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Glucagon-like peptide-1 medicines and cancer

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Glucagon-like peptide-1 (GLP-1) medicines reduce food intake, body weight, insulin resistance and inflammation, thus improving outcomes for people with type 2 diabetes and obesity and potentially contributing to decreased cancer incidence. GLP-1 medicines acting through weight loss-dependent and weight loss-independent mechanisms hold potential for suppression of tumorigenesis and reduction of rates of obesity-associated cancer. In this Perspective, we summarize data on cancer incidence from trials and registries in individuals with type 2 diabetes, describe the actions of GLP-1 medicines on preclinical cancer models and highlight possible direct and indirect mechanisms linking GLP-1R signaling to cancer development and progression.

Clinical evidence reports that type 2 diabetes (T2D) and obesity increase cancer risk[1,2]. There is considerable interest in understanding whether interventions directed at lowering glucose or body weight impact the risk of incident cancer.

Such interventions include glucagon-like peptide-1 (GLP-1) medicines (Table 1). These medicines are currently based on the activation of receptors for the incretins GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), which are endogenous gut peptides that augment postprandial insulin secretion, thereby reducing blood glucose levels while simultaneously decreasing food intake and gastric emptying[3] (Fig. 1). Real-world data suggest that individuals living with overweight/obesity and/or T2D treated with GLP-1 medicines may exhibit reduced incidence of multiple cancers[1,2,4] (Table 2). However, the mechanisms by which such medicines affect tumor cell biology, tumor development and cancer risk directly (Fig. 2) or indirectly, remain to be determined.

In this Perspective, we summarize the data on cancer incidence from trials and registries in participants with T2D and obesity, describe the action of GLP-1 medicines on preclinical models of experimental cancer and highlight the possible direct and indirect mechanisms linking their signaling to cancer development and progression. A deeper understanding of how existing and emerging GLP-1 medicines may reduce cancer incidence and influence tumorigenesis will identify further opportunities for GLP-1 medicines in cancer prevention and treatment.

Metabolic diseases and cancer

T2D and cancer

Epidemiological reports link T2D to an elevated risk of cancer and increased cancer-related mortality[1,5,6]. A new diagnosis of diabetes also leads to greater scrutiny and higher rates of cancer detection[4]. Collectively, metabolic disturbances, such as hyperinsulinemia, high leptin and low adiponectin (Fig. 1), foster a pro-oncogenic and proliferative environment[7] (Figs. 1 and 3).

Insulin and metformin are associated with opposing cancer risks. Insulin exhibits growth factor-like activity through the insulin and IGF-1 receptors and acts as a tumor promoter in preclinical models of cancer, whereas hyperinsulinemia is frequently associated with increased rates of cancer in real-world studies[8]. Insulin therapy is frequently added later in the T2D disease course, often in older individuals who may already have an increased cancer risk. Conversely, metformin is frequently the first glucose-lowering agent prescribed in younger individuals, and its use is associated with modest weight loss. Despite numerous preclinical studies linking metformin to reduced cancer growth, clinical evidence from randomized controlled trials remains less compelling[9].

Obesity and cancer

Obesity drives cancer growth through increased circulating levels of growth factors, enhanced inflammation and modification of the pro-oncogenic tumor microenvironment (TME)[10] (Fig. 3). Analysis of the Cancer in North America database demonstrated steep rises in 6 of 12 obesity-related cancers in young adults, including colorectal, uterine corpus, gallbladder, kidney, multiple myeloma and pancreatic[11]. Similarly, obesity duration, degree (that is, greater body mass index (BMI)) and early diagnosis are linked to a higher risk of 18 different cancers in Spain[2]. Cancer is also a major contributor to obesity-related morbidity and mortality[12] with over a dozen human neoplasms classified as obesity-associated cancers[2].

Bariatric surgery, which leads to long-term weight loss, reduces rates of obesity-associated cancer mortality and morbidity[13,14].

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Table 1 | Overview of approved GLP-1 medicines and key indications

Drug	Action	Pharmacokinetics	Approved indication	References
Exenatide	GLP-1RA	Short-acting	T2D	105
Lixisenatide	GLP-1RA	Short-acting	T2D	106
Liraglutide	GLP-1RA	Long-acting	Obesity T2D	107 108
Dulaglutide	GLP-1RA	Long-acting	T2D	109
Semaglutide	GLP-1RA	Long-acting	T2D Obesity ± heart disease Chronic kidney disease Metabolic liver disease	94 110–116
Tirzepatide	GLP-1R–GIPR dual agonist	Long-acting	T2D Obesity Obstructive sleep apnea	23 117 118

Achievement of reduced weight with lifestyle interventions such as diet and exercise also reduced rates of obesity-associated cancers in the Look AHEAD trial after a median 11 years of follow-up[15]. Hence, there is great interest in understanding whether and how new interventions and medicines for glucose control or weight loss may alter cancer risk in people with T2D and/or obesity.

GLP-1 medicines

GLP-1 medicines such as exenatide, liraglutide, dulaglutide, semaglutide and tirzepatide (Table 1) activate GLP-1 and/or GIP signaling via their respective receptors, GLP-1 receptor (GLP-1R) and GIP receptor (GIPR).

GLP-1 and GIP signaling

GLP-1 and GIP are gut peptides that are secreted at low basal levels in the fasting or interprandial state and levels are increased after meal ingestion due to the presence of macronutrients in the gut[16]. They bind to their receptors GLP-1R and GIPR in pancreatic β islet cells, acinar cells, neurons, astrocytes and other non-neuronal cell types, activating cyclic AMP (cAMP)-dependent signal transduction pathways to promote glucose disposal, weight loss and reduction of systemic inflammation (Fig. 1).

Mode of action of GLP-1 medicines

GLP-1 stimulates insulin and suppresses glucagon secretion, food intake and gastric emptying, with sustained administration of GLP-1 medicines producing meaningful weight loss[3] (Fig. 1). Classic actions of GLP-1 are mediated through GLP-1R on β cells, signaling through cAMP-dependent pathways to increase the expression of transcription factors such as PDX1 and NFAT, leading to augmentation of β cell growth and induction of insulin biosynthesis (Fig. 1). GLP-1 also acts directly on central nervous system (CNS) neurons to reduce appetite and inflammation and directly on intestinal intraepithelial lymphocytes (IELs) to reduce gut inflammation[17,18] (Fig. 1). Weight loss in turn reduces adipocyte mass and restores normal adipocyte physiology and adipokine secretion, decreasing the pro-oncogenic environment (Fig. 1). The predominant adverse events associated with GLP-1 medicines are gastrointestinal, principally nausea, diarrhea, constipation, vomiting and gallbladder events[19]. Modern GLP-1 medicines (Table 1), such as semaglutide and the GIPR–GLP-1R coagonist tirzepatide, are administered once weekly and are approved for T2D, as well as for weight loss in people with overweight/obesity. GLP-1 medicines also reduce rates of myocardial infarction, stroke, cardiovascular death and heart failure in people with T2D and/or obesity and decrease progression of chronic kidney disease[20]. Semaglutide also reduces the severity of metabolic liver disease and osteoarthritis[20,21], whereas tirzepatide ameliorates metabolic liver disease[22] and improves symptoms and outcomes in people with obstructive sleep apnea[23]. The extent to which GLP-1 medicines produce benefits through weight loss-independent mechanisms, including reduction of inflammation, remains uncertain[24].

