Modulation of the tumor microenvironment by incretins and glucagon: Metabolic and immune mechanisms (Review)

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Received February 4, 2026; Accepted April 2, 2026

DOI: 10.3892/etm.2026.13178

Abstract. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and therapies targeting glucose-dependent insulinotropic polypeptide (GIP) have demonstrated efficacy in the treatment of type 2 diabetes (T2D) and obesity. GLP-1 and GIP are collectively referred to as incretins. The strong epidemiological link between T2D/obesity and cancer risk suggests that GLP-1 and GIP may serve a substantial role in tumor metabolism. The effects of incretin hormones and the counter-regulatory hormone glucagon (GCG) on tumor biology may have important implications for understanding tumor microenvironmental regulation and for informing cancer therapy. The present review summarizes the mechanisms by which these hormones influence the tumor microenvironment. Beyond the fundamental biology of incretins and GCG, the present review details how GLP-1RAs regulate immune cell functions, including the functions of T cells, neutrophils, natural killer cells and macrophages, to foster an antitumor immune microenvironment. Furthermore, the present review explores their roles in tumor metabolic reprogramming, affecting tumor cell cycle progression, extracellular matrix remodeling and mitochondrial function. Although preclinical and clinical data suggest that GLP-1RAs can reduce the incidence and progression of certain obesity-related cancer types, such as pancreatic and liver cancer, their impact on other malignancies, such as breast and endometrial cancer, remains controversial, with GLP-1RAs potentially exhibiting context-dependent pro-tumor effects. However, based on current evidence, the benefits of incretin hormones and GCG in cancer therapy appear to outweigh the risks. The present review suggests that targeting incretin and GCG signaling holds considerable promise in oncology, but necessitates a deeper mechanistic understanding and more careful patient stratification to fully harness its clinical utility while minimizing potential risks.

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Abbreviations: AMPK, AMP-activated protein kinase; cAMP, cyclic adenosine monophosphate; CRC, colorectal cancer; CREB, cAMP-response element binding protein; DC, dendritic cell; EC, endometrial cancer; ECM, extracellular matrix; Epac, exchange protein directly activated by cAMP; GCG, glucagon; GCGR, glucagon receptor; GIP, glucose-dependent insulinotropic polypeptide; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; GLP-1RA, GLP-1 receptor agonist; HCC, hepatocellular carcinoma; MTC, medullary thyroid carcinoma; NET, neutrophil extracellular trap; PD-1, programmed cell death protein-1; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; PKA, protein kinase A; PSMA2, proteasome subunit α type-2; ROS, reactive oxygen species; TCA, tricarboxylic acid; TME, tumor microenvironment; Treg, regulatory T cell; T2D, type 2 diabetes

Key words: GLP-1, immune microenvironment, metabolic reprogramming, TME, mechanism

Contents

1. Introduction

In most countries worldwide, cancer rank among the leading causes of mortality (1). Consequently, preventing cancer and delaying its recurrence and metastasis represent primary objectives in antitumor strategies. Beyond genetic mutations, the tumor microenvironment (TME) is recognized as a critical factor in cancer progression, providing essential support for tumor cell survival, proliferation and immune evasion. Key characteristics of the TME include hypoxia, acidosis and nutrient deprivation (2). Epidemiological studies (3,4) have demonstrated that diabetes and obesity are associated with an

increased risk of various malignancies, including pancreatic cancer (5,6) and breast cancer (7). This association suggests a potential interplay between systemic metabolism and tumorigenesis. Among incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) serve as key regulators of metabolism (8), and GLP-1 receptor agonists (GLP-1RAs) have been established as first-line therapies for type 2 diabetes (T2D) and obesity (9). Beyond their roles in regulating glucose and lipid metabolism and suppressing appetite, drugs targeting GLP-1R and glucagon receptor (GCGR) exhibit anti-inflammatory and cardioprotective effects, and have demonstrated promising synergistic outcomes in combination with antitumor therapies (10,11). However, the efficacy of these agents remains controversial in conditions such as breast cancer and endometrial cancer (EC), underscoring the importance of elucidating their mechanisms of action in malignancies (12-14). A central question is whether these hormones can treat or prevent cancer by modulating the immune TME and tumor cell metabolism. The present review aims to: i) Briefly summarize the fundamental biology of GLP-1, GIP and GCG, with a focus on phenomena and mechanisms relevant to tumor biology; ii) evaluate their diverse roles in the TME, particularly in immune regulation; iii) analyze their impact on tumor metabolic reprogramming; and iv) synthesize current preclinical and clinical evidence across various cancer types, highlighting both protective effects and potential cancer-promoting effects, to guide future research and clinical translation.

