The double trouble of metabolic diseases: the diabetes–cancer link

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ABSTRACT **The recent recognition of the clinical association between type 2 diabetes (T2D) and several types of human cancer has been further highlighted by reports of antidiabetic drugs treating or promoting cancer. At the cellular level, a plethora of molecules operating within distinct signaling pathways suggests cross-talk between the multiple pathways at the interface of the diabetes–cancer link. Additionally, a growing body of emerging evidence implicates homeostatic pathways that may become imbalanced during the pathogenesis of T2D or cancer or that become chronically deregulated by prolonged drug administration, leading to the development of cancer in diabetes and vice versa. This notion underscores the importance of combining clinical and basic mechanistic studies not only to unravel mechanisms of disease development but also to understand mechanisms of drug action. In turn, this may help the development of personalized strategies in which drug doses and administration durations are tailored to individual cases at different stages of the disease progression to achieve more efficacious treatments that undermine the diabetes–cancer association.**

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THE NOT-SO-SURPRISING LINK BETWEEN CANCER AND DIABETES

Recent progress in medical sciences suggests that understanding the pathology of a disease is much like understanding a theater production; first, one must understand the scene on the stage, before then examining the main actors and determining the critical interactions while also anticipating the hidden twists that will lead to the set conclusion of the play. This complexity of interactions appears to apply when viewing the most prevalent form of metabolic disorders in humans, diabetes mellitus, only to be surprised by a twist that reveals its link to another common metabolic disease, cancer.

As far back as 1932, clinical observations noted an association between the two diseases (Wilson and Maher, 1932), but it is only recently that the scientific community has formally acknowledged it. Scientific organizations in the United States and the United Kingdom convened a meeting in 2009 to examine the issue and concluded that type 2 diabetes (T2D) is associated with an increased risk of some cancers but a reduced risk of prostate cancer (Smith and Gale, 2010). In 2012, the National Institutes of Health (NIH) held a workshop to discuss the association between diabetes, pancreatitis, and pancreatic cancer (Andersen *et al.*, 2013). While the previous conferences had focused on the clinical aspects, the American Society for Cell Biology (ASCB) sponsored a conference in 2014 that brought cell biologists and clinicians together to examine the subject from a different perspective. The insights gained from the talks presented at this conference have inspired the main points of this review.

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Abbreviations used: AGE, advanced glycation end product; ASCB, American Society for Cell Biology; EGF, epidermal growth factor; ER, endoplasmic reticulum; F-2,6B, fructose-2,6-bisphosphate; GLP-1, glucagon-like peptide 1; GLP-1R, GLP-1 receptor; GPCR, G protein–coupled receptor; HGP, hepatic glucose production; IGF-1R, insulin growth factor-1 receptor; IR, insulin receptor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NAFLD, nonalcoholic fatty liver disease; NIH, National Institutes of Health; PanINs, pancreatic intraepithelial neoplasia; PFK1, phosphofructokinase 1; PI3K, phosphoinositide 3-kinase; PISC, pancreatic islet–derived stem cell; ROS, reactive oxygen species; SNP, single-nucleotide polymorphism; T1D, type 1 diabetes; T2D, type 2 diabetes; T3c, type 3c diabetes; UPR, unfolded-protein response; VIP, vasoactive intestinal neuropeptide.