Cancer biology of GLP-1Rs and GIPRs

The pleiotropic actions of incretins GLP-1 and GIP and their respective receptors, GLP-1R and GIPR, including attainment of weight loss, has fostered interest in whether GLP-1 medicines may reduce rates of obesity-associated cancers. A great deal of the available data stem from analysis of registry databases studying predominantly people with T2D treated with GLP-1 medicines (Table 2).

GLP-1R and GIPR signaling, proliferation and tumorigenesis

GLP-1Rs and GIPRs are expressed in multiple tumor subtypes, including several types of brain cancer, neuroendocrine tumors, prostate and breast cancer (Fig. 2), raising the possibility of direct effects on tumor growth and survival (Fig. 1). GLP-1 medicines may exert direct proliferative effects on normal and neoplastic GLP-1R$^+$ cells[25,26] (Fig. 2), effects that are frequently dependent on PKA or MEK activity (Fig. 1). GLP-1R binding sites are detected in endocrine, nervous system, embryonic and ovarian tumors (Fig. 2) using ^{125}I-labeled GLP-1(7–36)[27]. A greater number of tumors express GIPR binding sites (Fig. 2), including medullary thyroid carcinomas (MTC), gastrointestinal tumors and bronchial tumors[28–30]. Detection of class B G-protein-coupled receptor expression, including GLP-1R and GIPR, is challenging due to low-level receptor expression and suboptimal sensitivity and specificity of antibodies[31,32], rendering the literature difficult to interpret[31,32]. Furthermore, the doses of GLP-1 medicines used in experimental cancer studies of cell lines and small animals are often greater than regimens used in humans, and drug exposure within the TME (Fig. 3) remains unknown.

GLP-1Rs and GIPRs and the TME

Higher *GLP1R* expression is associated with increased survival in breast cancer, esophageal carcinoma, renal clear cell carcinoma, renal papillary cell carcinoma and thyroid carcinoma[33] (Fig. 2). However, *GLP1R* expression in these tumors is very low, the cellular localization of *GLP1R* expression within these tumors is not clearly defined, and whether detection of *GLP1R* mRNA corresponds to translation of functional receptors within the TME has not been determined.

Both semaglutide and the investigational GLP-1–GIP–GCG triple agonist retatrutide attenuate pancreatic ductal adenocarcinoma growth in mice to a greater extent than observed with calorie restriction and weight loss alone, with retatrutide also attenuating tumor engraftment[34]. Notably, pancreatic tumors from retatrutide-treated mice exhibit upregulation of TNF signaling, interferon-γ and interferon-α and inflammatory pathways and interleukin-2 (IL-2), STAT5 and allograft rejection pathways, corresponding to enhanced antitumor immunity[34]. Nevertheless, the key cell types within the TME (Fig. 3) exhibiting these transcriptional responses remain unidentified. In the Broad Institute single-cell and spatially resolved transcriptomics analysis of human breast cancers atlas, *GLP1R* expression was detected in CD4$^+$ T cells, differentiated perivascular-like cells, myoepithelial cells, luminal progenitor cells and endothelial cells within breast cancer tissue[35] (Fig. 3).

Within the immune system, GLP-1R is expressed on T cells, predominantly in gut IELs in the distal small bowel[18,36]. Expansion of GLP-1R$^+$ T cells, mostly terminally differentiated CD4$^+$ and exhausted CD8$^+$ T cells, occurs in the spleen as a direct response to tissue allograft transplantation, and these T cells were found to infiltrate grafts[37]. Like PD-1, GLP-1R activation acts as a co-stimulatory molecule, reducing T cell graft infiltration and prolonging allograft survival. Preclinical studies demonstrate that adenoviral delivery of GLP-1 reduces tumor infiltration of polymorphonuclear myeloid-derived suppressor cells, resulting in activation of the antitumor activity of CD8$^+$

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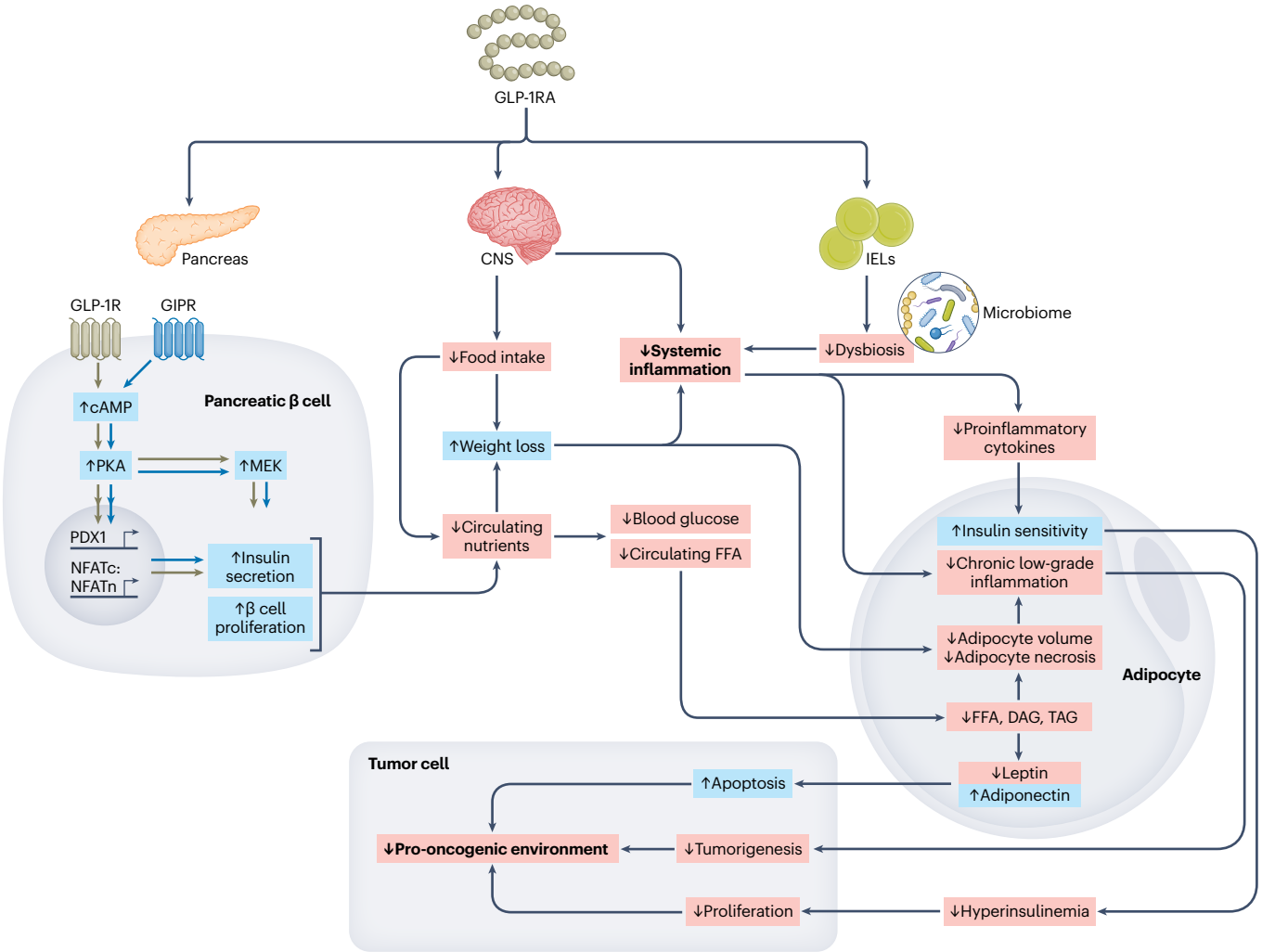

