be interesting to explore whether changes in ROS production alters the interactions of  $\beta$ -catenin with LEF1 and p300.

Earlier studies suggested that overexpressed p300–CBP interacted with the C-terminus of  $\beta$ -catenin (Hecht *et al.* 2000), leading to lysine acetylation. Binding to TCF–LEF factors (Lévy *et al.* 2004) and nuclear entry of  $\beta$ -catenin (Wolf *et al.* 2002) followed and correlated with increased oncogenic potential (Ma *et al.* 2005). However, the evidence for a definitive role for p300-mediated acetylation of  $\beta$ -catenin was inconclusive as mutation of the identified lysine (K345) targeted by p300–CBP did not significantly alter  $\beta$ -catenin-driven transcriptional activation. The nature of the pathophysiological stimulus that increased acetylation and oncogenic potential also remained unknown. Under WNT signaling, high glucose has been revealed as a pathophysiological stimulus whose combined action, inducing p300 acetyltransferase and inhibiting sirtuin deacetylase activities, targets  $\beta$ -catenin acetylation. High glucose induced acetylation of lysine K354 in  $\beta$ -catenin, which induces nuclear retention and transcriptional activation through enhanced p300–LEF1– $\beta$ -catenin interactions (Chocarro-Calvo *et al.* 2013).

Interestingly, interaction of SIRT1 with both  $\beta$ -catenin and LEF-1 is favored by high glucose in the absence of WNT signaling, even though the levels of SIRT1 remain unchanged. During caloric restriction, sirtuin levels are upregulated (Mantel & Broxmeyer 2008), likely facilitating formation of SIRT1– $\beta$ -catenin and SIRT1–LEF1 complexes and outcompeting LEF1– $\beta$ -catenin complex formation which is associated with proliferation. In addition, under caloric restriction, there is enough supply of NAD<sup>+</sup>, as a cofactor needed for sirtuin activity favoring de-acetylation of  $\beta$ -catenin K354, which diminishes its interaction with LEF1 and transcriptional activity. This hypothetical mechanism would explain the decreased cancer risk associated with calorie-restricted diets. In this scenario, accumulation of  $\beta$ -catenin in response to WNT signaling and high glucose may outcompete SIRT1 and provide enough  $\beta$ -catenin to form LEF1– $\beta$ -catenin complexes, which will ensure the nuclear accumulation of LEF1– $\beta$ -catenin. The low levels of  $\beta$ -catenin observed in the

absence of a WNT signal would be insufficient to activate gene expression even in the presence of glucose as it would not outcompete SIRT1–LEF1 interactions. However, it can be argued that interactions may depend more on protein conformation or exposure of the right domains than on levels, otherwise the most abundant proteins would exhibit the most interactions. A clear example is that upon WNT signaling cytosolic  $\beta$ -catenin increases but its interactions with E-cadherin are not increased.

Taken as a whole the results by Chocarro-Calvo *et al.* (2013) suggest that the ability of LEF1 to bind p300 may depend more on stabilizing a conformation through the LEF1– $\beta$ -catenin complex (that requires both WNT and glucose), rather than simply relying on p300 levels. Interactions promoted by high glucose upon WNT stimulation (LEF1– $\beta$ -catenin with p300) differ from those promoted in its absence (LEF1–SIRT1 and  $\beta$ -catenin–SIRT1), which may appear logical if we consider that WNT imposes dramatic and well-known increases in the availability of  $\beta$ -catenin. Thus, the combined effect of glucose and WNT on p300 levels and SIRT activity are crucial to shift the balance of acetylation and allow the formation of the LEF1– $\beta$ -catenin complex that accumulates inside the nucleus.