2. Biological effects and mechanisms of incretin and GCG

To facilitate the understanding of the potential roles of incretins, including GLP-1, GIP and GCG, in oncology, this section provides a concise overview of the core physiology of GLP-1, GIP and GCG. Although they share common signaling modules such as cyclic adenosine monophosphate (cAMP), their receptor distribution and principal metabolic functions underlie their distinct influences on the TME (15,16). Fig. 1 summarizes the fundamental mechanisms of action of these three hormones.

GLP-1. GLP-1 is secreted by intestinal L-cells following nutrient intake (17). GLP-1 binds to GLP-1Rs expressed in multiple organs, including the pancreas, liver, gastrointestinal tract and brain, exerting pleiotropic effects such as enhancing insulin secretion (18), reducing blood glucose levels, suppressing GCG release (19), delaying gastric emptying (16), decreasing food intake (20), promoting weight loss and providing cardiovascular protection (21,22). The GLP-1R is a G protein-coupled receptor that primarily signals through the Gs subunit (23), initiating a cascade that stimulates adenylate cyclase activity and cAMP production (24). Subsequently, cAMP activates protein kinase A (PKA) and the exchange protein directly activated by cAMP (Epac) (15), which collectively contribute to insulin biosynthesis and inhibition of GCG secretion (25). PKA further activates the cAMP-response element binding protein (CREB) and the transducer of regulated CREB activity 2, leading to enhanced insulin receptor substrate 2 gene expression and promotion of β-cell proliferation (26). Activated CREB promotes expression of pro-survival factors such as Bcl-2, thereby supporting β-cell survival and function (27).

Beyond the Gs pathway, GLP-1R engages multiple signaling mechanisms. GLP-1R activates the PI3K/Foxo1 pathway to promote β-cell survival, and can also recruit β-arrestins, which regulate receptor trafficking and desensitization, and can also modulate downstream extracellular signal-regulated kinases (ERK1/2), thereby influencing β-cell function in a context-dependent manner (28,29). Additionally, GLP-1 attenuates palmitic acid-induced inflammation by inactivating mTORC1 signaling, serving a pivotal role in modulating insulin resistance, inflammation and autophagy (30). These diverse intracellular signaling pathways are summarized in Fig. 1 (15,31). In summary, GLP-1 signaling supports β-cell survival, glucose-dependent insulin secretory responses and systemic metabolic regulation. This suggests its dual role in oncology: PI3K/Akt and ERK pathways activated by GLP-1RAs are classical pro-survival pathways that may be utilized by tumor cells in some contexts. GLP-1RAs exert strong systemic metabolic regulation and immune regulation effects, which may indirectly inhibit tumor growth. The ultimate effect of GLP-1R activation in a given cancer will most likely depend on whether tumor cells express functional GLP-1R and how GLP-1R downstream signaling is integrated with oncogenic signals.

GIP. GIP is secreted by K-cells in the proximal small intestine, and shares considerable functional overlap with GLP-1 (32). In pancreatic β-cells, upon binding to its receptor [glucose-dependent insulinotropic polypeptide receptor (GIPR)], GIP similarly elevates intracellular cAMP levels, activating both PKA and Epac (15,33), thereby enhancing glucose-stimulated insulin secretion (34). In adipose tissue, the lipogenic effects of GIP appear to be context-dependent and influenced by insulin availability and metabolic status (35). GIP promotes β-cell proliferation and survival through the PI3K/Akt and MAPK/ERK pathways (36,37), while inhibiting apoptosis via regulation of Bcl-2 and Bax expression (38,39). These diverse intracellular pathways are also illustrated in Fig. 1. A key distinction between GIP and GLP-1 lies in the role of GIP in adipose tissue, where it promotes fatty acid storage (40) and modulates lipolysis in an insulin- and context-dependent manner (41). These metabolic effects may alter nutrient availability and thereby influence tumor growth under obese conditions in a context-dependent manner (42).