Fig. 1 | GLP-1 and GIP control β cell, adipocyte and tumor biology via direct and indirect mechanisms. GLP-1R agonists (GLP-1RAs) and GIPR agonists signal to neurons in the hindbrain and hypothalamus to reduce food intake and body weight, resulting in improved insulin sensitivity by reducing circulating free fatty acids, hyperinsulinemia and systemic inflammation. GLP-1R activation in the pancreas results in an increase in the cAMP–protein kinase A (PKA) axis, leading to increased mitogen-activated protein kinase kinase (MEK) activity and the induction of transcription factor expression that increases insulin biosynthesis and secretion, pancreatic neogenesis and β cell proliferation, ultimately enhancing glucose disposal. The IEL GLP-1R reduces local gut inflammation and microbiome dysbiosis, which reduces systemic inflammation. Weight loss reduces adipocyte volume and necrosis, which restores normal secretion of adipokines such as leptin and adiponectin. Normalization of adipokine and insulin secretion and reduction of circulating inflammatory markers favorably modify the pro-oncogenic environment and reduce the likelihood of tumor growth. CNS GLP-1R$^+$ neurons also convey signals that reduce systemic inflammatory responses, potentially impacting tumor growth. Collectively, actions of GLP-1RAs on multiple organs and cell types impact the TME to modify cancer development and growth. AKT, protein kinase B; CREB, cAMP response element-binding protein; DAG, diacylglycerol; FFA, free fatty acids; IEL, intestinal intraepithlial lymphocyte; NFAT, nuclear factor of activated T cells; PDX1, pancreatic duodenal homeobox 1 transcription factor; TAG, triacylglycerol.

tumor-infiltrating lymphocytes in experimental models of pancreatic cancer[38] (Fig. 3). Nevertheless, the use of insufficiently validated GLP-1R antisera challenges precise localization of GLP-1R to specific cell types in these studies[32].

GIPR expression is detected in the bone marrow, predominantly on myeloid cells, including macrophages[39]. *Gipr* deletion in mice upregulates inflammation within adipose tissue, the intestine and the aorta, whereas activation of GIPR signaling reduces systemic and tissue inflammation[39–41]. GLP-1 medicines reduce inflammation in animals and humans independent of weight loss[17,42]. However, continuous GIP infusion in participants with type 1 diabetes did not reduce circulating or adipose tissue biomarkers of inflammation[43]. Furthermore, whether specific cell types within the TME upregulate or downregulate the expression of *GLP1R* or *GIPR* in various cancers (Fig. 3) has not been established, and many antisera used to detect GIPR exhibit poor sensitivity and specificity[31,44].

GLP-1 medicines and cancer growth

Use of exenatide, liraglutide, dulaglutide, semaglutide and tirzepatide (Table 1) is associated with reduced incidence of cancers in participants with overweight/obesity and/or T2D[45]. A retrospective propensity-matched cohort with over 93 million adults with a BMI of >30 kg m^{-2} from TriNetX demonstrated reduced rates of colorectal, liver/biliary, uterine, prostate, melanoma and respiratory cancers in people with exposure to GLP-1 medicines[46] (Fig. 2 and Table 2). Retrospective registry and cohort studies of individuals with T2D and/or obesity associate the use of GLP-1 medicines with reduced incident rates for multiple cancers[47], with some studies revealing lower all-cause mortality in participants with T2D and a concomitant cancer diagnosis[48]. Nevertheless, the extent to which these findings correlate with the degree of exposure, medication adherence and extent of weight loss is generally not reported. Multiple preclinical studies demonstrate that GLP-1 medicines reduce cancer cell migration, proliferation and

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Table 2 | Clinical evidence assessing rates of cancers in people treated with GLP-1 medicines

