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REVIEW ARTICLE

Cancer biology in diabetes

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ABSTRACT

Diabetes is a serious metabolic disease that causes multiple organ dysfunctions. Recent evidence suggests that diabetes could contribute to the initiation and progression of certain cancers in addition to the classic diabetic complications. Furthermore, some of the drugs used clinically to treat patients with diabetes might affect cancer initiation, progression and mortality. The recent discovery of the possible anticancer effects of metformin, a classic antidiabetic drug, has led physicians and scientists to reconsider the interaction between diabetes and cancer. In the present review, we analyze recent reports in this field, and explore possible mechanistic links between diabetes and cancer biology.

INTRODUCTION

Diabetes is characterized by defects in glucose homeostasis and proper insulin function. Diabetes can be classified into two types: type 1 diabetes, which is pathologically based on deficiencies in insulin secretion; and type 2 diabetes, which is characterized by insulin resistance and higher insulin levels. Longer disease duration is associated with multiple organ dysfunctions, such as nephropathy, retinopathy, neuropathy, atherosclerosis and heart disease. These symptoms are due largely to microangiopathy and/or macroangiopathy. Decades of epidemiological evidence have now been accumulated that support the link between diabetes and an increased incidence of certain cancers in different populations after adjusting for age and other confounding factors, such as obesity. In addition, epidemiological studies report that those with diabetes who develop cancer have a worse prognosis after treatment with chemotherapy or surgery and have a greater mortality than those without diabetes[1–4]. In addition to these classic complications of diabetes, recent evidence suggests the existence of possible mechanistic links between diabetes and certain types of cancer, including breast, endometrium, colorectal, liver, pancreatic, urinary bladder and non-Hodgkin's lymphoma[5–15]. There are many risk factors that diabetes and cancer have in common, such as aging, obesity, male sex and so on[16]. Indeed, both type 1 and type 2 diabetes have been associated with an increased incidence of some cancers[13].

Diabetes is a common metabolic abnormality. From a survey of the International Diabetes Federation, there were 366 million people with diabetes in 2011, and the total number is expected to rise to 552 million by 2030[17]. Type 1 diabetes accounts for 5–10% of the total cases of diabetes and type 2 diabetes accounts for 90–95%[18]. Additionally, cancer is one of the most serious health problems in clinics today. The association of cancer with diabetes has largely been overlooked by diabetologists, because the epidemiological data did not have enough impact on their clinical practice as a result of the lack of clear mechanistic evidence, confirmation in specific populations, the protective effect in some tumors[13,19–21] and the lack of special guidelines for cancer screening in patients with diabetes. However, recent discoveries regarding the possible reduced incidence of cancer in patients treated with metformin, a well-studied antidiabetic drug, has led both diabetologists and oncologists to reconsider the mechanistic connections between diabetes and cancer. Therefore, understanding the possible pathophysiological links between diabetes and cancer would be significant.

DIABETES TYPE AND CANCER

Type 1 diabetes is characterized by a deficiency in insulin secretion as a result of autoimmune destruction of the pancreatic β-cells. Two cohort studies have been carried out to investigate the association between type 1 diabetes and the incidence of cancer, each comprising approximately 30,000 individuals. The first study, carried out by Zendehdel *et al.*[22] found that the overall risk of cancer was increased by 20% in type 1 diabetic patients. Regarding specific organs, they found patients with type 1 diabetes had elevated risks of cancers in the stomach, cervix and endometrium. In a second study, Swerdlow *et al.*[23] found that ovarian cancer incidence and mortality were more

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than doubled in patients with type 1 diabetes diagnosed under 30 years-of-age, and type 1 diabetes carried the greatest risks for those diagnosed at ages 10–19 years[23]. In their analysis, there was no increased risk of cancer associated with type 1 diabetes except for ovarian cancer[23]. Another report showed that the incidence of pancreatic cancer has been shown to be higher in the type 1 diabetic population[24].

Increasing evidence suggests an interaction between type 2 diabetes and the risk of cancer in several organs, such as the endometrium, breast, stomach, colorectal, pancreas, liver and blood (for a more complete discussion of specific cancer sites, Srokowski *et al.*[1] Additionally, gallbladder cancer rates have been reported to be higher in the type 2 diabetic population independent of body mass index[25]. Interestingly, the incidence of prostate cancer is low in the type 2 diabetic population[13,19–21]. Both hyperglycemia and hyperinsulinemia have been cited as possible mechanisms through which diabetes might stimulate tumor growth[26]. There are many factors apart from hyperinsulinemia and hyperglycemia that are important in the relationship between diabetes and cancer metabolism, including oncogenes and tumor suppressor genes, glutamine metabolism, inflammation, and obesity; these relationships have recently been reviewed elsewhere[27–31].