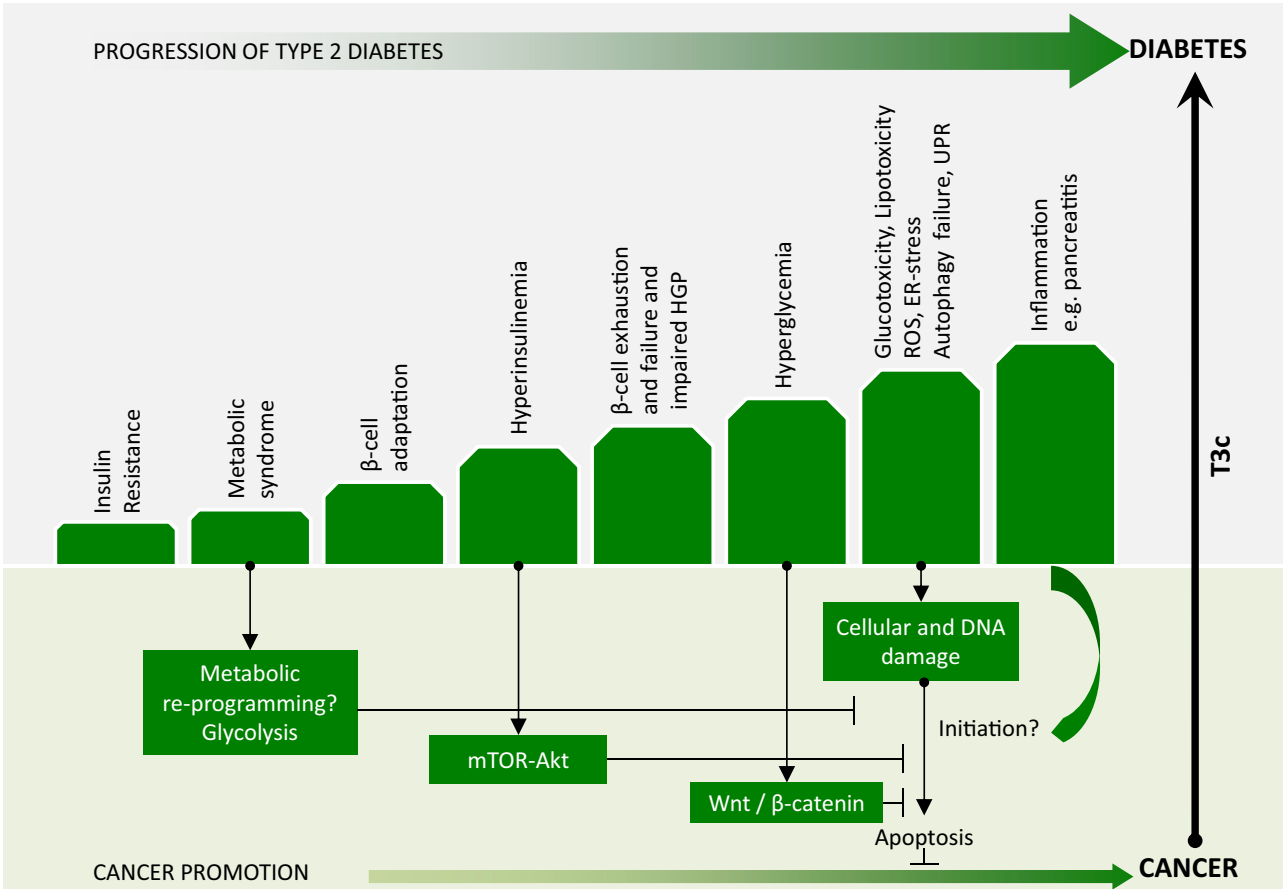

FIGURE 1: Shared factors in diabetes and cancer promotion. The sequence of metabolic deregulation that ultimately leads to T2D includes insulin resistance, beta-cell dysfunction, and impaired hepatic glucose production (HGP), and precedes the development of hyperglycemia by years or even decades. Insulin resistance is a primary pathogenic lesion, and beta cells are able to compensate for a variable length of time by secreting supraphysiological amounts of insulin. Over time, however, beta-cell function deteriorates, and relative insulin deficiency induces fasting hyperglycemia through the loss of insulin inhibition of HGP. The gradual failure of beta cells to compensate for insulin resistance, accompanied by hyperinsulinemia, marks the beginning of frank T2D. Obesity and metabolic syndrome, together with the enhanced compensatory workload experienced by beta cells, might lead to metabolic reprogramming and the switch to glycolysis. Hyperinsulinemia may sustain the activated mTOR-Akt pathway through stimulation of IGF and/or EGF receptors, while hyperglycemia may cooperate with the mitogenic Wnt/β-catenin pathway. In turn, this could lead to the inhibition of apoptosis in cells damaged by glucotoxicity, enhanced ROS production, and stress-induced endoplasmic reticulum (ER) accumulation of unfolded-protein response (UPR) components due to the inhibition of autophagy. ROS and ER stress responses then precipitate in inflammation, which collaborates with the mitogenic and metabolic pathways to initiate or promote cancer from premalignant lesions. Inversely, pancreatic cancer resection or treatment leads to T3c diabetes.

SOME CRITICAL PLAYERS IN THE DIABETES–CANCER LINK

Recently a wide range of molecular factors has been implicated in the connection between diabetes and cancer, and they cannot all be covered here. These factors can vary according to the distinct type of diabetes and perhaps likely subtypes yet to be identified. In addition to the two known broad types of diabetes, type 1 and 2, medical researchers have recently identified what could be a third type, which has been designated as type 3c (T3c). However, T2D is the most prevalent type and is responsible for 95–97% of all diabetic conditions, in which it is generally associated with obesity. Type 1 diabetes (T1D) is an autoimmune disease that results in the loss of beta cells, whereas T3c is described as a pancreatogenic type that arises from the destruction of islets or following a pancreas resection and may be associated with pancreatic cancer (American Diabetes Association, 2010; Whitcomb, 2014). While beta-cell mass and adaptation seem to be shared factors among these types of diabetes, what distinguishes them at the molecular level has not yet been resolved. Beta-cell mass can dynamically alter in order to maintain the physiologically narrow levels of euglycemia; therefore beta-cell adaptation depends on the homeostatic mechanisms that control beta-cell numbers. Threshold(s) associated with beta-cell number homeostasis probably determine when metabolic adaptation will become exhausted and diabetes is clinically and pathologically exacerbated (Figure 1).

Although adaptive hyperinsulinemia occurs only in T2D, both T1D and T2D result in the progressive loss of beta-cell mass and function, leading to persistent hyperglycemia and, consequently, oxidative stress, DNA damage, glucotoxicity, and lipotoxicity (Unger, 1995; Unger and Grundy, 1985; Prentki *et al.*, 2002), resulting

in a vicious cycle of beta-cell deterioration (Figure 1). In T2D, the loss of beta cells triggers the adaptive expansion of beta cells to compensate for the increased insulin demand due to hyperglycemia. This appears to be primarily driven by replication, as evidenced by studies in rodent models (Dor and Melton, 2004; Dor *et al.*, 2004; Okamoto *et al.*, 2006). Okamoto *et al.* (2006) proposed that beta-cell compensation to insulin resistance is a proliferative response of existing beta cells to growth factor signaling and requires FoxO1 nuclear exclusion. Studies in humans, however, have suggested that neogenesis from a potential progenitor niche (stem cells) or transdifferentiation from other pancreatic cell types also contributes to the production of new beta cells (Demeterco *et al.*, 2009; Thorel and Herrera, 2010; Thorel *et al.*, 2010; Bonner-Weir *et al.*, 2012; Wang *et al.*, 2014). At present, neogenesis appears controversial, since lineage tracing of genetically marked beta cells following a 70% pancreatectomy failed to demonstrate new beta cells arising from non insulin-expressing stem or progenitor cells (Dor *et al.*, 2004).