Cancer type	Study design	Risk change	Sample size	Additional notes	Reference
Breast cancer	Systematic review (50 trials)	No change (RR=0.98 malignant; RR=0.98 benign neoplasms)	48,267 GLP-1RA; 40,755 controls	Low number of events (130 GLP-1RA versus 107 controls)	65
Breast cancer	TCGA-BRCA database for survival	No survival difference linked to *GLP1R* expression	273 *GLP1R* expression high; 272 *GLP1R* expression low	Receptor expression nonprognostic	33
CNS neoplasms	TriNetX US Collaborative network cohort (2013–2023); 93 million total participants; 5,085,136 participants with a BMI of >30	↓ versus non-GLP-1RA (HR=0.66)	76,422 GLP-1RA; 358,309 controls	Includes eye cancers; unclear how many contribute to this number; HR calculated from 5-year risk	46
Cholangiocarcinoma	Administrative registers in Sweden, Denmark and Norway registry cohort (2007–2018)	No change (aHR=1.25)	96,813 GLP-1RA; 142,578 SU	Low event numbers (92 GLP-1RA versus 157 SU)	76
Cholangiocarcinoma	US TriNetX cohort (2010–2021); 3,197,112 participants with T2D newly initiated glucose-lowering medications	↓ versus other (HR=0.49)	485,942 GLP-1RA; 2,711,170 controls	Low event numbers (137 GLP-1RA versus 280 other)	77
CRC	US TriNetX cohort (2005–2019); 101.2 million participants; 7.4 million with T2D	↓ versus insulin (HR=0.56)	1,221,218 with T2D; GLP-1RA 22,572 matched	Compared GLP-1RA to metformin, DPP4i, SGLT2i, sulfonylureas and thiazolidinediones	70
Endometrial cancer	US TriNetX obesity cohort of 113 million participants; 1,651,452 participants with T2D	↓ versus insulin (HR=0.74)	In 25,750 instances of endometrial cancer, 160 GLP-1RA events versus insulin with 210 events	Suggestive protective effect; event numbers low	45
Esophageal cancer	US TriNetX cohort of 113 million participants; 1,651,452 participants with T2D	↓ versus insulin (HR=0.60)	In 48,437 reports of esophageal cancer, 49 GLP-1RA events versus insulin with 77 events	Event numbers low; more studies are required	45
Esophageal cancer	TriNetX US cohort (7-year timeframe); 2,748,431 participants with T2D	↓ versus non-GLP-1RA (HR=0.341)	167,077 GLP-1RA; 2,581,354 non-GLP-1RA	Effect independent of BMI; low event numbers (63 GLP-1RA versus 190 non-GLP-1RA events)	86
Gastric cancer	TriNetX US cohort (7-year timeframe); 2,748,431 participants with T2D	↓ versus non-GLP-1RA (HR=0.417)	167,077 GLP-1RA; 2,581,354 non-GLP-1RA	Effect independent of BMI; low events (79 GLP-1RA versus 197 non-GLP-1RA events)	86
Hematologic cancers	A retrospective study of US TriNetX (2005–2023); 1,601,334 participants with T2D	↓ versus insulin (HR=0.46)	51,617 GLP-1RA with 127 events; 938,602 insulin with 420 events	No difference compared to metformin	119
HCC	Taiwanese cohort consisting of participants with T2D (2013–2018)	↓ versus insulin (SDHR=0.45)	7,633 GLP-1RA; 49,081 insulin	Small number of events; obesity imbalance between groups; no weight loss assessment	120
HCC	Taiwan National Health Insurance cohort (2008–2018); 3,432,732 newly diagnosed T2D	No change (aHR=0.91)	Propensity score matched 31,183	Small number of events (85 total)	73
HCC	The Decoding the Epidemiology of LIVER disease in Sweden (DELIVER; 2010–2020) cohort; 442,367 participants with chronic liver disease and T2D	↓ versus non-GLP-1RAs; major adverse liver outcomes (RR=0.51)	1,026 GLP-1RA; 15,633 controls	HCC not analyzed separately; small number of events; no weight loss assessment	74
HCC	US multicenter cohort (2013–2019); 111.7 million participants total; 1,890,020 participants with T2D prescribed antidiabetes medications	↓ versus insulin (HR=0.20)	47,578 GLP-1RA; 1,148,166 insulin	Reductions versus users of insulin and sulfonylureas	75
Lung cancer	TriNetX US cohort (2005–2019) with 105.9 million participants; 1,040,341 participants with T2D prescribed glucose-lowering medications	↓ versus insulin for lung cancer (HR=0.49 after propensity matching)	29,850 GLP-1RA; 628,808 insulin	Underpowered for analysis of subtypes of lung cancer	87
Meningioma	US TriNetX cohort of 113 million participants; 1,651,452 participants with T2D	↓ risk versus insulin (HR=0.37)	48,983 GLP-1RA with 11 events; 1,044,745 insulin with 29 events	Event numbers low	45

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Table 2 (continued) | Clinical evidence assessing rates of cancers in people treated with GLP-1 medicines

Cancer type	Study design	Risk change	Sample size	Additional notes	Reference
Neuroendocrine tumors	TriNetX US Collaborative network cohort (2013–2023); 93 million total participants; 5,085,136 participants with a BMI of >30	No difference (HR=0.874)	76,422 GLP-1RA; 358,309 controls	Only 133 total cases over 5 years	46
Ovarian cancer	US TriNetX cohort of 113 million participants; 1,651,452 participants with T2D	↓ versus insulin (HR=0.52)	In 25,739 cases of ovarian cancer, 51 GLP-1RA events versus 91 insulin events	Consistent reduction; limited sample size	45
Pancreatic cancer	TriNetX Multicenter retrospective cohort (2006–2021); 88,970,738 total participants; adult participants with diabetes and/or overweight obesity	↓ versus metformin (HR=0.47)	492,760 GLP-1RA; 918,711 metformin	351 GLP-1RA versus 956 metformin	121
Pancreatic cancer	TriNetX US cohort (7-year timeframe); 7,146,015 participants with T2D	↓ (HR=0.524)	736,015 GLP-1RA; 6.41 million non-GLP-1RA	Large cohort of individuals with reasonable number of events (985 GLP-1RA versus 1,419 other)	51
Pancreatic cancer	Israel Clalit Healthcare services cohort (2009–2017); 2.3 million total; 543,595 individuals with T2D	No change (HR=0.50; 95% CI, 0.15–1.71)	33,377 GLP-1RA; 106,849 insulin	Analysis of participants given GLP-1RAs 5–7 years before pancreatic cancer diagnosis	52
Pancreatic cancer	US TriNetX cohort (2013–2019); 113 million participants with 1,636,056 eligible participants prescribed diabetes medications	↓ versus insulin (HR=0.42) and metformin (HR=0.74)	167,091 GLP-1RA; 1.63 million T2D cohort	5-year follow-up; 100 GLP-1RA versus 213 insulin events; 111 GLP-1RA versus 142 metformin events	53
Prostate cancer	Nationwide register-based cohort study from multiple Danish registries (2007–2019)	No difference (HR=0.91)	14,206 GLP-1RA; 21,756 insulin	Events (236 GLP-1RA versus 261 insulin)	81
Prostate cancer	UK Clinical Practice Research Datalink cohort (2007–2019)	↓ versus sulfonylureas (wHR=0.65)	5,063 GLP-1RA; 112,955 SU	Large imbalance in sample size is evident	82
Skin cancer	UK Clinical Practice Research Datalink cohort (2007–2019)	No difference (HR=0.96 melanoma; HR=1.03 nonmelanoma)	11,786 GLP-1RA; 207,788 SU	Large UK cohort shows no increased melanoma/NMSC risk; low event numbers	89
Thyroid cancer	US database (2005–2019); 63 million total participants	↑ versus metformin (aOR=1.65)	64,230 GLP-1RA; 619,340 metformin	BMI higher in the GLP-1RA group; small exposed sample size	122
Thyroid cancer	French national insurance (2006–2018); >66 million participants with 3,746,672 participants with T2D	↑ thyroid (aHR=1.58) and medullary (aHR=1.78) cancers	2,562 cases; 45,184 exposed	No control for detection bias	57
Thyroid cancer	Korean national cohort (2014–2020); ~50 million participants	No difference (HR=0.98)	21,722 GLP-1RA; 326,993 SGLT2i	Low event rates 23 GLP-1RA versus 524 events for SGTL2i	123
Thyroid cancer	Scandinavian registry (2007–2021); participants who started GLP-1RAs versus DPP4i or SGLT2i	No difference (HR=0.93)	145,410 GLP-1RA; 291,667 DPP4i	Follow-up for use of GLP-1RA 3.9 years versus DPP4i 5.4 years	58
Thyroid cancer	Second-Line Therapies for Patients with T2D and Moderate CVD Risk study (2014–2021); 351,913 participants with T2D at risk for CVD that received glucose-lowering medication	No difference (HR=1.24)	41,112 GLP-1RA; 310,801 other	Dx based on ICD codes; higher 1-year thyroid cancer risk with GLP-1RA only; effect reflects early detection	124
Thyroid cancer	Active comparator new-user cohort study from six national-level and four health system data sets from the United States	No difference (HR between 0.78 and 1.03 compared to all)	460,032 GLP-1RAs, 717,792 SGLT2i, 2,055,583 DPP-4i, 1,119,868 SU	Propensity scoring methods used for confounding control	125