There are possible differences between type 1 and type 2 diabetes with regard to diabetes-associated carcinogenesis events (Table 1)[23,32–41]. Type 1 diabetes is an autoimmune disease, which are often associated with an increased risk of cancer. For example, systemic lupus erythematosus has been associated with an increased risk of cancer, notably non-Hodgkin's lymphoma[42,43]. Furthermore, rheumatoid arthritis, a common autoimmune disease, has been associated with an increased incidence of hematological malignancies and lung cancer[44]. Therefore, an increased risk of cancer could be independent of type 1 diabetes itself, but might be associated with autoimmune defects. Also, current epidemiological research investigating the link between type 1 diabetes and cancer has resulted in mixed findings, which varied by the research methods used. Case–control studies found no statistically significant link between the two diseases, whereas meta-analyses did. The need for further detailed research to be undertaken that explores the nature of the relationship between type 1 diabetes and cancer is strongly suggested[45].

In most cohort studies, specific diabetic types were not analyzed sufficiently; however, most of such studied subjects would have type 2 diabetes. Type 2 diabetes is characterized by insulin resistance and hyperinsulinemia. Hyperinsulinemia induces breast cancer development in experimental animal models[46]. Type 2 diabetes is often associated with obesity, which is another risk factor for cancer[47]. Additionally, patients with type 2 diabetes show increased levels of insulin-like growth factor (IGF)-1, a potent mitogen that can contribute to carcinogenesis[48]. IGF-1 promotes liver metastasis in xenograft colon adenocarcinoma models in obese mice[49]. Furthermore, insulin resistance in type 2 diabetes is closely associated with an accumulation of diacylglycerol (DAG) in cells[50,51]; DAG accumulation can cause activation of the protein kinase C family of serine-threonine kinases[51],

Table 1 | Recent research about the relationship between diabetes and cancer

Year	Author	Sample	Specific diabetes type	Risk of specific cancer
2010	Shu *et al.*[32]	24,052 diabetic patients	Type 1	Stomach RR = 3.36 (1.44–6.66), skin RR = 4.96 (2.83–8.07) leukemia RR = 2.02 (1.15–3.29)
2005	Swerdlow *et al.*[23]	28,900 insulin treated diabetics including 23,834 with type 1 diabetes	Type 1	Ovarian SMR = 2.90 (1.45–5.19)
2003	Zendehdel *et al.*[22]	29,187 patients	Type 1	Stomach SIR = 2.3 (1.1–4.1), cervix SIR = 1.6 (1.1–2.2), endometrium SIR = 2.7 (1.4–4.7)
2012	Wang *et al.*[33]	18,258/3,626,369	Diabetes*	Liver RR = 2.01 (1.61–2.51)
2011	Ren *et al.*[34]	1,836/165,861	Diabetes*	Biliary tract RR = 1.43 (1.18–1.72),
2011	Ben *et al.*[35]	20,410/21,616,592	Diabetes*	Pancreas RR = 1.94 (1.66–2.27)
2011	Ge *et al.*[36]	3,211/60,731	Diabetes*	Stomach RR = 0.97 (0.64–1.46)
2011	Jiang *et al.*[37]	61,690/8,201,654	Diabetes*	Colorectum RR = 1.27 (1.21–1.34)
2011	Larsson *et al.*[38]	9,520/5,769,987	Diabetes*	Kidney RR = 1.42 (1.06–1.91)
2012	Castillo *et al.*[39]	8,000 cases	Type 2	Leukemia OR = 1.22 (1.03–1.44) Myeloma OR = 1.22 (0.98–1.53)
2011	Liao *et al.*[40]	730,069 patients	Diabetes*	Breast RR = 1.25 (1.20–1.29)
2012	Kitahara *et al.*[41]	674,491 patients	Diabetes*	Thyroid cancer Women: HR = 1.19 (0.84–1.69) Men: HR = 0.96 (0.65–1.42)

*Specific diabetic types were not analyzed sufficiently in most publications. In such papers, it is likely that most were type 2 diabetes; we described these as 'diabetes' in the table if not distinguished clearly in the publication. HR, hazard ratio; OR, odds ratio; RR; relative risk; SIR, standardized incidence ratio; SMR, standard mortality ratio.

which play important roles in cancer biology[52]. Thus, the molecular mechanisms of cancer development might be very different between type 1 and type 2 diabetes.

DIABETES, CANCER AND SEX

Several reports have shows the presence of sex differences in the incidence of cancer in diabetic patients[53–58]. Recently, Chodick *et al.*[13] reported an interesting observation regarding sex differences in cancer incidence and diabetes in a large population-based cohort study in Israel. In that report, the authors found that type 2 diabetes is associated with increased rates of cancer in women, but not in men[13]. With regard to the types of cancer, the increased risk of cancer in diabetes patients was apparent in the digestive, genital and urinary organs[13]. Furthermore, diabetes in men was associated with a reduced risk for prostate cancer when compared with non-diabetic subjects[13,19–21]. Interestingly, diabetes is associated with a decreased incidence of skin cancer in women, but such a reduction was not found in diabetic men[13]. Another large-scale population-based cohort study from Japan found almost no difference in total cancer incidence, but the incidence of particular types of cancer was markedly different between sexes[11]. These reports suggest that diabetes-associated cancer risks could be partially explained by sex-specific factors, such as sex hormone-dependent and social-environmental factors.