GCG. GCG is secreted by pancreatic α cells, and its secretion is stimulated by hypoglycemic conditions or by elevated levels of certain amine hormones such as epinephrine (43). As the primary counter-regulatory hormone to insulin, it collaborates with insulin to maintain glucose homeostasis (44). Upon binding to the GCGR on hepatocytes, GCG couples with Gs and Gq proteins (45). Activation of Gs stimulates the cAMP/PKA signaling pathway, which drives hepatic gluconeogenesis (46-48) and glycogenolysis (49). The Gq pathway activates phospholipase C (50), generating inositol trisphosphate and diacylglycerol, thereby mobilizing intracellular calcium ions (51). This signaling upregulates key gluconeogenic enzymes, including phosphoenolpyruvate carboxykinase and glucose-6-phosphatase (52,53). Additionally, GCG

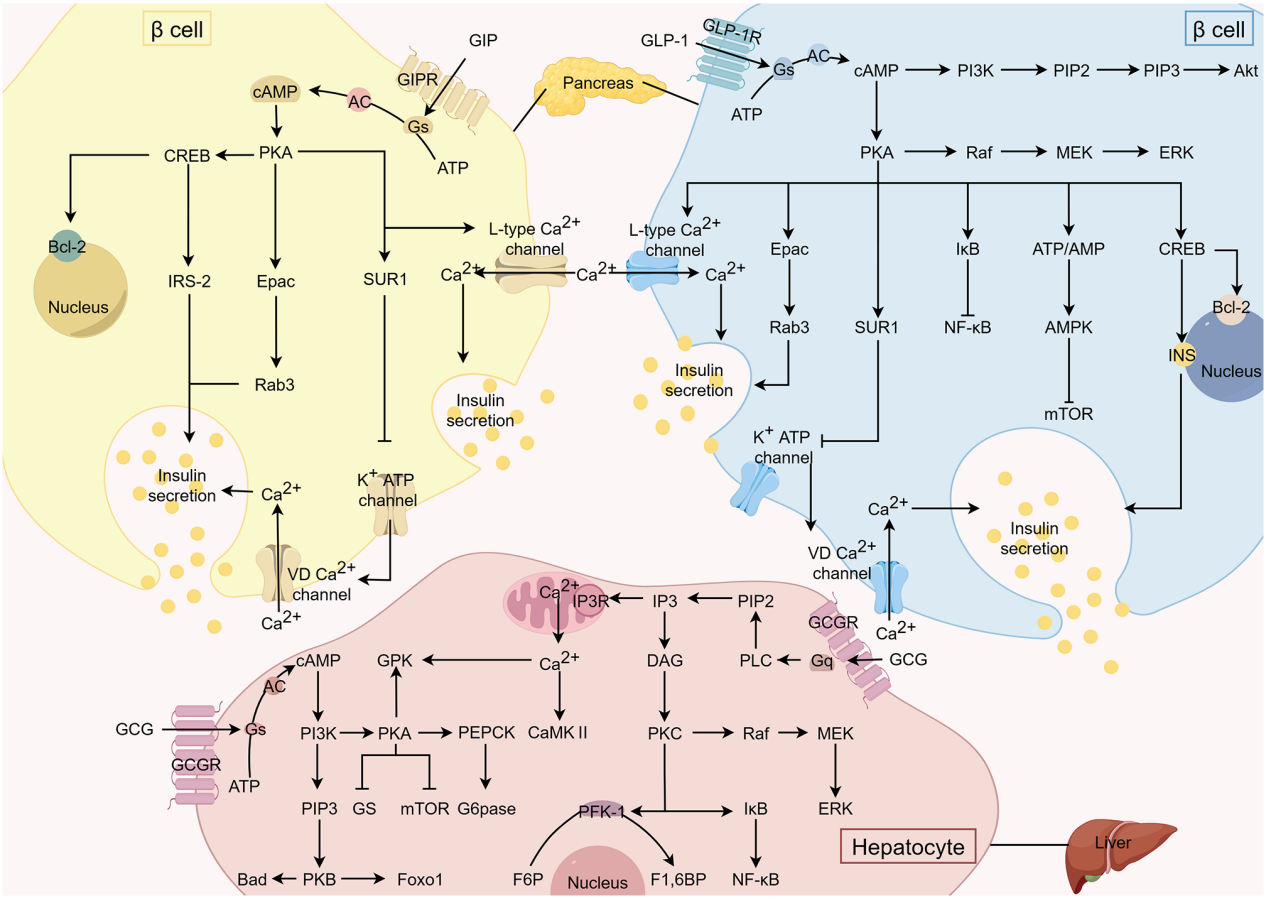

Figure 1. Core signaling pathways of GLP-1, GIP and GCG. GLP-1 and GIP enhance glucose-dependent insulin secretion in pancreatic β-cells via Gs-mediated cAMP production, which activates downstream PKA and Epac signaling linked to secretory responses and survival-associated signaling. GCG activates hepatic glucose production and fatty acid oxidation by engaging both Gs/cAMP/PKA and Gq/IP3/Ca^{2+} pathways in hepatocytes. cAMP signaling produces distinct cell-specific physiological outputs, including hormone secretion and survival-associated signaling in pancreatic isleT cells. Created with Figdraw. com. AC, adenylate cyclase; AMPK, AMP-activated protein kinase; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CREB, cAMP-response element-binding protein; DAG, diacylglycerol; Epac, exchange protein directly activated by cAMP; ERK, extracellular signal-regulated kinase; F1,6BP, fructose 1,6-bisphosphate; F6P, fructose 6-phosphate; FASN, fatty acid synthase; G6Pase, glucose-6-phosphatase; 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; GPK, glycogen phosphorylase kinase; GS, glycogen synthase; INS, insulin; IP3, inositol 1,4,5-trisphosphate; IP3R, inositol 1,4,5-trisphosphate receptor; IRS-2, insulin receptor substrate 2; PEPCK, phosphoenolpyruvate carboxykinase; PFK-1, phosphofructokinase-1; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; Rab3, Ras-related protein Rab-3A; SUR1, sulfonylurea receptor 1; VD Ca^{2+} channel, voltage-dependent Ca^{2+} channel.

stimulates lipolysis and ketogenesis (54), suppresses fatty acid synthesis while enhancing fatty acid oxidation (55), improves mitochondrial function (56) and reduces oxidative stress (57). GCG also modulates hepatic lipid metabolism through CREBH- and Insig-2-related transcriptional programs and other acetylation-dependent regulatory mechanisms (58). The intricate signaling network of GCG in hepatocytes is detailed in Fig. 1 (59,60).