Abbreviations: 95% CI, 95% confidence interval; aOR, adjusted odds ratio; CVD, cardiovascular disease; DPP4i, dipeptidyl peptidase-4 inhibitors; ICD, internal classification of diseases; Dx, diagnosis; HR, hazard ratio; aHR, adjusted hazard ratio; wHR, weighted hazard ratio; NMSC, non-melanoma skin cancer; RR, relative risk; SDHR, subdistribution hazard ratio; SU, sulfonylurea; TCGA-BRCA, The Cancer Genome Atlas-Breast Invasive Carcinoma.

tumor growth by improving metabolism and reducing inflammation and possibly through direct engagement of GLP-1Rs on some cancer cells or through indirect modification of the TME (Figs. 1 and 3). These experiments were performed using structurally distinct GLP-1 medicines, studied at varying concentrations, with multiple tumor models, end points and treatment intervals[34,49,50].

Pancreatic cancer

Pancreatic endocrine cells and exocrine cells express a functional GLP-1R (Fig. 2a); some, but not all, preclinical studies suggest that GLP-1R agonism promotes the development and growth of pancreatic cancer. Nevertheless, analysis of 21 human pancreatic adenocarcinomas did not detect evidence for GLP-1 binding sites[27], and use of

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a

Area of body	GLP-1R expression	GIPR expression
Brain/spine	Meningioma Astrocytoma Glioblastoma Ependymoma Medulloblastoma	
	Pituitary adenoma Schwannomas	
Head and neck	Medullary thyroid carcinoma	
	Non-Hodgkin's lymphoma Parathyroid carcinoma	
Breast	Breast carcinoma	Breast carcinoma
Liver/biliary		Cholangiocarcinoma
	HCC	HCC
Stomach		Gastrinomas Gastric adenocarcinoma
	Gastric adenocarcinomas	
Pancreas		Nonfunctional pancreatic neuroendocrine tumors Pancreatic adenocarcinoma Glucagonomas Insulinomas VIPomas
	Pancreatic adenocarcinoma Ductal pancreatic carcinomas	
Gut/colorectal		Ileal neuroendocrine tumors
	Colorectal adenocarcinoma	Colorectal adenocarcinoma
Kidney	Pheochromocytoma Paraganglioma Nephroblastoma Neuroblastoma	
	Renal cell carcinoma Adrenal cortical adenoma	
Ovary/prostate	Ovarian carcinoma Prostate carcinoma	

Expression No expression

b

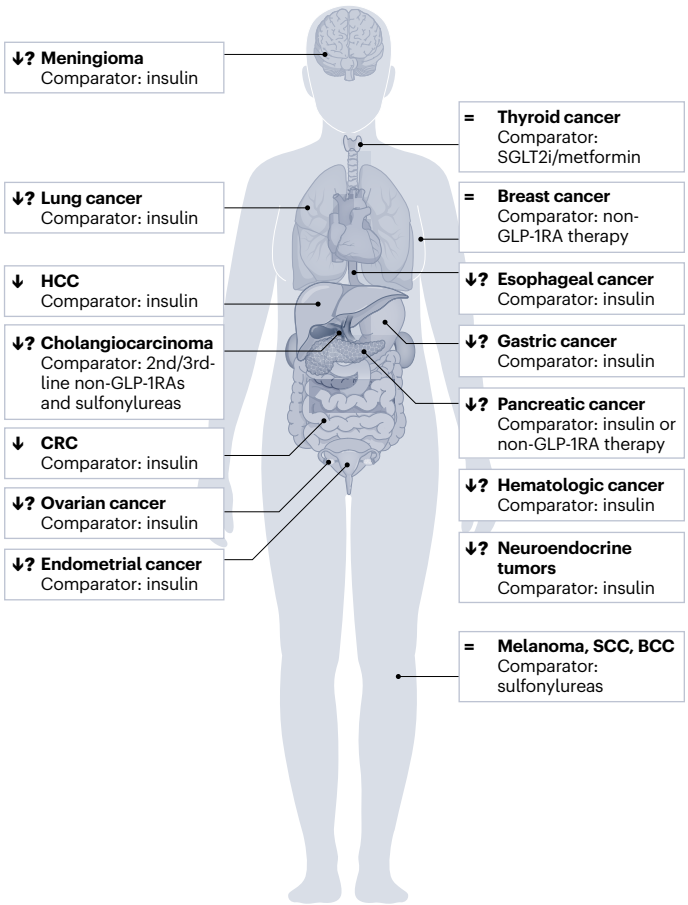

Fig. 2 | Expression of GLP-1R and GIPR in human tumors. a, Approximation of GLP-1R and GIPR protein expression through ligand binding studies is depicted in blue. Human tumors express different levels of GLP-1R in the CNS, thyroid, kidney, ovary and prostate. GIPR is more robustly expressed in breast, stomach, bile tract, gut and pancreatic tumors. Conversely, there are various tumor types that do not express GLP-1 or GIP binding sites, depicted in red. **b**, Reduction of incident cancers with GLP-1 medicines. Data from human cohort studies show a reduction in cancer risk in individuals using GLP-1RAs, such as exenatide, liraglutide and semaglutide, compared to non-GLP-1RA glucose-lowering therapies, such as insulin, metformin, sodium-glucose transporter 2 inhibitors (SGLT2i) and sulfonylureas. Lower risk of meningioma, lung cancer, hepatocellular carcinoma (HCC), cholangiocarcinoma, colorectal carcinoma (CRC), ovarian cancer, endometrial cancer, esophageal cancer, gastric cancer and pancreatic cancer is observed. Some trials suggest there may be an increase in medullary thyroid cancer, but these data are inconclusive due to small numbers of cases. BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

GLP-1 medicines is associated with either no increase or lower rates of pancreatic cancer in clinical trials and in real-world human studies (Fig. 2b). However, the number of cases reported is generally small in many studies[51–53].

Thyroid cancer

GLP-1 medicines stimulate calcitonin secretion and proliferation of thyroid C cells in mice and rats, leading to C cell hyperplasia and MTC[54]. These preclinical studies prompted a 'black box' warning despite a lack of evidence to link GLP-1 medicines to MTC in humans. By contrast, GLP-1R expression is very low or undetectable in normal thyroid C cells from monkeys and humans, and GLP-1 medicines do not stimulate calcitonin secretion or C cell proliferation in humans[19,55]. Furthermore, MTC has an incidence of 1:25,000–1:150,000, varying with age and region, necessitating a large sample size over a sufficient duration to determine whether GLP-1 medicines increase rates of MTC. A US registry for cases of MTC associated with GLP-1 medicines was established in 2010 and has yet to report data[56]. Nevertheless, GLP-1 medicines remain contraindicated in people with a history of MTC or multiple endocrine neoplasia type 2. Some reports (Table 2) link the use of GLP-1 medicines to increased rates of well-differentiated thyroid cancer[57,58]. However, most of these studies do not control for ascertainment bias and do not report on the number of completed ultrasounds[59].