A number of factors can influence the loss of beta-cell function. These include enhanced apoptosis (Butler *et al.*, 2003), the failure of beta cells to proliferate (Dhawan *et al.*, 2009; Talchai *et al.*, 2012), the delay to compensate for hyperglycemia, and beta-cell de- or transdifferentiation (Talchai *et al.*, 2012; Wang *et al.*, 2014). Interestingly, taken together, these findings indicate that the natural history of diabetes consists of multiple factors also known to be relevant to cancer development. These factors include glucotoxicity/lipotoxicity, which lead to oxidative and DNA damage leading to cancer initiation. Apoptosis can prompt epithelial proliferation in processes known as "apoptosis-induced proliferation" required for regeneration and potentially lead to cancer development (Ryoo and Bergmann, 2012). Mechanistic studies are required for determining whether beta cell–derived tumors such as insulinoma and neuroendocrine tumors arise from mitogenic response of apoptotic beta cells in diabetes.

Epidemiological studies have demonstrated that T2D increases the risk, incidence, and mortality of pancreatic cancer by 1.5–2 times (Huxley *et al.*, 2005), as well as of other cancers, including liver (El-Serag *et al.*, 2006), colorectal (Larsson *et al.*, 2007), kidney (Washio *et al.*, 2007), bladder (Larsson *et al.*, 2006), endometrial (Friberg *et al.*, 2007), and breast (Larsson *et al.*, 2007) cancers and non-Hodgkin lymphoma (Mitri *et al.*, 2008). T1D has been similarly linked to cancer and, in a recent Swedish study, was reported to be associated with a higher risk for developing stomach, endometrial, and cervical cancer (Shu *et al.*, 2010). A comprehensive clinical review of meta-analysis data highlighted the increased incidence of thyroid cancer and thyroid disorders associated with diabetes (Buyukbese, 2014); however, diabetes seems to decrease the risk of prostate cancer (Kasper and Giovannucci, 2006). Overall diabetes can provide favorable conditions for the development and progression of cancer through one or a combination of the following mechanisms:

1. General mechanism(s) promoted by the diabetic milieu in T2D, such as high levels of circulating glucose (hyperglycemia) and/or high levels of circulating insulin (hyperinsulinemia).
2. Aberrant cell signaling pathways (e.g., mTOR or Wnt/β-catenin) that control cell homeostasis may serve as initiator lesions or exacerbate the effect of other factors (e.g., hyperinsulinemia, hyperglycemia, or inflammation) toward promoting cancer in the pancreas and other organs.
3. Site-specific mechanisms, such as inflammation within the liver or pancreas.

THE ROLE OF IMPAIRED INSULIN AND GLUCOSE HOMEOSTASIS

The etiopathology of diabetes and its link to cancer is unclear. The reverse causality explicitly demonstrated in pancreatic cancer (Silverman *et al.*, 1999) and the missing link between high glucose levels and carcinogenesis have both contributed to an underestimation of the association between cancer and diabetes. More recently, a large meta-analysis of nearly 900,000 participants from 16 prospective cohort studies underscored that impaired glucose tolerance and impaired fasting glucose levels were indicators of prediabetes relevance to cancer. Prediabetes was found to be associated with an elevated risk of developing liver, endometrial, and stomach/colorectal cancer (Huang *et al.*, 2014).

Hyperinsulinemia is associated with cancer development primarily through stimulation of the insulin receptor (IR). Insulin can activate the IR and also the insulin growth factor-1 receptor (IGF-1R), which shares around 80% homology with IR and forms hybrid receptors with it (Soos *et al.*, 1993; Arcidiacono *et al.*, 2012). It has been proposed that a hybrid IR/IGF-1R receptor is activated under conditions of hyperinsulinemia, such that insulin elevates IGF-1 bioavailability (Ricart and Fernandez-Real, 2001; Calle and Kaaks, 2004), thus sustaining growth and proliferation, known conditions that underlie cancer promotion. However, the levels of circulating IGF-1 alone seem not to be associated with the risk of cancer progression (Kaplan *et al.*, 2012). Hyperinsulinemia plays a favorable role in the development of kidney, bladder, colorectal, and breast cancer (Kim, 1998; Pisani, 2008; van Kruijsdijk *et al.*, 2009; Fang *et al.*, 2013; Hauner and Hauner, 2014; Zhang *et al.*, 2014), and this has been partly attributed to the association of higher levels of bioactive estrogens resulting from a decrease in estrogen-binding globulins and a reduction in the hepatic expression of insulin-like growth factor–binding protein (IGFBP)-1 and 2 (Wolf *et al.*, 2005).

Moreover, the function of the exocrine pancreas seems to be modulated by the endocrine pancreas and impacts on cancer development. Indeed, insulin has been shown to regulate amylase secretion and acinar cell growth (Barreto *et al.*, 2010), which was postulated to underlie pancreatic cancer originating from the exocrine pancreas (Trajkovic-Arsic *et al.*, 2013). An increase in the ductal epithelial replication rate in patients with T2D often precedes the development of pancreatic cancer (Butler *et al.*, 2010). IGF-1R has been found to be overexpressed (Hakam *et al.*, 2003) and to be associated with a higher tumor grade and poor survival rates in patients with pancreatic tumors (Valsecchi *et al.*, 2012). Altered IGF-1R correlates with sustained mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) signaling (Appleman *et al.*, 2012) in combination with pancreatic cancer with an invasive phenotype (Tanno *et al.*, 2001). Patients undergoing insulin substitution therapy are at higher risk of developing pancreatic cancer compared with those undergoing metformin treatment (Grouven *et al.*, 2010), thus underscoring the carcinogenic potential of the growth-promoting properties of insulin signaling.