GCG is an energy mobilization hormone. GCG-driven hepatic glucose export and lipolysis may provide abundant fuel for tumor cells that are dependent on glucose and lipids. However, the oncological significance of GCG signaling remains insufficiently defined, and the currently available evidence does not support a uniform conclusion that GCGR activation exerts a direct antitumor effect (61). In this context, the antitumor activity reported for incretin-based polyagonists should not be interpreted as evidence for GCGR agonism alone, but rather as an indication that coordinated multi-receptor targeting may induce favorable systemic metabolic remodeling (62,63). The apparent physiological opposition between GLP-1 and GCG does not preclude pharmacological synergy, since GLP-1/GCG dual agonists are engineered to achieve balanced receptor activation rather than simple co-administration of two counter-regulatory hormones (61,64). Such agents may retain the anorectic and insulin-sensitizing effects of GLP-1 while utilizing the effects of GCG on energy expenditure and lipid metabolism without causing excessive hyperglycemia (65). In this context, their potential antitumor relevance is biologically plausible, as they may improve metabolic dysfunction, reduce obesity-related chronic inflammation, and influence nutrient availability and metabolic reprogramming in the TME (66-68). Indirect support for this hypothesis comes from preclinical studies of related incretin-based polyagonists. Tirzepatide, a dual GIPR/GLP-1R agonist, has shown antitumor effects in models of EC and colorectal cancer (CRC) (69), whereas retatrutide, a triple GIPR/GLP-1R/GCGR agonist, has shown antitumor activity in pancreatic and lung cancer models (70). Nevertheless, the

currently available evidence remains indirect and is insufficient to directly demonstrate either a synergistic antitumor effect of GLP-1/GCG co-agonism or an antitumor effect mediated through GCGR activation alone. At present, the proposed antitumor relevance of GLP-1/GCG co-agonism, and, more specifically, any antitumor effect attributable to GCGR activation alone, should be regarded as a mechanistic hypothesis requiring direct validation in tumor-specific models.

Comparative physiology and oncological potential. GLP-1, GIP and GCG are key peptide hormones that regulate metabolic homeostasis; however, they have distinct origins, receptors and frequently opposing metabolic functions (71). The clinical translation of their receptor agonists has revealed divergent oncological properties (72). GLP-1RAs are well-established for managing T2D and obesity (61,73,74), and exhibit emerging antitumor potential in related cancers, such as colorectal and endometrial cancers (75,76). The role of GIPR modulation in oncology remains poorly defined, while investigations into GCGR agonism to increase whole-body energy expenditure in obesity and metabolic disease are still in progress, although its potential hyperglycemic effects necessitate caution (61,66). Table SI systematically compares the secretion, signaling transduction and metabolic actions of GLP-1, GIP and GCG, and summarizes their impacts on the TME offering a foundational theoretical basis for their integrated assessment in cancer biology (15,16,45,61,62,66). This comparative analysis emphasizes that shared signaling pathways can generate antagonistic physiological outcomes, a concept critical for elucidating their microenvironment-dependent functions in cancer (31,77).