Breast and mammary cancer

Breast cancer cell lines treated with GLP-1 medicines before or concomitant with chemotherapy exhibit reduced growth and increased sensitivity to chemotherapy agents[60]. Similarly, Ehrlich tumors exhibit a greater reduction in tumor volume when mice are treated with chemotherapy combined with liraglutide than either liraglutide or chemotherapy alone[61]. Mice with diet-induced obesity inoculated with mammary tumors and treated with increasing concentrations of tirzepatide showed reduced tumor mass, largely driven by reductions in food intake and weight loss[62]. It remains unclear whether GLP-1 acts directly on breast cancer cells or cells within the TME to modify breast cancer cell growth and proliferation.

The *GIPR* missense variant (rs1800437, E354Q) is associated with increased GIP binding time, enhanced receptor internalization and impaired GIPR signaling[63]. In a Mendelian randomization analysis of individuals with breast cancer versus healthy individuals from a

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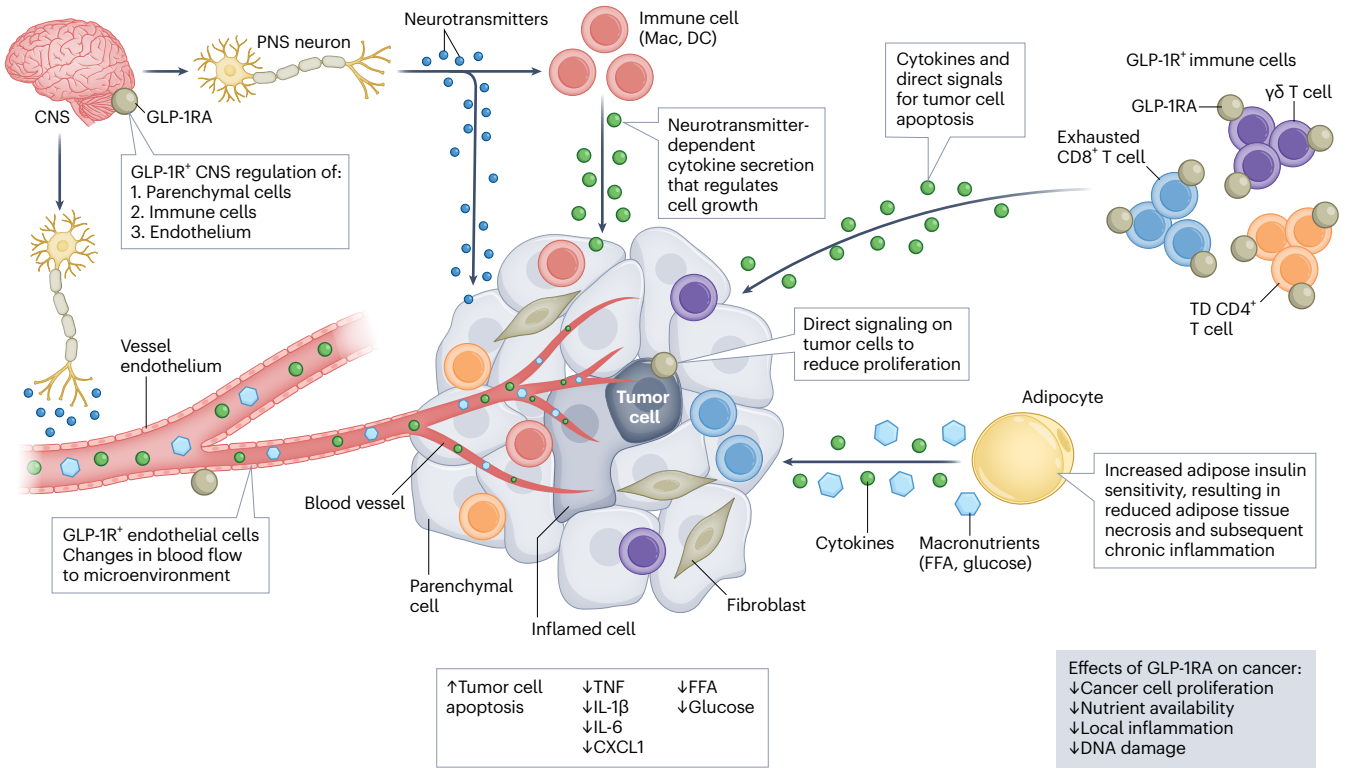

Fig. 3 | Systemic and local mechanisms by which GLP-1R$^+$ cell types impact the TME. Activation of GLP-1R in the CNS may influence systemic inflammation indirectly through neural pathways or GLP-1 medicines may directly reduce endothelial or immune cell release of cytokines such as TNF, IL-1β, IL-6 and CXCL1. GLP-1R activation may also increase insulin release, shunting free fatty acids and glucose to insulin-dependent tissues (that is, muscle, adipose and liver tissue), whereas weight loss may reduce local adipose tissue mass and activity and reduce insulin levels yet increase insulin sensitivity. Insulin-dependent reductions in free fatty acids and glucose may shunt energy substrates for tumor growth. Additionally, GLP-1R on endothelial cells or smooth muscle cells may alter blood flow. Certain subpopulations of T cells that originate in the thymus, such as γδ T, terminally differentiated (TD) CD4$^+$ T and exhausted CD8$^+$ T cells, may express GLP-1R. Whether these immune cell types contribute to cytokine release or local immune responses that modify cancer cell growth or apoptosis has not yet been determined. Some tumor cells express GLP-1R, potentially enabling direct GLP-1RA activation coupled to changes in tumor cell proliferation and oncogenesis. Despite antiproliferative effects attributed to gut hormones across various in vitro models, the verification of functional GLP-1R or GIPR protein expression in normal or neoplastic cells is technically challenging. DC, dendritic cell; Mac, macrophage; PNS, peripheral nervous system.

genome-wide association meta-analyses, each copy of E354Q was associated with modestly increased breast cancer risk, findings substantiated by elevated breast cancer risk among individuals with the E354Q variant in the FinnGen consortium of individuals with breast cancer versus healthy individuals[64] (Fig. 2b). Whether these associations reflect changes in body weight or cardiometabolic status or the biology of the mutant GIPR within the TME is not known.

A systematic review and meta-analysis of 52 trials from people with overweight/obesity or T2D treated with GLP-1 medicines, with a minimum 24-week follow-up, did not reveal differences in the incidence of malignant or benign breast neoplasms[65] (Fig. 2b). Analysis of The Cancer Genome Atlas-Breast Invasive Carcinoma database did not detect differences in survival between individuals with breast cancer tumors with the highest or lowest quartile of *GLP1R* expression[60] (Table 2).

