Table SI. Comparison of the biology and summarized tumor microenvironment-related roles of GLP-1, GIP and GCG.

Feature	GLP-1	GIP	GCG
Cell source	Intestinal L-cells (distal gut)	Intestinal K-cells (proximal gut)	Pancreatic α-cells
Primary stimulus for secretion	Nutrient intake (carbohydrates, fats and proteins)	Nutrient intake (especially fats and carbohydrates)	Hypoglycemia, fasting, sympathetic activation
Receptor	GLP-1R	GIPR	GCGR
Primary signaling pathway	Gs-mediated cAMP/PKA/Epac signaling	Gs-mediated cAMP/PKA/Epac signaling	Gs-mediated cAMP/PKA signaling; Gq-mediated IP3/PKC signaling
Core metabolic function	Anabolic (postprandial): i) Enhances glucose-dependent insulin secretion; ii) inhibits GCG secretion; iii) slows gastric emptying; and iv) promotes satiety	Anabolic (postprandial): i) Enhances glucose-dependent insulin secretion; and ii) promotes lipid storage in adipose tissue	Catabolic (fasting): i) Raises blood glucose levels (glycogenolysis and gluconeogenesis); and ii) stimulates lipolysis and ketogenesis
Key Clinical Drugs	GLP-1RAs such as liraglutide and semaglutide	Less common as monotherapy; dual GIP/GLP-1 RAs (such as tirzepatide)	Rare as monotherapy for diabetes; dual GLP-1/GCGR agonists, such as cotadutide and survodutide, are in clinical development.
Summary of roles in the TME and cancer	Mostly antitumor effects (context-dependent): Modulates immune cells (↓NETs, ↑NK cell function and polarizes macrophages); inhibits tumor cell proliferation and induces apoptosis; potential pro-tumor effects in specific contexts (for example, in some breast cancers)	Less defined/context-dependent: Shares some signaling with GLP-1, but its role in cancer is less clear; may influence tumor metabolism via its effects on systemic lipid metabolism	Dual/context-dependent role: Potential pro-tumor effects include the possibility that hyperglycemia may fuel tumor growth, while glucagon/GCGR signaling has been reported to promote proliferation in some colorectal cancer models through AMPK deactivation and MAPK activation; putative antitumor relevance remains indirect and is mainly inferred from GCGR-containing polyagonists rather than from GCGR activation alone; current evidence is insufficient to conclude a direct antitumor effect of GCGR agonism

Data summarized from (15,16,45,61,62,66). AMPK, AMP-activated protein kinase; cAMP, cyclic adenosine monophosphate; CRC, colorectal cancer; Epac, exchange protein directly activated by cAMP; Gs, stimulatory G protein α-subunit; Gq, Gq protein α-subunit; GCG, glucagon; GCGR, glucagon receptor; GIP, glucose-dependent insulinotropic polypeptide; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; GLP-1RA, glucagon-like peptide-1 receptor agonist; IP3, inositol 1,4,5-trisphosphate; NET, neutrophil extracellular trap; NK, natural killer; PKA, protein kinase A; PKC, protein kinase C; TME, tumor microenvironment.

Table SII. Role of incretin and glucagon-related drugs in different tumors (*in vivo* and *in vitro* experiments).