Aside from insulin signaling, glucose has been considered a systemic mitogen that induces beta-cell proliferation in vivo by increasing the glycolytic flux via the action of glucokinase (Alonso *et al.*, 2007; Levitt *et al.*, 2011; Porat *et al.*, 2011). Hyperglycemia may increase the risk of cancer through a direct mechanism involving the carbohydrate response element–binding protein, ChREBP (Metukuri *et al.*, 2012), promoting its binding to glycolytic and lipogenic genes and thereby mediating glucotoxicity (Poungvarin *et al.*, 2012). Herman and colleagues identified a ChREBP variant that was involved in linking lipogenesis in white adipose tissue to insulin sensitivity and was associated with a subset of genes also relevant to

cancer promotion (Herman *et al.*, 2012). Hyperglycemia can also deploy indirect mechanisms involving increased insulin and IGF-1 bioavailability (Rajaram *et al.*, 1997), the increased secretion of inflammatory cytokines and adipokines (Devaraj *et al.*, 2005; Gonzalez *et al.*, 2012), and a decrease in immunosurveillance through the competitive inhibition of ascorbic acid transport within immune cells (Krone and Ely, 2005).

Additionally, hyperglycemia and insulin resistance increase the advanced glycation end product (AGE) of plasma proteins that stimulate receptor-mediated reactive oxygen species (ROS) within endothelial and mesangial cells and macrophages, leading to inflammation (Giardino *et al.*, 1994). Chronic AGE signaling during stress activates the AGE receptor (RAGE) and can lead to sustained inflammation, favoring epithelial transformation, as well as the enhanced resistance of tumor cells to oxidative stress (Sparvero *et al.*, 2009). Not only does inflammation support a vicious cycle through the induction of hepatic gluconeogenesis and hyperglycemia, it also cooperates with hyperglycemia to induce glycolysis, a prevailing cancer-associated metabolic program (Hsu and Sabatini, 2008). High glucose levels can exert indirect effects on the cell cycle through enhancing E2F1 expression (Masur *et al.*, 2011) and epidermal growth factor (EGF) signaling in the pancreas (Han *et al.*, 2011).

Abnormal glucose metabolism is a hallmark of tumor cells (Warburg effect), and most tumors adapt highly effective mechanisms for increased glucose uptake independent of insulin. Abnormal glucose levels may result from the aberrant turnover of pancreatic beta cells. The stimulation of beta-cell proliferation results in an enhanced risk of pancreatic cancer (Pour and Kazakoff, 1996), whereas beta-cell destruction, for example, by alloxan in animals, results in diabetes but reduces tumor growth (Heuson *et al.*, 1972). Interestingly, this suggests that hyperglycemia alone may not increase neoplastic growth under conditions of insulin deficiency. A high dietary glycemic load may increase the risk of pancreatic cancer because of the adverse effects of high postprandial glucose levels and the resulting enhancement of insulin levels (Hine *et al.*, 2003). In this context, epigenetic mechanisms by which initiated beta cells lose key lineage-specific markers might contribute to diabetes development through perturbing the balance between beta and alpha cells, thereby favoring pancreatic carcinogenesis (Dhawan *et al.*, 2011). Thus whether glucose is responsible for the association between hyperglycemia and the increased risk of pancreatic cancer or is merely a surrogate marker for causative factor(s) such as insulin resistance requires further investigation.

THE ROLE OF THE CANONICAL WNT SIGNALING

Accumulating evidence implicated the aberrant activation of the canonical Wnt signaling pathway in the hepatic metabolic switch (Liu *et al.*, 2011) in cancer promotion (Polakis, 2000) and cancer cell metabolic reprogramming through directing glycolysis (Warburg effect; Sethi and Vidal-Puig, 2010; Esen *et al.*, 2013; Pate *et al.*, 2014; Sherwood, 2015) and in adipogenesis leading to obesity and diabetes (Christodoulides *et al.*, 2009; Donati *et al.*, 2014). Furthermore, it has been suggested that a positive-feedback loop between Wnt signaling and glucagon-like peptide 1 (GLP-1), whereby GLP-1 activates Wnt signaling, enhances beta-cell proliferation and suppresses apoptosis (Bordonaro, 2009). Similarly, recent evidence has implicated noncanonical Wnt signaling, through Wnt5a, in adipose tissue inflammation leading to obesity-associated metabolic dysfunction (Fuster *et al.*, 2015). Thus the role of the Wnt pathway in the diabetes–cancer link has been extensively documented in recent years and was the subject of a recent review (Garcia-Jimenez *et al.*, 2014).

Aberrant canonical Wnt signaling is most likely to result from inappropriate gene activation mediated by stabilized β-catenin, which then translocates to the nucleus and stimulates transcription of target genes via a complex with the transcription factor TCF/LEF (T-cell factor/lymphoid-enhancing factor). Among several target genes of the β-catenin pathway, c-Myc and cyclin D1 functions are consistent with control of cellular growth, differentiation, and survival and have been widely implicated in cancer. Sustained growth and proliferation has been suggested to result in cooperativity between hyperglycemia and Wnt/β-catenin signaling (Chocarro-Calvo *et al.*, 2013).

In addition to epigenetic activation, some genetic evidence also implicates Wnt signaling in T2D and cancer. Noncoding single-nucleotide polymorphisms (SNPs, rs7903146) in the TCF7L2 locus encoding TCF were associated with an increased risk of T2D, and it was suggested they represent the strongest genetic link to diabetes across various ethnicities (Lyssenko, 2008). The T2D-associated region in TCF contains *cis*-regulatory elements, and variation in this noncoding region can positively enhance the expression of TCF7L2. Interestingly, transgenic mice harboring multiple TCF7L2 copies and overexpressing this gene display glucose intolerance (Savic *et al.*, 2011). Recent meta-analyses data demonstrated that TCF7L2 gene polymorphisms (rs12255372 and rs7903146) are associated with an increased susceptibility to breast cancer; alone, the TCF7L2 rs7903146 polymorphism is associated with a risk of breast, prostate, and colon cancers (Chen *et al.*, 2013; Lu *et al.*, 2015). A TCF4 SNP has been found to exert a gain-of-function increase in circulating basal glucose levels and insulin production and the secretion of insulin and insulin receptor expression, most probably through the stimulation of incretin hormones, which are regulators of glucose-dependent insulin secretion (Garcia-Martinez *et al.*, 2009). However, it remains unclear whether the presence of these SNPs is a cause or a consequence of the associated aberrations.