Colorectal cancer

People with obesity exhibit increased rates of colorectal cancer (CRC)[66]. *GLP1R* and *GIPR* mRNA transcripts are detected in human CRC (Fig. 2) but at lower levels than in adjacent non-neoplastic colon tissue[67]. Preclinical studies suggest that GLP-1R agonism reduces CRC cell migration, viability and growth in vitro and attenuates CRC growth in mice with implanted tumors in vivo. For example, exendin-4 induced apoptosis and inhibited proliferation in a GLP-1R-expressing mouse colon cancer cell line via a cAMP–PKA–GSK3 signaling axis, actions abrogated by the GLP-1R antagonist exendin (9–39)[49]. A fivefold increase in tumor apoptosis was observed in CRC cells propagated in mice treated with exendin-4 for 2 weeks, together with a reduction in proliferation[49]. Exendin-4 also reduced cell proliferation in small bowel polyps and reduced basal crypt cell proliferation in the jejunum of *Apc$^{Min/+}$* mice[67]. Intriguingly, injection of the GLP-1R antagonist exendin (9–39) in CRC tumor-bearing mice reduced tumor size, which was associated with increased CD3$^+$ T cell infiltration and activated effector memory CD8$^+$ T cells[37]. These findings were inferred to reflect the activation of GLP-1R$^+$ T cells facilitating immune-mediated inhibition of cell growth and survival (Fig. 3); incubation with tirzepatide had no direct effect on CRC cell proliferation in vitro. By contrast, tirzepatide reduced CRC and breast cancer tumor volume in mice with diet-induced obesity to a similar extent as that observed in pair-fed control mice, implicating weight loss in driving underlying mechanisms[68]. The markedly reduced affinity of tirzepatide for the mouse versus human GIPR limits mechanistic conclusions surrounding tirzepatide engagement with the mouse GIPR[69].

Among individuals with T2D prescribed glucose-lowering therapy in the TriNetX database, new users of GLP-1 medicines developed fewer CRCs than users of other glucose-lowering therapies (Fig. 2b and Table 2). This reduction was greater in individuals with obesity/overweight than in individuals with T2D; however, weight loss was not reported[70].

Hepatobiliary cancer

GLP-1R is not expressed in hepatocytes; however, *Glp1r* mRNA is detected in mouse intrahepatic T cells and endothelial cells and in cholangiocytes from bile duct-ligated rats[71,72] but not in hepatocellular carcinoma (HCC) cells[27] (Fig. 2a). Rates of HCC in Taiwan were not

influenced by the use of GLP-1 medicines in people with T2D; however, liver-related death and all-cause mortality was reduced[73]. Observational data from Swedish health care registries revealed a 49% reduction in major adverse liver outcomes, such as decompensated cirrhosis, HCC, liver transplantation or liver-related death, in users of GLP-1 medicines compared to noninitiators of GLP-1 therapy[74]. Nevertheless, only 42 HCC cases in GLP-1 medicine users versus 1,079 in noninitiators were reported, and weight loss was not recorded[74]. A retrospective cohort study of US participants with T2D showed that individuals prescribed GLP-1 medicines had a reduced risk of HCC and major adverse liver outcomes compared to individuals given insulin only[75]. The reduction in rates of HCC with GLP-1 medicines remained evident after controlling for obesity, fibrosis, cirrhosis and fatty liver disease[75]. The potential benefit of GLP-1 therapy in this population is uncertain due to the low number of events and hyperinsulinemia in the insulin-treated control group, which is linked to an increase in HCC.

Whether GLP-1 medicines impact the risk of cholangiocarcinoma is less clear. A retrospective registry study incorporating data from Denmark, Sweden and Norway reported no difference in cholangiocarcinoma risk in GLP-1 users compared to sulfonylurea users after adjustment for demographic and disease status[76]. In a US study, the use of GLP-1 medicines as a first-line therapy for T2D was associated with a reduced risk of cholangiocarcinoma compared to use of other glucose-lowering agents[77] (Fig. 2b and Table 2). However, the number of cholangiocarcinoma cases was relatively low, precluding clear conclusions.

Prostate cancer

Reduced proliferation and increased sensitivity to chemotherapeutic agents and radiotherapy is reported with GLP-1 medicines in studies of prostate cancer cell lines[78,79]. Fewer individuals in the LEADER cardiovascular outcome trial developed prostate cancer on liraglutide than those on placebo (26 versus 47, respectively), with a follow-up of 3.8 years (ref. 80). A Danish registry study found reduced rates of prostate cancer in men 50 years or over with T2D treated with GLP-1 medicines, with even lower relative risk in older men aged 70 years or over[81]. A UK population-based cohort study using the Clinical Practice Research Datalink analyzed 60 million individuals with T2D from 200 general practices and found a reduced risk of prostate cancer in people treated with GLP-1 medicines versus sulfonylureas[82] (Table 2).

CNS tumors

Meningiomas, astrocytomas, glioblastomas and ependymomas exhibit GLP-1 binding sites[27] (Fig. 2). A retrospective cohort study of obesity-related cancers in 113 million US participants reported that use of GLP-1 medicines was associated with a reduced risk of meningioma compared to insulin; however, the number of meningioma events was small (11 versus 29 for GLP-1 versus insulin, respectively) within the meningioma cohort[45] (Fig. 2b). Although changes in body weight were not reported in this study, lower BMI is associated with reduced incidence of meningiomas[83]. Use of GLP-1 medicines was also associated with reduced rates of eye, brain and CNS neoplasms in humans with obesity in the TriNetX Network database[46].

Neuroendocrine tumors

GLP-1R and GIPR expression is detected in neuroendocrine tumors (Fig. 2a), and preclinical studies link GLP-1R signaling to the growth of neuroendocrine cell lines and tumors[84]. Use of GLP-1 medicines in the TriNetX database was not associated with differences in neuroendocrine tumor incidence after a 5-year follow-up[46].

Esophageal and stomach cancer

GLP-1R expression has not been reported in the esophagus; however, low levels of *GLP1R* mRNA are detected in the stomach[85] (Fig. 2a). Users of GLP-1 medicine with T2D showed a lower risk of esophageal cancer than individuals treated with insulin[45] (Fig. 2b). Propensity-matched analysis of participants with T2D and a BMI of <25 in the US Collaborative Network database found that users of GLP-1 medicines had lower risks of gastric cancer and esophageal cancer after 7 years of follow-up[86] (Table 2). Although weight loss was not reported, use of GLP-1 medicines in this cohort was associated with reduced risks of cancer in the absence of overweight or obesity[86].

Lung cancer

GLP1R is expressed at low levels in human lung[85], with the cellular localization of pulmonary *GLP1R* poorly defined in humans. In individuals with T2D analyzed in the TriNetX platform after propensity matching, users of GLP-1 medicines exhibited lower rates of squamous cell carcinoma, adenocarcinoma, large cell carcinoma and small cell lung cancers than insulin users; however, the number of cases was small, and weight loss as a variable was not reported[87].

Skin cancer

GLP-1R expression has not been localized to specific cells within human skin; however, *GLP1R* mRNA was reported in skin biopsies from individuals with psoriasis[88]. In a large population-based cohort study that leveraged the Clinical Practice Research Datalink in the UK, use of GLP-1 medicines versus sulfonylureas was not associated with an increased risk of melanoma or nonmelanoma skin cancer (Table 2)[89].