CANCER AND DIABETES TREATMENT

Insulin and Insulin Analogs

Increased levels of insulin in the body are believed to contribute to diabetes-associated cancer. The activation of the insulin receptor might lead to the proliferation and survival of cancer cells. Insulin glargine is a long-acting insulin analog that was introduced to provide basal insulinization with a lower risk of hypoglycemia than neutral protamine hagedorn insulin. Some epidemiological analyses reported an interesting connection between glargine and cancer risks. Hemkens *et al.*[59] reported that, considering the overall relationship between insulin dose and cancer, and the lower dose of insulin glargine, the cancer incidence with insulin glargine appeared to be higher than expected compared with human insulin. Several other studies also supported this result in some types of cancer, such as prostate or breast cancer[60–67].

However, certain conclusions are in doubt[68–71]. In 2011, Blin *et al.*[72] found that cancer risk increased with exposure to insulin or sulfonylureas in these patients. There was no excess risk of cancer in type 2 diabetic patients on insulin glargine alone compared with those on human insulin alone[72]. Tang *et al.*[73] found that insulin glargine use was associated with a lower risk of cancer compared with non-glargine insulin use. Insulin glargine did not increase the odds of breast cancer. Compared with non-glargine insulin, no evidence of an association was found between insulin glargine and prostate cancer, pancreatic cancer and respiratory tract cancer[74–77]. Another study found that the overall risk of death or cancer in patients on insulin glargine was approximately half that of patients on human insulin, thereby excluding a competitive risk bias[78].

At this time, the US Food and Drug Administration and the European Medicines Agency have not concluded that insulin glargine increases the risk of any cancer, and the review of this safety concern is still ongoing[79,80]. Analysis of the Outcome Reduction with Initial Glargine Intervention trial did not show an increase in incident cancers (hazard ratio 1.00, 95% confidence interval 0.88–1.13; $P = 0.97$), death from cancer (hazard ratio 0.94; 95% confidence interval 0.77–1.15; $P = 0.52$), or cancer at specific sites, and the data do not support epidemiological analyses that have linked insulin in general or insulin glargine in particular to incident cancers during several years of exposure[74].

Therefore, insulin-glargine treatment provides a valuable clinical treatment option for diabetes therapy. For this reason, well-designed, large, randomized control trials between insulin glargine and other types of insulin would be difficult to carry out because of the inherent ethical issues. The accumulation of observational studies must continue to better understand the safety of glargine. Additionally, the new long-acting insulin, degludec, has been introduced to the market, and it is important to monitor the potential carcirogenic effects of this new insulin analog[81].

Sulfonylureas

Sulfonylureas are a class of antidiabetic drugs used to treat type 2 diabetes. They have also been associated with an increased risk of cancer in a few studies. The study by Currie *et al.*[12] showed that diabetic patients treated with sulfonylurea monotherapy exhibited a significantly increased incidence of cancer similar to insulin-treated patients when compared with untreated patients. Such an increased incidence of cancer in sulfonylurea-treated patients was reversed by co-administration of metformin[12].

A population-based cohort study showed that sulfonylureas increased cancer-related mortality at a level similar to that observed in insulin-treated patients when compared with metformin-treated patients[82]. That study did not include a non-treatment diabetic group, making it unclear whether sulfonylureas increased the risk of cancer-associated mortality or metformin decreased it.

Particular types of sulfonylureas could be associated with different rates of cancer incidence. A retrospective observational cohort analysis that was carried out by Monami *et al.*[83] found that cancers in diabetic patients treated with glibenclamide showed significantly higher mortality rates when compared with patients treated with gliclazide. The same group reported a case–control study showing that glibenclamide use in diabetic patients is strongly associated with an increased risk of cancer when compared with gliclazide treatment, and this trend is dependent on a drug exposure interval of up to 36 months[84]. Again, none of these studies was a randomized control trial. Recently, the newer oral insulin secretagogues, such as, glimepi-

ride, and the glinide-class of drugs, have also been reported to increase the incidence of cancers[85].

Metformin

Metformin belongs to the biguanide class of antidiabetic drugs, which are prescribed mainly for patients with type 2 diabetes. Metformin is a biguanide widely prescribed as a first-line antidiabetic drug in type 2 diabetes mellitus patients[86].

Accumulating evidence suggests that metformin reduces cancer incidence in the diabetic population. Evans *et al.*[87] published the first report investigating the decreased incidence of cancer in diabetic patients treated with metformin. Bowker *et al.*[82] carried out a 5-year follow-up study of 12,309 diabetic patients and found that metformin-treated patients showed significantly lower cancer-related mortality compared with the patients treated with insulin or sulfonylureas. More recently, a large-scale observational cohort study showed that cancer occurred in 7.3% of 4,085 metformin users compared with 11.6% of 4,085 controls, with median incidence times of 3.5 and 2.6 years, respectively[88]. However, in a systematic review and collaborative meta-analysis of randomized clinical trials, Stevens *et al.*[89] found no statistically significant beneficial effect of metformin on cancer outcomes. Metformin had little effect on overall mortality compared with other active diabetic therapies, and a statistically non-significant 10% reduction in mortality compared with placebo or usual care[89].