The mechanisms discussed above are under the control of the homeostatic pathways that control metabolism and cell growth and division, which themselves can be primary or major contributors to the diabetes–cancer link. We consider in brief representatives of these homeostatic pathways below.

THE ROLE OF IMBALANCED MITOGENIC AND GLYCOLYTIC PATHWAYS

The mechanisms that control cell size and division are crucial for maintaining cell homeostasis, which in turn impacts on many complex human diseases, including diabetes and cancer. IQGAP1, a widely conserved effector and regulator of the GTPases Cdc42 and Rac1, is an oncoprotein that couples cell size and division in order to regulate cell proliferation, while also acting as a metabolic sensor (Osman *et al.*, 2013). It modulates glucose-induced insulin secretion and beta-cell proliferation via different domains according to the nature of external signals (Rittmeyer *et al.*, 2008; Wang *et al.*, 2009; Tekletsadik *et al.*, 2012). In addition, IQGAP1 regulates the activity of the metabolic hubs, the mammalian target of rapamycin (mTOR), and the PI3K pathway through binding to mTORC1 and the PI3K substrate Akt1/PKB in response to specific nutrient and growth factor conditions (Wang *et al.*, 2009; Tekletsadik *et al.*, 2012). Under both these conditions, expression of full-length IQGAP1 or of the C-terminal domain of IQGAP1 bypasses the requirements for growth factors, thereby accelerating the cell cycle and inducing transformed phenotypes, while also reducing the cell size (Wang *et al.*, 2009). Under growth factor conditions, expression of the mTORC1–Akt1-binding region (IR-WW) leads to attenuated activity of the MAPK and inactivated glycogen synthase kinase 3α/β, a known substrate for Akt (Tekletsadik *et al.*, 2012). Interestingly, this

also results in the accumulation of high levels of phosphorylated (active) Akt1 and reduced levels of S6K1 activity, leading to sustained cell proliferation and EGF-dependent transformed phenotypes (Tekletsadik *et al.*, 2012; Osman, 2014). In contrast, under certain nutrient conditions, this mutant ($IQGAP1^{IR\text{-}WW}$) acts as dominant negative during cell proliferation, similar to an IQGAP1 knockdown, enhancing insulin secretion and cell size and predisposing cells to apoptosis (Wang *et al.*, 2009; Osman, 2014). Furthermore, this is consistent with the reduced (signal loss) IQGAP1 levels found within beta cells isolated from patients with T2D (Osman, 2014).

Overall, in vitro and in vivo analyses of IQGAP1 in several cell lines, including beta cells and human tissues, has revealed its physiological role as a regulatory scaffold that acts like a rheostat to couple insulin secretion to mTORC1–S6K1→Akt1-mediated cell growth and division (Osman *et al.*, 2013). Uncoupling IQGAP1 from the mTOR-Akt pathway could produce an autonomously deregulated mTOR-Akt pathway leading to either diabetes or cancer pathologies (Osman *et al.*, 2013). Additionally, IQGAP1 appears to control cell division at two distinct points within the cell cycle, the S phase and cytokinesis, and it represents a rapamycin-sensitive node (Wang *et al.*, 2009; Tekletsadik *et al.*, 2012). This could present rapamycin as a selective anticancer and/or antidiabetic drug in cases defined by IQGAP1 deregulation (Osman *et al.*, 2013), and thus it could be repurposed for personalized medicine.

It is not only canonical mitogenic pathways but also known metabolic pathways such as glycolysis that can transmit mitogenic signals physiologically during the G_1/S-phase transition of the cell cycle or after ectopic expression of glycolytic enzymes in the G_0 quiescence phase (Colombo *et al.*, 2011; Tudzarova *et al.*, 2011; Tudzarova-Trajkovska and Moncada, 2014). Up-regulation of glycolytic enzymes occurs in the blood of diabetic patients and is apparently induced by various mechanisms, including the down-regulation of sirtuin deacetylases associated with a high-fat diet in obesity and T2D (Zhong *et al.*, 2010). In addition, an integrated genome approach has identified the abundant presence of the key glycolytic gene *PFKM*, coding for the muscle-type phosphofructokinase 1 (PFK1) isoform, in the skeletal muscle of T2D patients (Keildson *et al.*, 2014). A shift to glycolysis has been demonstrated in some organs, as has the stimulation of beta-cell proliferation through glycolysis in vivo (Porat *et al.*, 2011). Moreover, fructose-2,6-bisphosphate (F-2,6B or Fru-2,6P2), a metabolite regulator of glycolysis and gluconeogenesis, is essential in the maintenance of the glycolytic flux necessary for providing energy and biosynthetic precursors for the regeneration of diabetic liver tissue (Duran *et al.*, 2009). F-2,6B enhances the activity of the glycolytic enzyme PFK1 generated by phosphofructokinase/2,6-biphosphatase, PKFB3, which has been shown to lead to hepatocyte proliferation in a streptozotocin-induced diabetic mouse liver (Duran *et al.*, 2009).