Dual roles of incretin therapies in oncology. Among the three hormones GLP-1, GIP and GCG, GLP-1 has been the most extensively studied in the field of malignant tumors (74,78,79). Thus, the antitumor potential of GLP-1RAs represents the primary focus of the present review.

Studies have demonstrated that GLP-1RAs confer therapeutic benefits in various T2D- or obesity-related conditions, including polycystic ovary syndrome (80), metabolic syndrome (81), non-alcoholic fatty liver disease (82) and obesity- or diabetes-associated malignancies, such as gallbladder, ovarian and esophageal cancers (73,79). However, their effects are not uniformly beneficial. Under certain circumstances, these hormones may exhibit pro-tumorigenic properties. The cAMP signaling pathway serves as a central pathway shared by these three hormones, capable of transmitting either pro- or anti-proliferative signals depending on the cellular context (78,79). For instance, GLP-1 has been shown to promote the progression of medullary thyroid carcinoma (MTC) in rodent models (83). In some breast cancer models, liraglutide enhances tumor cell proliferation via the NADPH oxidase 4 (NOX4)/reactive oxygen species (ROS)/VEGF signaling pathway (84). Similarly, in EC, upregulation of GLP-1R facilitates cell proliferation and migration while conferring resistance to ferroptosis, thereby driving tumor progression (85). These divergent findings highlight that the net effect on tumorigenesis is modulated by the interplay among tumor cell-intrinsic factors, host systemic metabolism and pharmacological characteristics. Thus, elucidating the contextual determinants underlying these dual effects is essential for the safe and effective application of these agents in oncology.

3. Incretin and GCG and the TME

The TME is a complex ecosystem composed of tumor cells, immune cells, fibroblasts and the extracellular matrix (ECM). The TME serves as a dynamic interface, where interactions between malignant and non-malignant components promote tumor growth, invasion and metastasis (86,87). The TME is characterized by nutrient deprivation, hypoxia and an acidic milieu, driven by aberrant tumor vasculature and the Warburg effect (a preference for aerobic glycolysis even in the presence of oxygen), which collectively facilitate immune evasion by tumor cells (88,89). The release of acidic metabolites such as lactate, generated by tumor cells via glycolysis, exacerbates local acidosis within the TME (90). This acidic environment not only suppresses immune cell function but also activates pro-angiogenic factors (91,92). Immune cells serve a pivotal role in the TME. Cytotoxic $CD8^+$ T cells serve as the primary effectors of antitumor immunity (93,94); however, their function is often suppressed by regulatory T cells (Tregs), myeloid-derived suppressor cells (95) and tumor-associated macrophages (TAMs) (96). Metabolic competition for nutrients such as glucose and amino acids between tumor cells and immune cells further impairs effective immune responses (97). Given the potent immunomodulatory and metabolic effects of GLP-1, GIP and GCG, therapies targeting these pathways may influence the TME by modulating nutrient competition and immune-cell function; however, current mechanistic evidence is strongest for GLP-1-related agents (98) Based on this premise, the present review summarizes the important roles of GLP-1-related agents within the tumor immune microenvironment, for which the current evidence base is the most extensive, as shown in Fig. 2 (98,99).

T cells. T cells are core components of adaptive immunity and central to antitumor immunotherapy. Cytotoxic T cells are primarily characterized by CD8 expression, helper T cells by CD4 expression, and Tregs by co-expression of CD25 and CD4 expression (100). During tumor progression, cancer-associated fibroblasts, M2-type macrophages and Tregs can establish an immunosuppressive barrier that counteracts $CD8^+$ T cell-mediated antitumor immunity (101). Therefore, effective antitumor immunotherapy requires not only sufficient effector T cell activity but also the maintenance of T cell fitness and persistence. Current evidence suggests that the effects of GLP-1-related signaling on T-cell biology are context dependent (102,103).