Metformin reduces adenosine triphosphate (ATP) production and results in an increased ratio of adenosine monophosphate (AMP)-to-ATP[90], which leads to the activation of the liver kinase B1 (LKB1)–AMP-activated protein kinase (AMPK) signaling pathway. Subsequently, LKB1 induces AMPK phosphorylation and AMPK-mediated signal transduction (Figure 1)[16,91–93]. Some papers stated that metformin inhibits hepatic gluconeogenesis in an LKB1- and AMPK-independent manner through a decrease in hepatic energy state as well[94]. Some other studies suggest that metformin potentially inhibits carcinogenesis/cancer cell growth through diverse pathways (Figure 1)[92–97].

The antitumor effects of metformin have also been confirmed in various animal models[93,98–104]. Metformin treatment mimics the gene expression profile of long-term calorie restriction[105], which is a nutritional intervention capable of both extending lifespan and reducing the incidence of many age-related diseases, including cancer[106,107]. Metformin inhibits tumor growth in mice receiving a high-fat diet, whereas metformin did not inhibit tumor growth in mice receiving a normal diet[108]. This suggests that the tumor suppressive effect of metformin might be dependent on the amelioration of a systemic metabolic profile, such as the synthesis of adipocytokines. Metformin might enhance CD8 (+) memory T-cell generation and show antitumor effects through AMPK[101]. Alternatively, metformin has been shown to kill cancer stem cells, which might play essential roles in cancer growth[103]. These reports show that

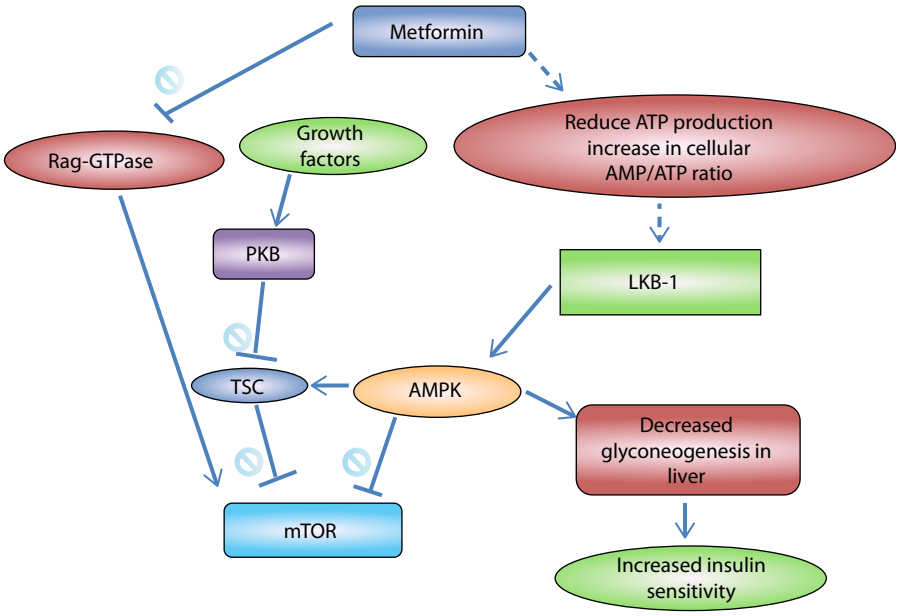

Figure 1 | Diverse mechanistic pathways of metformin. Metformin reduces adenosine triphosphate (ATP) production, increasing the cellular adenosine monophosphate (AMP)-to-ATP ratio, which leads to the activation of the liver kinase B1 (LKB1)–AMP activated protein kinase (AMPK) signaling pathway. Subsequently, LKB1 activates AMPK. AMPK inhibits mammalian target of rapamycin complex 1 (mTORC1) directly and the mTOR-inhibitor through tuberous sclerosis complex (TSC)1/2 activation. Such mTORC1-inhibition results in the inhibition of several carcinogenic molecules, such as ribosomal protein S6 kinase (S6K) and hypoxia-inducible factor-1α (HIF-1α). Several growth factors induce protein-kinase B (PKB)/Akt activation and counteract with AMPK-mediated TSC1/2 activation. Alternatively, metformin inhibits Rag-guanosine triphosphatase (GTPase), which activates mTORC1.

metformin could be a candidate drug for preventing tumor growth in diabetic patients through various mechanisms.

Furthermore, metformin might also retain its possible beneficial effects in non-diabetic cancer patients[109,110]. However, these favorable effects of metformin on cancer are not always corroborated by the data from retrospective clinical studies and smaller series of prospective trials using pathology end-points[110–112]. Some studies have been interpreted with limitations, some possible confounding factors and biases that might not have been fully adjusted for in the studies; some risk factors, such as cigarette smoking, alcohol intake, ages, treatment indication and hyperglycemia were not specified in studies, which might have rendered the results less valid. The long-term randomized prospective studies need to confirm the potential benefit.