In light of this evidence, the novel functional link between transient glycolysis and S-phase initiation in an IGF-1–dependent manner becomes interesting when envisaged as a possible cancer risk mechanism in diabetes. Indeed, recent evidence suggests that transient glycolysis is important for the initiation of the S phase through the IGF-1/Akt–dependent nuclear exclusion of Foxo3a, an event that occurs concomitantly with the fusion of mitochondria, both of which are required for cell cycle progression beyond the G_1 phase (Tudzarova-Trajkovska and Moncada, 2014). Therefore the shift to glycolysis (e.g., in the pancreas) could have a direct mitogenic effect that promotes premalignant lesions into cancer development. In summary, cross-talk between metabolic and mitogenic pathways plays a role in the diabetes–cancer link, and mediators of this cross-talk are worth more investigation in this respect.

THE ROLE OF INFLAMMATION

It is no surprise that chronic inflammation is emerging as a plausible link between diabetes and cancer, as it has been both implicated in promoting diabetes (Whitcomb, 2004a, 2014; Greer and Whitcomb, 2009; Butler, 2014b; Chari, 2014) and designated as a hallmark of cancer (Henao-Mejia *et al.*, 2014). It has been shown that a high-fat diet promotes pancreatic cancer by enhancing the levels of proinflammatory cytokines independently of hyperinsulinemia and hyperglycemia (Khasawneh *et al.*, 2009). Indeed, diabetes often is accompanied by a history of acute and chronic inflammation (Henao-Mejia *et al.*, 2014), such as pancreatitis (Chari, 2014; Chari *et al.*, 2005, 2008). Obesity has been reported to increase the severity of acute pancreatitis by amplifying immune responses to injury (Papachristou *et al.*, 2006; Evans *et al.*, 2010). Known mechanisms leading to chronic pancreatitis have been extensively reviewed (Whitcomb, 2004b) and thus will not be covered here.

However, some evidence suggests that pancreatitis and diabetes stem from distinct pathological mechanisms that can be identified according to the preservation of beta-cell function. This is dependent on whether pancreatic beta-cell function is intact or impaired in patients with advanced chronic pancreatitis of the tropics, a calcific form prevalent in tropical developing countries, and it can be distinguished from a pathological mechanism that will precipitate in chronic pancreatitis and a mechanism leading to diabetes (Rossi *et al.*, 2004). Yet other studies have suggested that about half of all patients with chronic pancreatitis develop diabetes due to the loss of islet mass and beta cells (Andersen *et al.*, 2013; Whitcomb, 2014). Thus the exact mechanisms linking pancreatitis and diabetes on one hand, and pancreatitis and cancer on the other, remain under investigation.

Nevertheless, diabetes under certain conditions can be a predictor of pancreatic cancer. For instance, when hyperglycemia and diabetes appear in a lean subject aged between 45 and 50 yr with no familial history of diabetes, it is considered a sufficient sign to warrant screening for pancreatic cancer (Chari *et al.*, 2008). In addition, elderly subjects with new-onset diabetes have an eight times higher risk of developing pancreatic cancer in the following 3 yr than nondiabetic subjects (Chari *et al.*, 2005). A meta-analysis study by Huxley *et al.* (2008) revealed an 85% increase in the pancreatic cancer risk for individuals with T2D. Furthermore, T2D has been suggested as a paraneoplastic phenomenon and a major comorbidity factor of pancreatic ductal adenocarcinoma (Rickels *et al.*, 2013; Chari, 2014). Interestingly, clinical evidence shows that T2D is reversed upon cancer resection, and conversely, pancreatic resection appears to lead to T3c diabetes (Andersen *et al.*, 2013). This situation presents an overwhelming obscurity that envelops the understanding of the causality of each of these conditions. Because diabetes may arise during the progression of pancreatitis, it is still unclear whether pancreatitis, diabetes, or both lead to the development of pancreatic cancer. Therefore more mechanistically based studies are required to decipher the underlying sequence of events that appear to eventually connect these conditions.

T2D also provides conditions favorable for cancer development indirectly via mechanisms other than inflammation. For example, hepatitis B and C infections are common in T2D patients (Wang *et al.*, 2015) and thus can predispose to liver cancer indirectly (Davila *et al.*, 2005; Wang *et al.*, 2015). In contrast, chronic local exposure to cytokine release from inflamed islets in the pancreas or from the liver during nonalcoholic fatty liver disease (NAFLD), which underlies conditions ranging from simple steatosis to steatohepatitis to end-stage liver disease, can also lead to the propagation of premalignant lesions arising from mutations that activate *KRAS* in the

pancreas or inhibit *TP53* in the liver (Vansaun *et al.*, 2013; Butler, 2014b). Additionally, NAFLD is an independent risk factor for T2D, in which increased hepatic and peripheral insulin resistance contribute to the pathogenesis of both NAFLD and diabetes.

Inflammation in a diabetic pancreas can be induced by a variety of factors, including glucotoxicity, AGE, and oxidative stress. Recently Butler and colleagues demonstrated that the accumulation of the misfolded protein, human islet amyloid peptide, was due to deficient autophagy in T2D and leads to both enhanced apoptosis and mitogen stimulation of the progenitor niche of beta cells (Costes *et al.*, 2014; Rivera *et al.*, 2014). Thus, overall, inflammation, which is the root cause of pancreatitis, represents a strong factor in mediating the diabetes–cancer link, but the direct mechanisms needs to be unraveled through more mechanistic studies.