In inflammatory settings, this immunoregulatory effect appears to be tissue-protective. Under alloimmune conditions, GLP-1R-expressing T cells are predominantly enriched within the exhausted $CD8^+$ T cell population, where GLP-1R signaling functions as a negative costimulatory pathway that restrains excessive T-cell activation and tissue-damaging inflammation (104). In a murine model of nephrotoxic serum nephritis, GLP-1R activation suppressed the proliferation of pro-inflammatory T helper 1 and T helper 17 cells, while reducing IL-6 production, thereby exerting renal protective

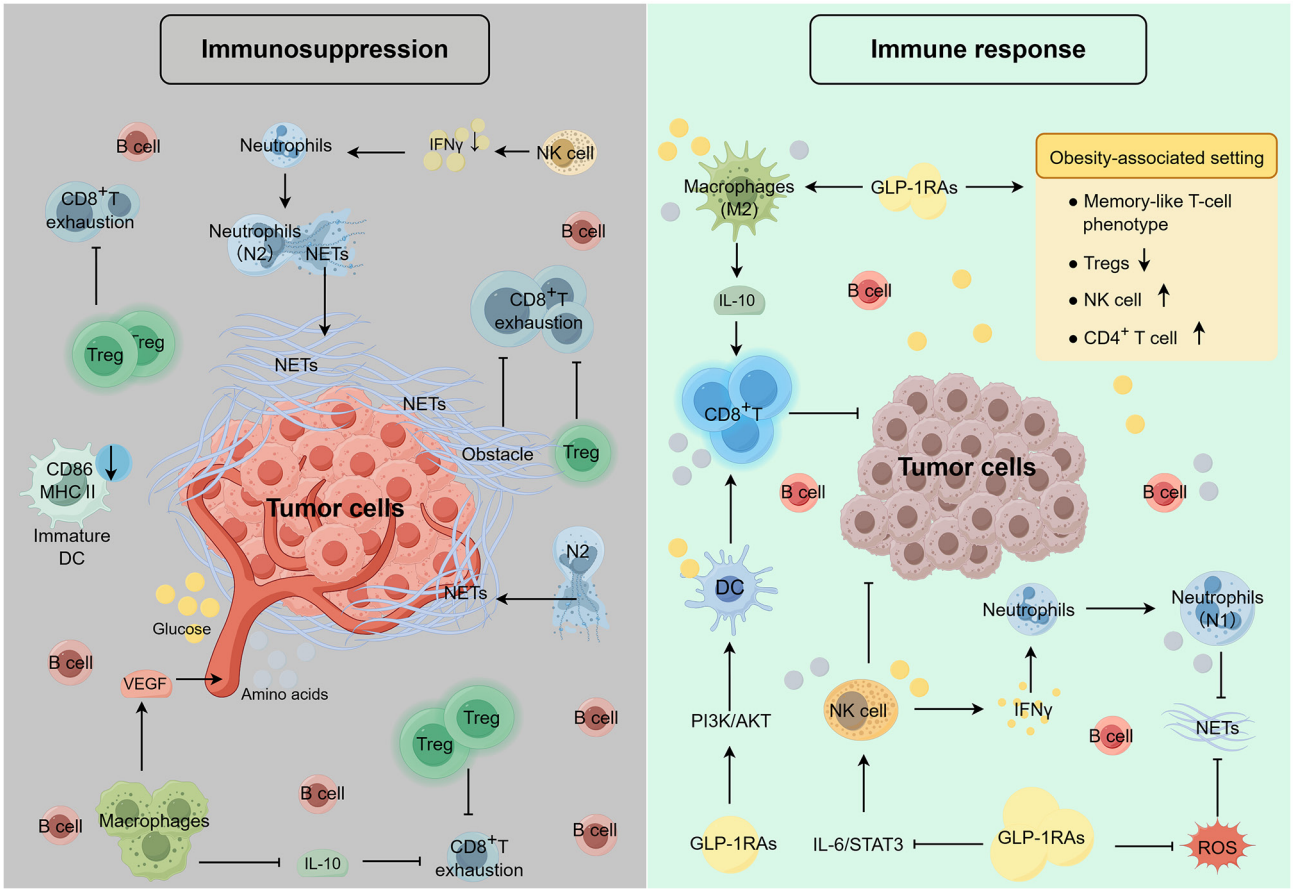

Figure 2. Modulation of the tumor immune microenvironment by GLP-1RAs. GLP-1RAs promote a shift from an immunosuppressive tumor microenvironment towards a more immunoresponsive state. Mechanistically, this is reflected by reduced neutrophil extracellular trap formation and ROS-associated immunosuppression, enhanced NK cell-mediated tumor lysis, promotion of DC maturation and antigen presentation, modulation of T-cell activity, and context-dependent regulation of macrophage polarization. Collectively, these effects support antitumor immunity by improving immune cell function and alleviating immunosuppressive signaling within the tumor microenvironment. Created with Figdraw.com. DC, dendritic cell; GLP-1RA, glucagon-like peptide-1 receptor agonist; MHC, major histocompatibility complex; NET, neutrophil extracellular trap; NK, natural killer; ROS, reactive oxygen species; Treg, regulatory T cell.