Thiazolidinediones, Peroxisome Proliferator-Activated Receptor-γ and Cancer

Thiazolidinediones (TZDs) are a class of drugs used to treat patients with type 2 diabetes. TZDs act as an agonist for the ubiquitous nuclear receptor, peroxisome proliferator-activated receptor-γ (PPARγ). TZDs show antidiabetic effects by inducing increased insulin sensitivity and differentiation of adipocytes[113]. Several studies showed that TZDs suppressed the growth of cancer cells *in vivo* and *in vitro*[114–122]. TZDs also act as anti-angiogenic drugs[123]. Thus, a beneficial effect of TZDs on cancer in the diabetic population was expected.

A total of 17 studies satisfying the inclusion criteria (3 case–control studies and 14 cohort studies) were considered[124]. Adequate evidence excludes an overall excess cancer risk in TZD users within a few years after starting treatment. However, there is a modest excess risk of bladder cancer, particularly with reference to pioglitazone[124]. There was no association with pancreatic, lung, breast and prostate cancers. Assuming that this association is real, the potential implications on the risk–benefit analysis of TZD use should be evaluated[124]. However, results so far have not supported the original hypothesis. An early study, reported by Govindarajan *et al.*[125] showed a 33% reduction in lung cancer incidence by TZDs in patients with diabetes; however, there was no information available regarding the smoking history of patients or the duration of TZD treatment in that study. Therefore, interpretation of this result was difficult. Next, three nested case–control studies reported on the risk of cancers (breast, colon and prostate) in diabetic patients treated with TZDs or other drugs[126], and found no impact of TZDs on cancer incidence[126]. A cross-sectional study using the Vermont Diabetes Information database showed that TZDs were significantly associated with cancer, and this trend is much stronger in patients who were treated with rosiglitazone, one of the TZDs[127]. This difference was found in women, but not in men. Additionally, another TZD, pioglitazone, did not show such an association with cancer[127]. Chang *et al.*[128] reported that both pioglitazone and rosiglitazone could reduce the risk of incident liver cancer in type 2 diabetic patients. In this report, a better protection against cancer occurrence associated with a longer use and higher doses of TZDs as described[128]. On the contrary, a recent meta-analysis using randomized clinical trials to assess the safety of rosiglitazone in patients with diabetes showed no association with cancer; however, most of the participants enrolled in that analysis underwent less than a year of rosiglitazone treatment[129]. Therefore, longer, more careful observation is required to evaluate the safety of TZDs in treating diabetes.

Incretin Drugs and Cancer

Incretins are a group of gastrointestinal hormones that cause a postprandial increase in the amount of insulin released from the β-cells, even before blood glucose levels become elevated[130]. The safe use of incretin therapy is mentioned by some research. In 2011, Elashoff *et al.*[131] found that pancreatic cancer was more commonly reported among patients who were treated with a glucagon-like peptide-1 (GLP-1)-based therapy compared with other therapies ($P < 0.008$, $P < 9 \times 10^{-5}$)[131]. All other cancers occurred similarly among patients compared with other therapies ($P = 20$). These findings raise caution about the potential long-term actions of these drugs in the promotion of pancreatic cancer[131]. In 2013, Butler *et al.*[132] also found that incretin therapy in humans resulted in a marked expansion of the exocrine and endocrine pancreatic compartments, the former being accompanied by increased proliferation and dysplasia, and the latter by α-cell hyperplasia with the potential for evolution into neuroendocrine tumors. Because GLP-1 is rapidly degraded *in vivo* by the enzyme dipeptidyl peptidase-4 (DPP-4; which is a 110-kDa cell surface glycoprotein also known as CD26, and has an important, but complex, function in tumor behavior, with its biological effect dependent on the tumor type and the microenvironment)[132], DPP-4 inhibition could result in higher levels of both endogenous GLP-1 and GLP-2, because GLP-2 degradation is also inhibited[133].

Glucose-dependent insulinotropic polypeptide (GIP), as well as GLP-1, belongs to the family of incretins[134]. Some research that assessed GIP receptor expression in a broad spectrum of human gastrointestinal and bronchial tumors found that high GIP receptor expression was found in neuroendocrine tumors (NET)[135–138]. Of these tumors, functional pancreatic NET, including insulinomas, gastrinomas, glucagonomas and VIPomas, as well as non-functional pancreatic NET, ileal NET and bronchial NET, are especially noteworthy. Conversely, GIP receptors were rarely found among the epithelial cancers. The highest incidence of GIP receptor expression, approximately 26%, was found in pancreatic tumors. In an *in vitro* experiment, Prabakaran *et al.*[139] found that the presence of GIP receptors in colorectal cancer (CRC) might enable ligand binding and, in so doing, stimulate CRC cell proliferation. The overexpression of GIP, which occurs in obesity, might therefore be contributing to the enhanced rate of carcinogenesis observed in obesity[139].