The catalytic activity of SIRT1 is important to prevent LEF1– $\beta$ -catenin nuclear accumulation and may interfere with LEF1– $\beta$ -catenin interactions, or with exposure of the nuclear localization signals, or with nuclear export. Inhibition of sirtuin deacetylase activity mimics glucose-driven nuclear retention of  $\beta$ -catenin and transcriptional activation in cells where cytosolic  $\beta$ -catenin has accumulated through WNT-induction (Chocarro-Calvo *et al.* 2013). Thus, high glucose not only increases p300 levels and acetylase activity but also inhibits sirtuin deacetylase activity, and therefore results in excess acetylation with the consequent transcriptional activation. A possible mechanism for high glucose inhibition of sirtuin activity in the presence of WNT signaling may be given by enhanced glycolysis in tumor cells. Increased glycolytic flux leads to rapid turnover of the NAD<sup>+</sup> obtained by lactic acid production from pyruvate. NAD<sup>+</sup> is necessary for the next round of glycolysis, but it is also an essential sirtuin cofactor. Depletion of NAD<sup>+</sup> then limits its availability for sirtuins and consequently their deacetylase activity. In this respect, it would be interesting to determine the location and activity of sirtuins and of  $\beta$ -catenin in the subpopulations of cells belonging to the tumor (or the surroundings) that release lactate (generating NAD<sup>+</sup>) and those that consume lactate (see Martinez-Outschoorn *et al.* (2013)). Importantly, high glucose-mediated amplification of cancer-associated WNT

signaling cannot be attributed to nonspecific changes in energy supplies or to a general nutrient requirement because both diabetogenic and physiological glucose concentrations render similar increases in ATP levels having opposite effects on  $\beta$ -catenin and the use of an alternative carbon source had no effect (Chocarro-Calvo *et al.* 2013).

### Concluding remarks and future perspectives

The World Health Organization (WHO) predicts that the obese and diabetic population will double from the year 2000 to 2030 and the epidemiological data clearly establish a link between diabetes and cancer. This represents an enormous emotional and financial cost for society and knowledge should guide new policies that maximize prevention and find new treatments at low cost. A close cooperation between epidemiologists, who establish the correlations, and basic scientists, who uncover the mechanisms, may provide the clues to refine and confirm the epidemiological findings and help to implement new policies based on prevention.

There are still many unanswered questions. For example, which WNT signals are required for incretin expression, which WNT signals are released in cancer, and which cooperate with high glucose? When or where is the cancer-related WNT signal released? Are there other signals such as other nutrients, hormones, or cytokines that cooperate with high glucose to induce nuclear accumulation of  $\beta$ -catenin? Can we find natural metabolites, hormones, etc., that oppose the effects of high glucose on WNT signaling? And if so, would it be possible to direct these signals specifically toward cancer cells and not toward healthy cells? How does glucose alter SIRT1 interactions without altering its levels to promote SIRT1- $\beta$ -catenin and SIRT1-LEF1 complexes in the absence of WNT signaling? And how does WNT signaling disrupts these complexes? How can we use the knowledge gained to find new therapeutic targets that explore the ability of diet, hormones, or cytokines to interfere with the acetylation processes specifically in cancer cells? Does glucose impact on other WNT signaling components? How does high glucose impact on other well-known cancer-associated signaling pathways such as MAPK/ERK signaling? Some of these questions are being approached already and others represent new exciting research areas.

Insulin, as a growth factor, has been considered the prime suspect for increased cancer risk in the diabetic population, while metabolic factors have been considered as subordinate modulators of AMPK or mTOR. While the modulation exerted by ROS of both metabolic enzymes

and cancer-associated signaling pathways (such as MAPK or PI3K, see Ray *et al.* (2012)) is widely recognized, little is known about how the metabolic intermediates (for example  $\text{NAD}^+$  levels) may alter cancer pathways such as WNT/ $\beta$ -catenin.

We hope that this review will remind the reader that metabolism may drive cancer cell reprogramming. During the last international meeting on Prediabetes, much attention was given to the fact that early detection of hyperglycemia and policies that change life style may prevent T2D; perhaps also some cancers might be prevented through the same policies. High glucose amplification of WNT signaling is an example of how metabolism can remodel a cancer-associated signaling pathway. Identifying the molecules and understanding the processes underlying metabolic remodeling of cancer-associated signaling will empower new preventive, diagnostic, and therapeutic approaches toward curing cancer.

#### Declaration of interest

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

#### Funding

This work was financed by FIS (PI12/01201). C G-J is professor in Universidad Rey Juan Carlos, J M G-M, and A C-C were supported by teaching contracts from Universidad Rey Juan Carlos (URJC, Madrid). A D V is a researcher and head of Endocrine tumor Unit in the Instituto de Salud Carlos III.

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Received in final form 15 September 2013

Accepted 18 September 2013

Accepted Preprint published online 18 September 2013