effects (105). Furthermore, in intestinal intraepithelial lymphocytes, GLP-1R activation inhibits proximal T cell receptor signaling in a PKA-dependent manner, suppressing T cell activation and attenuating local IFN-γ-driven inflammation (106). Through direct suppression of T helper cell-mediated hyperinflammation and PKA-dependent modulation of local immune responses, GLP-1RAs help protect normal tissues (107). These findings support a role for GLP-1R signaling in limiting T-cell-mediated hyperinflammation and preserving immune homeostasis in normal tissues.

This anti-inflammatory effect should not be interpreted as uniformly detrimental to antitumor immunity (104). GLP-1RAs appear to support antitumor immunity mainly through remodeling of the suppressive TME rather than through direct restoration of exhausted intratumoral $CD8^+$ T-cell function (108). In a syngeneic 4T1 breast cancer model, semaglutide increased intratumoral T-cell infiltration, promoted dendritic cell maturation, reduced $FoxP3^+$ Tregs and enhanced $CD8^+$ T-cell cytotoxicity despite showing no direct tumoricidal activity *in vitro* (108). Similarly, exenatide enhanced the efficacy of programmed cell death protein-1 (PD-1) blockade in LLC- and MC38-based lung and colon cancer models (109), and liraglutide did so in LLC- and Hepa1-6-bearing mice, mainly by attenuating neutrophil extracellular trap (NET)- and ROS-driven immunosuppression and thereby permitting stronger $CD8^+$ T-cell effector responses (110).

In obesity-related tumor settings, the immunological effects of GLP-1R agonism appear to be more pronounced. In diet-induced obese mice bearing subcutaneous KPN1.1 tumors, liraglutide reduced tumor burden, whereas in an autochthonous KRAS/p53-driven non-small cell lung cancer model, semaglutide improved tumor control and survival. These effects were accompanied by increased intratumoral $CD4^+$ T-cell and natural killer (NK) cell frequencies, a shift of $CD8^+$ and conventional $CD4^+$ T cells toward a memory-like phenotype, reduced regulatory T-cell abundance, and improved antigen-presenting cell-associated immune features (111).

Collectively, these findings support a role for GLP-1RAs in strengthening antitumor T-cell immunity mainly through TME remodeling, with particularly evident effects under obesity-associated metabolic conditions (111). However, current evidence remains insufficient to conclude that GLP-1 directly restores exhausted $CD8^+$ T-cell function or directly regulates the PD-1/programmed death-ligand 1 axis within tumors.

Neutrophils. The role of neutrophils in cancer therapy remains controversial. The N1 phenotype exhibits antitumor

properties, whereas the N2 phenotype promotes tumor progression (112). Studies have indicated that a key mechanism of neutrophil-mediated tumor promotion involves the formation of NETs, which can physically shield tumor cells from cytotoxic lymphocytes and NK cells (113), while also inducing T-cell exhaustion and functional impairment (114). In lung and liver cancer models, the combination of liraglutide and exenatide with anti-PD-1 therapy reduced ROS production, suppressed NET formation, and decreased the levels of peripheral myeloperoxidase-DNA complexes and elastase. These effects enhanced the cytotoxicity of $CD8^+$ T cells and their capacity to eliminate tumor cells, thereby augmenting the antitumor efficacy of PD-1 inhibitors (109,110). Thus, in modulating neutrophil activity, GLP-1RAs primarily exert indirect antitumor effects by reducing NET formation. Furthermore, serum NET levels may serve as a biomarker for predicting the efficacy of immunotherapy (115), offering valuable insights for drug selection in patients with malignancies.

NK cells. NK cells are innate cytotoxic lymphocytes that surveil and eliminate tumor cells through the release of cytolytic granules (116). NK cells also coordinate with other immune cells via pro-inflammatory cytokines and chemokines (117). Obesity impairs NK cell function (118), and GLP-1 analog therapy has been shown to restore NK cell effector functions in individuals with obesity. After 6 months of treatment with GLP-1 analogs, the levels of IFN-γ and granzyme B produced by NK cells were markedly elevated, indicating partial restoration of NK cell functionality (118). Phenotypic differentiation of neutrophils is regulated by NK cells, which can promote neutrophil polarization toward the N1 phenotype through an IFN-γ-dependent mechanism (119). In NK cell-depleted mouse models, neutrophils tend to adopt the N2 phenotype, characterized by upregulated VEGF-A expression, thereby promoting tumor growth and angiogenesis (119). Furthermore, malignant tumors often exhibit hyperactivation of the IL-6/STAT3 signaling pathway, which dampens $CD4^+$ T cell activity and subsequently suppresses NK T cell function (120). In hepatocellular carcinoma (HCC) models, liraglutide enhanced NK cell-mediated tumor lysis by inhibiting the IL-6/STAT3 pathway (121). Thus, GLP-1 analogs not only directly restore NK cell function but also augment antitumor immunity through coordinated immune network interactions.