DPP-4 is associated with a high level of clinical aggressiveness in some tumors, but a lower level in others[140]. DPP-4 itself could be a novel therapeutic target. Anti-CD26 monoclonal antibody treatment resulted in both *in vitro* and *in vivo* antitumor activity

against several tumor types, including lymphoma and renal cell carcinoma[141]. The role of CD26/DPP-4 activity in cancer, and the potential usefulness of this protein in therapeutics and diagnostics have been discussed[142].

In healthy CD1 mice, a DPP-4 inhibitor did not promote dysplasia in the colon[143], and the DPP-4 inhibitor showed no tumor promoting effects and non-considerable growth effects[143]. In 2013, Femia *et al.*[144] reported that long-term treatment with a DPP-4 inhibitor, sitagliptin, reduces colon carcinogenesis and reactive oxygen species in 1,2-dimethylhydrazine-induced rats, and this protective effect of DPP-4 against colon carcinogenesis could be explored in chemoprevention trials. Also, a recent clinical trial showed that DPP-4 inhibition by saxgliptin was not associated with increased incidence of either pancreatic or other cancers[145].

Aoe *et al.*[146] found that there was a trend for an association between response rate to chemotherapy and CD26 expression, with a higher level of CD26 expression more likely to be linked to a better response to chemotherapy. Their *in vitro* and microarray studies[146] showed that mesothelioma cells expressing high CD26 displayed high proliferative activity, and CD26 expression was closely linked to cell-cycle regulation, apoptosis and chemotherapy resistance. In another study, Arwert *et al.*[147] found that skin wounding triggers tumor formation in InvEE mice (the transgenic mice express involucrin promoter-regulated constitutively activated MEK1 construct, with two phosphomimetic point mutations [S217E/S221E]) through a mechanism that involves epidermal release of interleukin-1α and attraction of a pro-tumorigenic inflammatory infiltrate, and DPP-4 levels were upregulated in keratinocytes expressing mutant MAPK kinase 1 and in the epithelial compartment of InvEE tumors. CD26 expression was increased in dermal fibroblasts after skin wounding, but was downregulated in tumor stroma[147]. Pharmacological blockade of CD26 reduced growth of InvEE tumors, whereas combined inhibition of interleukin-1α and CD26 delayed tumor onset and reduced tumor incidence[147].

Some other studies have analyzed the possible mechanistic connection between GLP-1 and cancer from duration, age, and some other factors[148–152], and they found that the GLP-1 receptor, and the phosphatidyl-inositol 3 kinase-protein kinase B renin–angiotensin system–extracellular regulated protein kinases pathways might play a role (Figure 2).

PERSPECTIVE

Diabetes and Angiogenic Abnormalities

Angiogenesis, the formation of new blood vessels from a pre-existing capillary network, is not always healthy and often accompanies the growth of cancers[153,154]. Several clinical trials have shown that anti-angiogenesis therapy is beneficial in the treatment of many cancers[155], suggesting that increasing angiogenesis signals are contributing to cancer progression. Hypoxia in tumor tissue is a strong stimulator of angiogenesis through accumula-

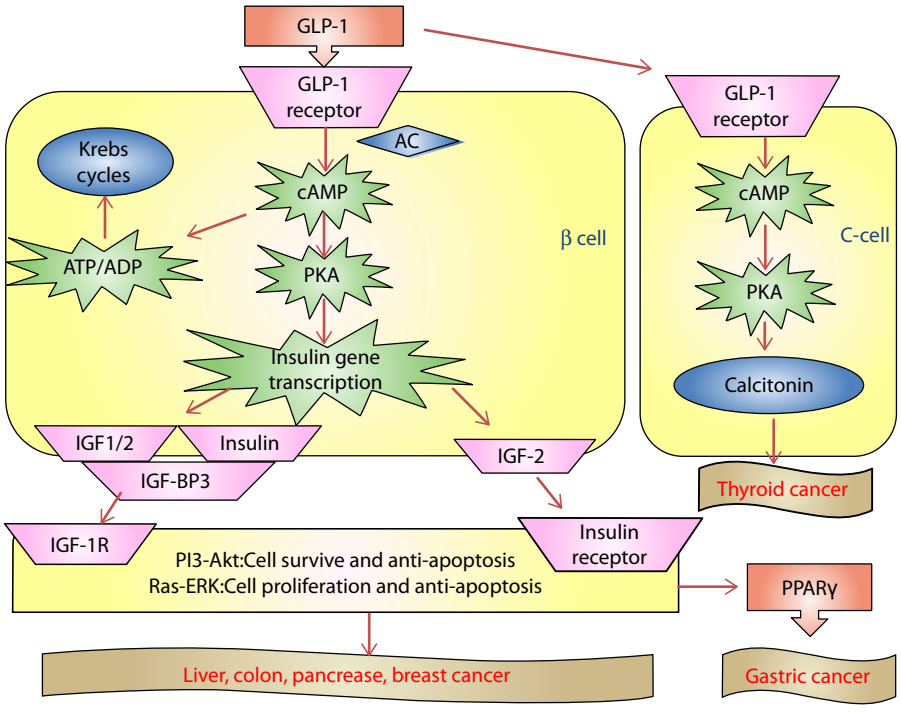

Figure 2 | Glucogen-like peptide-1 and cancer. Mechanism of GLP-1-potentiated insulin secretion in β-cells and a possible cancer pathway. AC, adenylatecyclase; ADP, adenosine diphosphate; ATP, adenosine triphosphate; IGF-BP3, insulin-like growth factor binding-protein 3; cAMP, cyclic adenosine monophosphate; IGF, insulin-like growth factor; PI3-Akt; phosphatidyl-inositol 3-kinase-Protein Kinase B; PKA, protein kinase A; PPARγ, peroxisome proliferator-activated receptor-γ; Ras-ERK, renin–angiotensin system–extracellular regulated protein kinases.