First author/s, year	Subjects	Research type	Disease	Cell lines	Treatment	Tumor-related interpretationa	Main function (result)	(Refs.)
Zhao *et al*, 2014	Mice	*In vitro* and *in vivo*	Pancreatic cancer	MIA PaCa-2 and PANC-1	Liraglutide	Positive (antitumor)	Liraglutide activated cAMP production and inhibited Akt and ERK1/2 signaling pathways in a GLP-1R-dependent manner, inhibited the proliferation and promoted apoptosis of human pancreatic cancer cell lines *in vitro*, and alleviated pancreatic tumor growth in a mouse xenograft model *in vivo*.	(151)
Zhao *et al*, 2020	Mice	*In vitro* and *in vivo*	Pancreatic cancer	PANC-1 and PANC-GR	Liraglutide	Positive (antitumor)	Liraglutide decreased the chemotherapy resistance of pancreatic cancer cells to gemcitabine and increased the chemotherapy sensitivity *in vivo* and *in vitro*.	(181)
Byrd *et al*, 2015	Rats and transgenic mice	*In vivo*	Thyroid cancer	-	Dulaglutide	Irrelevant (safety-focused rodent study)	In transgenic mice, dulaglutide-associated C-cell hyperplasia or tumors were not observed at any dose. Diffuse increases in C-cell mass did not occur during the initial 52 weeks of the rat carcinogenicity study.	(185)
Mao *et al*, 2024	db/db mice	*In vivo*	Nonalcoholic fatty liver disease	-	Semaglutide	Irrelevant (non-tumor disease model)	Semaglutide improved the gut microbiome, liver injury and lipid deposition in db/db mice.	(186)
Chen *et al*, 2013	Mice (BALB/c)	*In vitro* and *in vivo*	Intrahepatic cholangiocarcinoma	HuCC-T1 and HIBEpic	Exendin-4	Positive (antitumor)	Combination of oxaliplatin and exendin-4 could inhibit the proliferation of tumor cells and promote cell apoptosis.	(187)
Koehler *et al*, 2011	BALB/c mice	*In vitro* and *in vivo*	Colon cancer	CT26	Exendin-4	Positive (antitumor)	GLP-1R activation inhibited the proliferation and survival of CT26 colon cancer cells.	(152)
Kissow *et al*, 2012	CD1 mice	*In vivo*	Colon cancer	-	GLP-1RAs and DPP4 inhibitors	Irrelevant (no clear tumor-promoting effect observed)	Growth-promoting effects of GLP-1 analogues on the intestine of healthy mice. No agonism of GLP-1RAs on GLP-2 receptors was found, and no cancer promoting effect of GLP-1 analogues was found.	(188)
Iwaya *et al*, 2017	Athymic mice	*In vitro* and *in vivo*	Breast cancer	MCF-7, MDA-MB-231 and KPL-1	Exendin-4	Positive (antitumor)	Exendin-4 reduced Akt and IκB phosphorylation and attenuated breast cancer cell proliferation via activation of GLP-1R and subsequent inhibition of NF-κB activation.	(189)
Ligumsky *et al*, 2024	-	*In vitro*	Breast cancer	MCF-7 and MDA-MB-231	Exendin-4 and liraglutide	Positive (antitumor)	Exendin-4 and liraglutide reduced the levels of glycolytic metabolites and reduced ATP production, indicating that GLP-1 analogues impaired glycolysis and affected tumor cell viability.	(190)
Liu *et al*, 2022	BALB/cfC3H mice	*In vitro* and *in vivo*	Breast cancer	MDA-MB-231 and MDA-MB-468	Liraglutide	Negative (pro-tumor)	Slightly higher concentrations of liraglutide accelerated breast cancer progression *in vitro* and *in vivo* through NOX4/ROS/VEGF signaling after GLP-1R activation. GLP-1R inhibitor exendin- (9-39) inhibited the effect of liraglutide.	(13)
Mao *et al*, 2021	db/db mice	*In vitro* and *in vivo*	Cervical cancer	CUP-1	Exendin-4	Positive (antitumor)	Exendin-4 attenuated PSMA2 expression and tumor growth *in vivo* and *in vitro*.	(182)
Kong *et al*, 2024	Mice	*In vivo*	EC	-	Tirzepatide	Positive (antitumor)	Tirzepatide reduced mouse body weight and tumor growth by modulating metabolic and immune pathways in EC tumors that differed between obese and lean mice.	(69)
Zhang *et al*, 2021	-	*In vitro*	EC	Ishikawa and HEC1B	Exendin-4	Positive (antitumor)	Exendin-4 could alleviate HG-induced cisplatin chemoresistance in EC cells.	(183)
Li *et al*, 2022	BALB/c nude mice	*In vitro* and *in vivo*	EC	Ishikawa and RL95-2	Transfection of GLP-1R expression vector	Positive (antitumor)	Upregulation of GLP-1R promoted EC cell apoptosis and activated the cAMP/PKA signaling pathway, while hindering the proliferation of mouse EC cells and tumor growth.	(184)

[a]Positive indicates an antitumor effect; Negative indicates a tumor-promoting/pro-tumor effect; Irrelevant indicates that no direct antitumor or tumor-promoting effect was demonstrated, or that the study was a safety-focused/non-tumor model. DPP4, dipeptidyl peptidase-4; EC, endometrial cancer; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; GLP-1RA, glucagon-like peptide-1 receptor agonist; GLP-2, glucagon-like peptide-2; HG, high glucose; NOX4, NADPH oxidase 4; PKA, protein kinase A; PSMA2, proteasome subunit α type-2; ROS, reactive oxygen species.