THE IMPORTANCE OF UNDERSTANDING THE ACTION MECHANISMS OF ANTIDIABETIC DRUGS

Recently some antidiabetic drugs have been implicated in promoting several types of human cancer, a subject that has become the focus of heated debate and controversy. The awareness of the complexity of diabetes has caused the utility and safety of the three classical groups of antidiabetics, including sulfonylureas, biguanides, and thiazolidindions, to be reassessed. The majority of studies agree that the observed deterioration of beta cells can result from overweighing of one of the concurrent regulatory processes occurring during beta-cell adaptation, including apoptosis over mitogenic signaling and vice versa. As a consequence of this rare consensus on diabetes at the cellular level, there has been an intensive search for drugs that reconstitute the critical threshold for beta-cell mass and function, and a class of incretin mimetic GLP-1 compounds have been developed to overcome the inherent instability of natural GLP-1. GLP-1 is a proglucagon-derived peptide secreted from intestinal epithelial endocrine L cells in response to meal intake (Ebert and Creutzfeldt, 1987). The GLP-1 receptor (GLP-1R) is a G protein–coupled receptor (GPCR) expressed in rat and human pancreas islets and exocrine duct cells (Xu *et al.*, 2006; Tornehave *et al.*, 2008; Matveyenko *et al.*, 2009). GLP-1 mimetic–based therapies are used to lower glucose levels by enhancing insulin secretion, which potentially can lead to beta-cell proliferation (Perfetti and Merkel, 2000; Perfetti *et al.*, 2000).

GLP has demonstrated proliferative properties, and it has been reported previously that the GLP-1 analogue, exendin-4, facilitates beta-cell neogenesis in rat and human pancreatic ducts (Xu *et al.*, 2006). It has also been reported that GLP-1 decreases apoptosis and increases insulin biosynthesis and mRNA levels of the glucose transporter GLUT4 (Holst, 2007). While these properties have been viewed in light of their potential in T2D treatment, recent evidence has suggested that cells of the exocrine and endocrine pancreas proliferate upon GLP-1 treatment, causing an increase in pancreas weight (Elashoff *et al.*, 2011; Butler, 2014a; Butler *et al.*, 2013a). In rats and in a mouse model expressing an activating mutant of K-Ras (Pdx1-Cre; LSL-KrasG12D), treatment with exendin-4 led to expansion of the pancreatic duct glands, followed by metaplasia and low-grade pancreatic intraepithelial neoplasia (PanINs), preceded by chronic pancreatitis (Gier *et al.*, 2012). An involved signaling pathway was uncovered in human pancreatic duct cells, whereby exendin-4 induced cAMP–protein kinase A and MAPK phosphorylation of the cAMP-responsive element-binding protein and increased cyclin D1 expression (Gier *et al.*, 2012). These observations were taken to indicate a potential for GLP-1 mimetic drugs to induce pancreatic cancer in patients with T2D undergoing GLP-1 therapy.

However, it is as yet unclear whether the pancreatitis following GLP-1 treatment results from proliferation of duct epithelia leading to acinar stress, or whether GLP-1–based therapies enhance the risk of a superimposed effect of pre-existent low-grade pancreatitis and PanINs (Butler *et al.*, 2013b; Nauck, 2013). In response to this controversy, more mechanistic research and rigorous clinical studies incorporating substantial follow-ups have been either initiated (Moses *et al.*, 2014) or proposed (Andersen *et al.*, 2013). This controversy has also sparked a flurry of investigations into the contexts of pancreatic cancer (Butler, 2014a; Wada and Yagihashi, 2014) and thyroid cancer (Bjerre Knudsen *et al.*, 2010; Madsen *et al.*, 2012; Boess *et al.*, 2013; Waser *et al.*, 2014), with various results.

Several caveats should be considered at both the epidemiological and the molecular levels. At the clinical level, establishing a clear picture of the association of diabetes with cancer is expected to be confounded by factors arising from a heterogeneous cohort of patients and demographic factors, which are impossible to replicate from one study to another. Obesity, medication, underlying genetics, and environmental and other metabolic conditions may also exert confounding effects. At the molecular level, the combined effect of the expression of dominant active mutants of K-Ras in animal models, together with the persistent activation of GPCR, such as GLP-1R with a stabilized agonist, can produce unanticipated effects leading to site-specific increased cell proliferation tipping the activity of homeostatic signaling pathways that control metabolism and epithelial proliferation toward neoplastic transformation. K-Ras belongs to the superfamily of small GTPases whose sustained activation has been associated with human carcinomas (Bos, 1989; Vega and Ridley, 2008). Mutations at position 12 (or the equivalent position) in the Ras protein family result in a sustained GTPase activity, bypassing the requirement for growth factors and exerting oncogenic activity on epithelial cells (Bos, 1989, Vega and Ridley, 2008). Given that GLP-1 proliferative activity has been documented in the pancreas (Xu *et al.*, 2006; Holst, 2007), a sustained GLP-1R signaling could synergize with such oncogenic activity.

Indeed, MAPK is a shared hub for large and small G proteins, and cross-talk has been extensively documented between Ras family GTPases, their receptor tyrosine kinases, and GPCRs leading to aberrant cell signaling and cancer development (Bhattacharya *et al.*, 2004; McCudden *et al.*, 2005; Thomas *et al.*, 2006; Wang and Wu, 2012; Damoulakis *et al.*, 2014). It is still unclear whether such cross-talk, be it in K-Ras animal models or in humans with pre-existing neoplastic lesions treated with a GLP-1 mimetic, might be involved in activating downstream signaling pathways leading to carcinoma progression. This is particularly relevant to pancreatitis and pancreatic cancer, in which K-Ras activity is an established oncogenic signature (Andersen *et al.*, 2013). Therefore the pharmacological management of diabetes needs to be evaluated in light of the novel link between diabetes and cancer. Studies that combine mechanistic and clinical analyses will be crucial to uncovering the mechanism(s) of drug action and disease development for tailoring safer drug doses and their duration of administration at the individual level.