tion of hypoxia-inducible factors (HIFs) and their downstream targets, such as vascular endothelial growth factor (VEGF).

There is a possibility that these angiogenic abnormalities could be relevant to the association between cancer and diabetes. It is likely that the role of angiogenic signals in diabetes occurs by an organ-dependent mechanism. Diabetes is associated with increased angiogenesis and VEGF expression in the retina[156,157], whereas diabetic patients showed defective VEGF signaling cascade activation in the heart and peripheral vessels[158–160]. Furthermore, anti-angiogenic therapy inhibited diabetic retinopathy[157,158], and on the contrary, angiogenesis therapy rescued diabetic cardiac and peripheral vascular diseases[161,162]. It is also likely that abnormal angiogenesis is relevant to diabetic nephropathy[163]. In tumor cells, high levels of glucose induced the accumulation/expression of HIF-1α, whereas non-tumor cells showed decreased HIF-1α accumulation in response to high glucose levels[164,165], suggesting that impaired glucose homeostasis directly affects angiogenesis signals in tumors.

Glucose Utilization Defects and Cancer

Glucose metabolism is a complicated system essential for cell survival. It is still not clear how metabolic abnormalities and carcinogenesis are connected. With regard to glucose metabolism defects and carcinogenesis, an interesting possible connection has been reported. In 2009, Yun *et al.*[166] reported that low-glucose culture media exerts selection pressure on cells, which showed higher glucose transporter (Glut)-1 expression. Elevated Glut-1 expression in low-glucose conditions is associated with *de novo* mutation of oncogenes, such as *KRAS*/*BRAF*, in normal cultured cells[166]. Diabetes is associated with defects in glucose uptake, and results in lower available glucose for energy production in cells, despite significantly elevated levels of blood glucose. In fact, when analyzed by [^{13}C]-magnetic resonance spectroscopy, rates of insulin-stimulated glucose uptake and glycogen synthesis were 50% lower in diabetic patients when compared with control individuals[167]. Therefore, it could be possible that lower available glucose in cells might alter gene expression profiles responsible for nutrient uptake through overinduction of nutrition transporters and mutations in key oncogenes. On the contrary, Zhang *et al.*[168] reported that increased concentrations of glucose induced gene mutations partially by oxidative stress-dependent mechanisms in human lymphoblast cell lines. These reports show that defects in glucose homeostasis might directly induce mutation in genes and contribute to carcinogenesis. Le *et al.*[169] found that under glucose limitation, the tricarboxylic acid cycle could also be reprogrammed and driven solely by glutamine, generating citrate that consists of only glutamine carbons. Reductive carboxylation was first documented as a means for normal brown fat cells to synthesize lipids, and was subsequently implicated as a way for cancer cells to synthesize lipids from glutamine for their growth in hypoxic environments[170].

Targeting glucose metabolism could be a selective way to kill cancer cells. Several glycolytic enzymes are required to maintain a high glucose metabolism[171]. Some human carcinomas overexpress mitochondrial ATPase inhibitory factor 1(IF1), which blocks the activity of mitochondrial H^+-ATP synthase and facilitates metabolic adaptation to aerobic glycolysis. The overexpression of IF1 in human carcinomas is an additional epigenetic factor that contributes to the peculiar energy metabolism of mitochondria in cancer, and IF1 directly promotes the acquisition of the hallmarks of the cancer phenotype[172].

Inflammation and Cancer

Inflammation is a hallmark of cancer where diverse immune cells exert either pro- or antitumor properties[172,173], and affect therapeutic resistance[174]. During inflammation, the fate of the cell is dependent on the balance between pro- and antitumorigenic immune responses, and it is now believed that inflammation affects the three stages of cancer : tumor initiation, tumor promotion and tumor progression[175]. Tumor initiation is the process by which a normal cell becomes premalignant. The inflammatory environment, which consists of an increase in cytokines, chemokines, and reactive oxygen and nitrogen species, results in DNA mutations, epigenetic changes and genomic instability that can contribute to tumor initiation[175,176]. Tumor promotion involves the proliferation of genetically altered cells, and chronic inflammation promotes this by inhibiting apoptosis, and the acceleration of proliferation and angiogenesis[175,177]. Finally, tumor progression and metastasis, which involves an increase in tumor size, additional genetic changes and the spreading of the tumor from its primary site to multiple sites, are also influenced by inflammation.