Table SIII. Clinical studies of incretin- and glucagon-related drugs in different tumors.

First author/s, year	Research type	Objective	Drug	Disease	Age, years	Sex ratio	Sample size, n	With/without diabetes	Tumor-related interpretationa	Adverse events	Main function (result)	(Refs.)
Dankner *et al*, 2024	Cohort study	GLP-1RA treatment was compared with basal insulin treatment	GLP-1 RAs	Pancreatic cancer	Mean (SD), 59.9 (12.8)	51% female	543,595	T2DM	Irrelevant (no increased risk; safety-focused)	Not reported	No increased incidence of pancreatic cancer was found after initiation of GLP-1RA therapy over a 7-year period in adults with T2D in the study	(179)
Wang *et al*, 2025	Retrospective cohort study	Pancreatic cancer incidence in patients receiving GLP-1RA versus non-GLP-1RA drugs was compared	GLP-1 RAs	Pancreatic cancer	-	-	1,636,056	T2DM	Positive (reduced risk)	Not reported	GLP-1RAs were associated with a decreased incidence of pancreatic cancer in patients with T2DM	(200)
Monami *et al*, 2017	Systematic review and meta-analysis of randomized controlled trials	To assess whether GLP-1RA treatment was associated with pancreatitis, pancreatic cancer, and cholelithiasis compared with placebo or non-GLP-1RA treatments	GLP-1 RAs	Pancreatic cancer	-	-	113	T2DM	Irrelevant (safety-focused)	No significant increase in pancreatitis or pancreatic cancer was detected; cholelithiasis risk was increased (MH-OR, 1.30; 95% CI, 1.01-1.68)	GLP-1RA therapy was safe in pancreatitis and pancreatic cancer but was associated with an increased risk of cholelithiasis	(180)
Pasternak *et al*, 2024	Cohort study	Patients treated with GLP-1RA were compared with those treated with DPP4 inhibitors	GLP-1 RAs and DPP4 inhibitors	Thyroid cancer	-	-	437,077	T2DM	Irrelevant (no substantial increased risk)	Not reported	GLP-1RA use was not associated with a significant increase in thyroid cancer risk	(192)
Bezin *et al*, 2023	Case-control analysis	Estimated GLP-1RA-associated thyroid cancer risk	GLP-1 RAs	Thyroid cancer	Median, 64	Female, 67.0 and 67.2%	2,562 cases and 45,184 control subjects	T2DM	Negative (increased risk	Not reported	GLP-1 RA use for 1-3 years was associated with an increased risk of all thyroid cancers and medullary thyroid cancers	(193)
Feier *et al*, 2024	Systematic review	Incidence of thyroid cancer and spectrum of adverse events associated with semaglutide were assessed	GLP-1 RAs	Thyroid cancer	Mean, 57.3	Male, 47.2%	14,550	T2DM	Irrelevant (no clear thyroid cancer signal)	Nausea (2.05-19.95%), diarrhea (1.4-13%), vomiting (5.97%), nasopharyngitis (8.23%); increased lipase, headache, decreased appetite, dyspepsia and constipation were also reported; serious adverse events ranged between 7 and 25.2%	Data from the study showed a thyroid cancer incidence of <1% in semaglutide-treated patients, indicating no significant risk.	(194)
Wang *et al*, 2024	Retrospective cohort study	Evaluated the association of GLP-1RAs with the risk of HCC events in a real-world population	GLP-1RAs	HCC	Mean (SD), 56.1 (11.9) vs. 56.3 (14.7)	Women, 54.6% vs. 56.2% after propensity score matching	1,890,020	T2DM	Positive (reduced risk)	Not reported	GLP-1RA was associated with a reduced risk of HCC and hepatic decompensation in patients with T2DM compared with other antidiabetic agents	(175)
Newsome *et al*, 2021	RCT: Double-blind phase 2 trial	Evaluated the efficacy and safety of semaglutide in the treatment of NASH	Semaglutide	NASH	Mean, 55	Female, 61%	320	62% T2DM	Irrelevant (non-tumor trial)	Gastrointestinal disorders were the most common adverse events. In the semaglutide (0.4 mg) group versus the placebo group, nausea occurred in 42 vs. 11%, constipation in 22 vs. 12%, decreased appetite in 22 vs. 5%, vomiting in	Semaglutide treatment resulted in a higher percentage of patients with NASH resolution than placebo	(195)