Endometrium, ovarian and cervical cancer

The localization of *GLP1R* mRNA expression in human reproductive tissues remains inconclusive. Intraperitoneal injection of exenatide in endometrial cancer-bearing nude mice reduced tumor growth, actions likely mediated through AMPK signaling, with similar findings obtained in separate studies using liraglutide[90,91]. *GLP1R* mRNA transcripts are detected at low levels in human ovarian cancer and are not associated with overall survival[33]. GLP-1 medicines such as exenatide also reduce ovarian cancer cell growth in preclinical studies, which is associated with the induction of apoptosis and reduction of cell proliferation[92]. An analysis of obesity-related cancers in individuals with T2D in a US multicenter database suggested that use of GLP-1 medicines is associated with a reduced risk of endometrial and ovarian cancer compared to use of insulin over a 15-year follow-up period[45].

GLP-1 medicines for cancer prevention and therapy

Whether GLP-1 medicines reduce cancer incidence, morbidity and mortality in subsets of individuals with obesity and diabetes-related cancers is not definitively established. Current data are insufficient to support the use of GLP-1 medicines as prophylactic agents for cancer prevention. Consistent with findings from bariatric surgery[13,14] or lifestyle intervention trials[15], it seems likely that a substantial component of the putative anticancer benefit conferred by use of GLP-1 medicines reflects the impact of weight loss. A major gap in our current knowledge is whether and how, independent of weight loss, GLP-1 medicines reshape the composition, metabolic and inflammatory activity within the TME, potentially altering the development and growth of cancer (Fig. 3).

GLP-1R signaling may also regulate blood flow and hence delivery of nutrients GLP-1 medicines directly engage GLP-1Rs on T cells, and GLP-1R signaling in the brain acutely inhibits Toll-like receptor-mediated systemic inflammation in mice. Treatment of mice with the GLP-1 medicine retatrutide produced immune reprogramming within the TME[34], consistent with findings of increased infiltration of activated $CD3^+$ T cells within the TME of mice with CRC treated with the GLP-1R antagonist exendin (9–39 (ref. 37); Fig. 3). Mechanistically, adenoviral delivery of GLP-1 reduced infiltration of polymorphonuclear myeloid-derived suppressor cells in the TME of mice with pancreatic cancer[38], highlighting the importance of modifying the TME for a subset of the antitumor actions of GLP-1 medicines (Fig. 3).

Opportunities for GLP-1 medicines in the management of cancer

There is growing interest in the use of GLP-1 medicines to improve the health of people living with cancer. GLP-1 medicines reduce rates of cardiovascular disease[93,94] and decrease rates of heart disease and all-cause mortality in individuals with cancer with T2D using immune checkpoint inhibitors[95]. Weight gain after the diagnosis of breast cancer is associated with increased all-cause mortality, providing a testable hypothesis of whether use of GLP-1 medicines might reduce body weight and improve outcomes[96]. Although weight loss seems likely to reduce cancer incidence and tumor burden[97], weight loss-independent mechanisms continue to be discovered[24]. Despite considerable inter-individual heterogeneity in the extent of weight loss achieved with use of GLP-1 medicines, the use of biomarkers or genetics has not yielded insights into underlying mechanisms that might explain marked differences in clinical responses[98]. Whether the expanding use of GLP-1 medicines will contribute directly, or indirectly, to reduction in rates of obesity-associated cancer is not known, but it represents an important subject for investigation, with potential for improving health outcomes.

Conclusions and future directions

Clinical trials are examining the safety and utility of GLP-1 medicines in individuals with cancer. These include a study of tirzepatide and semaglutide for weight management and glucose control in individuals with endometrial cancer undergoing chemotherapy (NCT06751589). Separate trials will study whether tirzepatide-induced weight loss leads to favorable metabolic and hormonal changes in individuals with breast cancer (NCT06517212 and NCT06518837). The benefits of tirzepatide-induced weight loss before a prostatectomy in individuals with intermediate-risk prostate cancer (NCT06759701) will be scrutinized. A GLP-1 medicine will be studied together with standard progestin treatment to assess whether this combination leads to a higher complete response rate in young individuals with endometrial cancer/atypical hyperplasia who wish to preserve their fertility (NCT06073184). Collectively, these trials will inform the feasibility and potential benefit of using GLP-1 medicines as adjuvant therapy in people with cancer.

Limitations and unanswered questions

Reliable detection of GLP-1R and GIPR expression remains challenging[31,99]. Ligand binding detects binding sites, presumed to reflect canonical GLP-1R or GIPR expression, in human tumors, avoiding the pitfalls of using incompletely validated antisera (Fig. 2). Although dozens of preclinical studies link GLP-1 medicines to reduced growth of cancer cells, their interpretation is challenging because most do not report evidence for GLP-1R or GIPR expression using validated reagents. Even less is known about the putative effect of medicines modifying GIP action, such as tirzepatide, retatrutide or maritide[100], on cancer biology. Although sex-specific differences in cancer rates or outcomes in response to GLP-1R agonists (GLP-1RAs) have not been reported, women experience modestly greater weight loss with GLP-1 medicines[101–103]. Whether this differential weight loss will translate to a greater reduction in rates of cancer in women than in men is not known.

Although GLP-1 medicines hold promise for reducing cancer risk, biomarkers for potential responsivity to GLP-1 medicines for specific cancers and populations have not yet been identified. Whether weight loss is essential to achieve reduced rates of cancers is not known. The safety and tolerability of GLP-1 medicines in people undergoing active cancer therapy have not been extensively studied, and caution is needed to avoid gastrointestinal adverse events, excess weight loss and sarcopenia in susceptible individuals. Estimates link 10% or more weight loss and shifts to lower BMI categories achievable with GLP-1 medicines to substantial reductions in rates of cancer over 5–10 years (refs. 97,104). Nevertheless, these estimates assume no limitations in access to GLP-1 medicines and no challenges with persistence and adherence to these therapies over prolonged treatment periods. Although the hypothesis that the use of GLP-1 medicines might reduce rates of one or more cancers is attractive, current evidence is insufficient to support the use of GLP-1 medicines to reduce cancer rates in the clinic.

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J.M.Y. and D.J.D. were responsible for reviewing the research and drafting the manuscript.

Competing interests

J.M.Y. has no competing interests or conflict of interest. D.J.D. has served as a consultant or speaker within the past 12 months to Alnylam, Amgen, AstraZeneca, Crinetics, Eli Lilly, General Medicines Inc., Kallyope, Metsera, Novo Nordisk, Pfizer Protagonist Therapeutivs Inc and Sanofi. Neither D.J.D. nor his family members hold issued stock directly or indirectly in any of these companies. D.J.D. holds nonexercised options in Kallyope. Mt. Sinai Hospital receives grant support from Amgen, Eli Lilly and Zealand Pharma for preclinical studies in the laboratory of D.J.D.

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