In contrast to incretin-based drugs, the biguanide antidiabetogenic drug metformin seems to reduce the risk of cancer (Evans *et al.*, 2005; Tan *et al.*, 2011; Franciosi *et al.*, 2013; Pulito *et al.*, 2013). Metformin is currently the drug of first choice for the treatment of T2D and is prescribed to at least 120 million people worldwide (Luengo *et al.*, 2014). Metformin lowers blood glucose concentrations in T2D by reducing the hepatic glucose output without causing overt hypoglycemia (Viollet *et al.*, 2012), and it decreases hepatic glucose production mainly by inhibiting gluconeogenesis (Hundal *et al.*, 2000). Metformin is frequently described as an insulin

sensitizer, leading to a reduction in insulin resistance and fasting levels of plasma insulin that are ascribed to its positive effects on insulin receptor expression and tyrosine kinase activity (Tiikkainen *et al.*, 2004; Zi *et al.*, 2014). Other reports, however, indicate that metformin does not improve peripheral insulin sensitivity unless administered in high, nonclinically relevant dosages (Natali and Ferrannini, 2006). The molecular mechanisms of metformin action have just begun to be unraveled. The anticancer effect of metformin was attributed to the induction of AMPK and the inhibition of mTOR (Liu *et al.*, 2014). However, activation of AMPK by metformin in the liver and other tissues appears to be a consequence of a transient reduction in cellular energy, resulting from the specific inhibition of the respiratory-chain complex 1 in mitochondria (Brunmair *et al.*, 2004). Considering that these factors could be situation dependent, more mechanistic research will be required for personalized tailoring of these drugs, while the search for alternatives will continue.

IDENTIFICATION OF NEW THERAPEUTIC STRATEGIES AND DRUG TARGETS

As discussed earlier, T1D also appears to be associated with a higher risk of developing stomach, endometrial, and cervical cancers (Shu *et al.*, 2010). In light of this association, T1D management is relevant to this review, and strategies used for replacing beta cells can be applied to treating both T1D and T2D. A particularly relevant approach for treating T1D has recently been extended to gene therapy and cell-based immunological strategies. It has been proposed that the vasoactive intestinal neuropeptide (VIP) of the secretin family exerts potent immunosuppression based on T-helper cells and T-regulatory cells, with insulinotropic effects similar to those of GLP-1 (Sanlioglu, 2014b). Potent immunomodulation by VIP delivered via a lentiviral vehicle could be a viable therapeutic option for autoimmune T1D. An alternative approach, focusing on cell-based regenerative and repair treatments based on adipose tissue–derived mesenchymal stem cells, has also been tested for the treatment of T1D (Karaoz *et al.*, 2013). Encouraging results were reported for a protective role of pancreatic islet–derived stem cells (PISCs) in inhibiting islet inflammation and apoptosis when cocultured with pancreatic beta cells (Karaoz, 2014; Sariboyaci *et al.*, 2014). The anti-inflammatory and antiapoptotic effect of PISC is probably due to the induction of negative T-regulatory cells and a subset of antiapoptotic molecular markers relevant to the putative cell replacement therapy for T1D (Karaoz *et al.*, 2010a,b,c).

Moreover, T1D seems to be exacerbated in nonobese diabetic mice upon blocking of the function of the tumor necrosis factor (TNF)-related apoptosis-inducing ligand receptor (TRAIL), which is consistent with the finding that TRAIL$^{-/-}$ knockout mice develop T1D earlier than wild-type control mice when injected with streptozotocin (Dirice *et al.*, 2011), an antibiotic that specifically destroys beta cells. This has led to an assessment of the ability of soluble TRAIL (sTRAIL) to support beta-cell survival and proliferation via the suppression of TNF- and FAS (death receptor)-mediated apoptosis in mouse beta cells (Sanlioglu *et al.*, 2008, 2014a; Kahraman *et al.*, 2014). Unlike activation of the membrane-bound type II receptor TRAIL, sTRAIL appears to induce apoptosis only within tumor cells and not in normal cells (Ashkenazi et a*l.*, 1999; Walczak et a*l.*, 1999), which is apparently due to a neutralization effect resulting from a homotypic interaction with the membrane-bound TRAIL receptor (Wajant *et al.*, 2001). Such new antidiabetic approaches seem promising, but relevance to humans should be tested while taking into account the novel insights gained from the appreciation of the increased risk of cancer promotion in diabetes.

CONCLUDING REMARKS: MORE INTERDISCIPLINARY RESEARCH IS NOW REQUIRED

The link between cancer and diabetes is an emerging and rapidly growing field of study. Accumulating molecular and clinical evidence supports this link and implicates cellular-based mechanisms at the interface of the two diseases. Importantly, the underlying cellular basis of the pathology of both cancer and diabetes seems to implicate a lost net balance in achieving cellular homeostasis. Cellular adaptations to diabetic pathologies seem to engage frail mechanisms, which can in turn lead to the transformation or promotion of existing neoplastic lesions. There is now increasing molecular evidence that an altered metabolism may drive cancer metabolic reprogramming, which can be exacerbated by components of the diabetic milieu or obesity; therefore the management of diabetes also has to encompass cancer prevention. However, some strategies for treating cancer, as has been suggested in the case of pancreatic cancer, can often produce diabetes as a comorbidity, and the inverse is also true when treating diabetes. Uncovering new cancer- and/or diabetes-related generic mechanisms will help explain the epidemiological correlation between cancer and diabetes and will ideally guide more holistic strategies for the prevention, diagnosis, and therapy of both diseases.

In this respect, interdisciplinary research that involves clinicians and basic scientists will be crucial to identifying the signaling nodes that integrate metabolic and mitogenic pathways into the pathology of the two diseases. In light of the global increase in obesity and diabetes, deciphering mechanisms of drug action and how they have an impact upon the basic metabolic and signaling pathways that lead to the promotion of cancer in diabetics, and vice versa, will be a crucial element in developing more personalized strategies to combat this growing epidemic.

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