										15 vs. 2% and abdominal pain in 7 vs. 4%; discontinuation due to adverse events occurred in 7 vs. 5%; serious adverse events in 15-19 vs. 10%; gallbladder-related disorders in 5-7 vs. 2%; no acute pancreatitis was reported		
Abrahami *et al*, 2018	Cohort study	Determined whether medications that use incretin are associated with the risk of developing CRC in individuals with T2D	GLP-1 RAs and DPP4 inhibitors	CRC	-	-	112,040	T2DM	Irrelevant (no association)	Not reported	Incretin use was not associated with CRC incidence in patients with T2D	(196)
Wang *et al*, 2024	Retrospective cohort study	GLP-1RAs were compared with seven non-GLP-1RA antidiabetic agents to analyze their CRC risk	GLP-1RAs	CRC	Mean (SD), 55.6 (12.3)	GLP-1RA(+)/insulin(-): female, 56.0%	1,221,218	T2DM	Positive (reduced risk)	Not reported	GLP-1RAs were associated with reduced CRC risk in treatment-naive patients with T2D with and without obesity/overweight	(73)
Figlioli *et al*, 2024	Systematic review	Assessed GLP-1RA treatment of patients with gastrointestinal cancer risk	GLP-1 RAs	Gastrointestinal neoplasms	Mean, 59.7	Female, 43.4%	124,791	T2DM	Irrelevant (no significant effect)	Not reported	GLP-1RAs had no significant effect on the risk of gastrointestinal cancers, including liver, bile duct, gallbladder, esophagus, stomach, pancreatic, small bowel and colorectal cancer	(197)
Piccoli *et al*, 2021	Systematic review	Risk of breast neoplasia in GLP-1RAs-treated patients was assessed	GLP-1RAs	Breast cancer	-	-	90,360	T2DM	Irrelevant (no increased risk)	Not reported	Treatment of obesity and diabetes with GLP-1RAs did not increase the risk of breast tumors	(198)
Sun *et al*, 2024	Mendelian randomization	Causality analysis of GLP-1RA and cancer	GLP1RAs	Breast cancer	-	-	80,154 cases and 853,816 controls	T2DM	Positive (risk-reduction signal)	Not reported	GLP1RA may reduce the risk of breast and basal cell carcinoma	(199)
Mao *et al*, 2021	Transformed case-control study	Explored the relationship between GLP-1RA and cervical cancer	Exendin-4	Cervical cancer	-	-	-	T2DM	Positive (tumor-suppressive association)	Not reported	PSMA2 and GLP-1R expression levels were elevated in cervical cancer specimens from patients with T2D, and PSMA2 expression was positively associated with GLP-1R expression. In addition, exendin-4 inhibited PSMA2 expression and suppressed tumor growth.	(182)
Wang *et al*, 2024	Cohort study	Effects of insulin and GLP-1RAs on reducing the risk of specific OAC were compared	GLP-1RAs, insulin or metformin	Endometrial cancer	Mean (SD), 59.8 (15.1)	Male, 50.1%	1,651,452	T2DM	Positive (reduced risk vs insulin)	Not reported	GLP-1RAs were associated with a reduced risk of endometrial cancer compared with insulin	(73)

Values are presented as mean (SD) unless otherwise specified. aPositive indicates a favorable antitumor association or reduced cancer risk; Negative indicates a tumor-promoting association or increased cancer risk; Irrelevant indicates no significant tumor-related association, a safety-focused finding, or a non-tumor clinical outcome. CRC, colorectal cancer; DPP4, dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 receptor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HCC, hepatocellular carcinoma; MH-OR, Mantel-Haenszel odds ratio; NASH, nonalcoholic steatohepatitis; NR, not reported; OAC, obesity-associated cancer; PSMA2, proteasome subunit α type-2; RCT, randomized controlled trial; T2D, type 2 diabetes; T2DM, type 2 diabetes mellitus.