Heparanase might show shared molecular mechanics with inflammation, diabetes and cancer. Heparanase is a multifunctional molecule having both enzymatic and non-enzymatic functions. Previous studies have implicated heparanase in several facets of the inflammatory/autoimmune process including leukocyte recruitment, immune cell extravasation and migration, release of cytokines and chemokines, and activation of innate immune cells. Meirovitz *et al.*[178] reviewed the compelling evidence that heparanase is an important player in coupling inflammation with tumorigenesis, particularly as observed in colitis-associated colon carcinoma[178]. Several up-to-date reviews also nicely summarized the basic and translational aspects related to the involvement of heparanase in cancer progression[179,180]. Emerging evidence shows that heparanase plays important roles in diabetes (types 1 and 2)[181,182]. The review by Park EJ *et al.*[183] describes their exciting finding that heparan sulfate within β-cells in the pancreatic islet acts to protect these cells from free radical damage and death. This protective anti-apoptotic effect is neutralized when nearby autoreactive T cells secrete heparanase that subsequently degrades heparan sulfate, leading to the onset of type 1 diabetes[183]. Clearly, heparanase has emerged as a major player in the pathogenesis and natural history of various diseases that plague humans[184]. The role of heparanase in cancer, diabetes and inflammation has elevated the importance of developing clinically effective antiheparanase therapies.

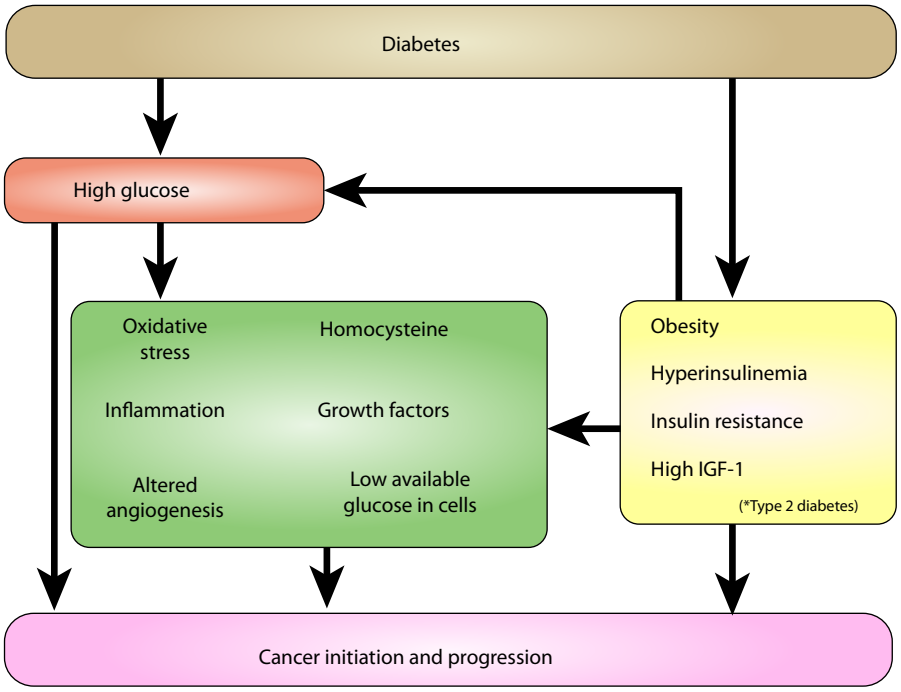

Figure 3 | Diabetes and cancer. Diabetes-associated conditions, such as high glucose, oxidative stress, inflammation, angiogenesis, homocysteine, growth factor and low available glucose in cells, could be connected to cancer initiation and progression. In type 2 diabetes*, other factors, such as obesity, hyperinsulinemia, insulin resistance and high insulin-like growth factor (IGF)-1, might contribute to cancer initiation and progression.

CONCLUSION

There are many theories and possible mechanisms at work in the biology of diabetes (Figure 3). Although diabetes and diabetes therapy could potentially be associated with cancer incidence/prognosis, it must be mentioned here that the majority of mortality is still as a result of classical diabetes-associated complications, such as cardiovascular disease and chronic renal failure. Blood glucose control is essential for preventing diabetes-associated complications; therefore, clinicians should not hesitate to use blood glucose lowering therapies on account of their possible cancer risks. Because of the characteristics of diabetes biology, carrying out long-term randomized controlled trials for assessing the connection between certain treatments and carcinogenesis is difficult. Therefore, the continuous accumulation of observational studies will be required. The anticancer effects of metformin highlight the possibility that some diabetes-associated cancers could be avoidable. It is necessary to have special guidelines for the screening of and the use of therapeutic strategies for diabetes-associated cancers when considering potential risk factors, such as blood glucose control, amount of insulin, types of cancer, angiogenesis, homocysteine level and so on. Diabetes might be associated with cancer; investigation into possible mechanistic links would shed new light on both diabetes and cancer biology, and would also provide clues for the development of useful novel drugs for these common diseases.

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