Macrophages. TAMs exhibit high plasticity and heterogeneous responses to environmental stimuli (122), enabling their polarization into either antitumor M1 or pro-tumor M2 phenotypes (123-125). In established tumors, TAMs can further promote immunosuppression and tumor progression by producing pro-angiogenic factors, such as VEGF, and by releasing IL-10-rich signals that impair effective cytotoxic T-cell responses (126). Multiple studies have demonstrated that GLP-1RAs promote the polarization of uncommitted macrophages toward an anti-inflammatory phenotype (127,128) and facilitate the transition from M1 to M2 polarization (129,130). In patients with obesity and T2D, GLP-1RA therapy reduces the levels of inflammatory cytokines (TNF-α, IL-1β and IL-6) and the macrophage activation marker soluble CD163, while increasing anti-inflammatory adiponectin (131). Although M2 polarization is generally associated with tissue repair, it exerts pro-tumor effects in established cancers (132). GLP-1RA treatment enhances IL-10 secretion by M2 macrophages (133), an effect that exhibits strong concentration dependence: Low IL-10 concentrations may facilitate tumor immune evasion, whereas high concentrations promote $CD8^+$ T cell proliferation, activation and cytotoxicity (134). The dosage and duration of GLP-1RA treatment, as well as the inflammatory status of the patient, collectively influence macrophage polarization (135). Thus, the dual effects of GLP-1RAs in breast cancer and EC may be linked to individual variations in macrophage polarization (136). Further investigation is required to determine the net impact of GLP-1RAs on TAMs and tumor outcomes. Identifying optimal dosing regimens may help resolve the context-dependent duality of GLP-1RAs in certain malignancies.

Dendritic cells (DCs). DCs serve a pivotal role in initiating and regulating T cell-mediated antitumor immune responses by enhancing the cytotoxicity of NK and T cells (137). Within the suppressive TME, immature or dysfunctional DCs typically exhibit reduced major histocompatibility complex (MHC) II and CD86 expression, which limits antigen presentation and impairs effective T-cell priming (138). Evidence indicates that GLP-1RAs markedly augment DC-mediated adaptive immunity (108). In a 4T1 breast cancer mouse model, semaglutide treatment markedly promoted the accumulation of $CD11c^+$ DCs in both the spleen and TME, while upregulating the expression of surface MHC II molecules and the co-stimulatory marker CD86, thereby facilitating DC maturation. Mechanistically, semaglutide enhanced the mRNA expression levels of antigen processing and presentation-related molecules (MHC I and transporter associated with antigen processing) in DCs by activating the PI3K/phosphorylated-Akt signaling pathway. These findings demonstrated that GLP-1RAs strengthened the ability of DCs to cross-present antigens and activate cytotoxic T lymphocytes, underscoring their central role in antitumor immunity (108).

B cells. B cells are key components of humoral immunity, contributing through antibody production and support of cellular immune responses (139). B cells are essential constituents of tertiary lymphoid structures, and their primary functions include antigen presentation and antibody secretion (140). Prognostically relevant B-cell subsets include stress-responsive memory B cells and tumor-associated atypical B cells (141). In gastric cancer, increased infiltration of $CD20^+$ B cells in gastric cancer tissues, as detected by immunohistochemistry, is associated with improved patient outcomes (142). However, the role of B cells in GLP-1RA therapy remains unclear. Given that their core function (antibody production) has limited direct links to energy metabolism, to the best of our knowledge, no direct studies have investigated interactions between B cells and GLP-1RAs. Early genetic engineering research has demonstrated that in transgenic mice constitutively expressing the exendin-4 precursor, lymphocyte infiltration occurred in multiple tissues. Specifically, $B220^+$ B cells accumulated in the pancreas and liver, while $CD4^+$ and $CD8^+$ T cells were increased in the liver and kidneys (143). These findings suggested that sustained proexendin-4 expression may break

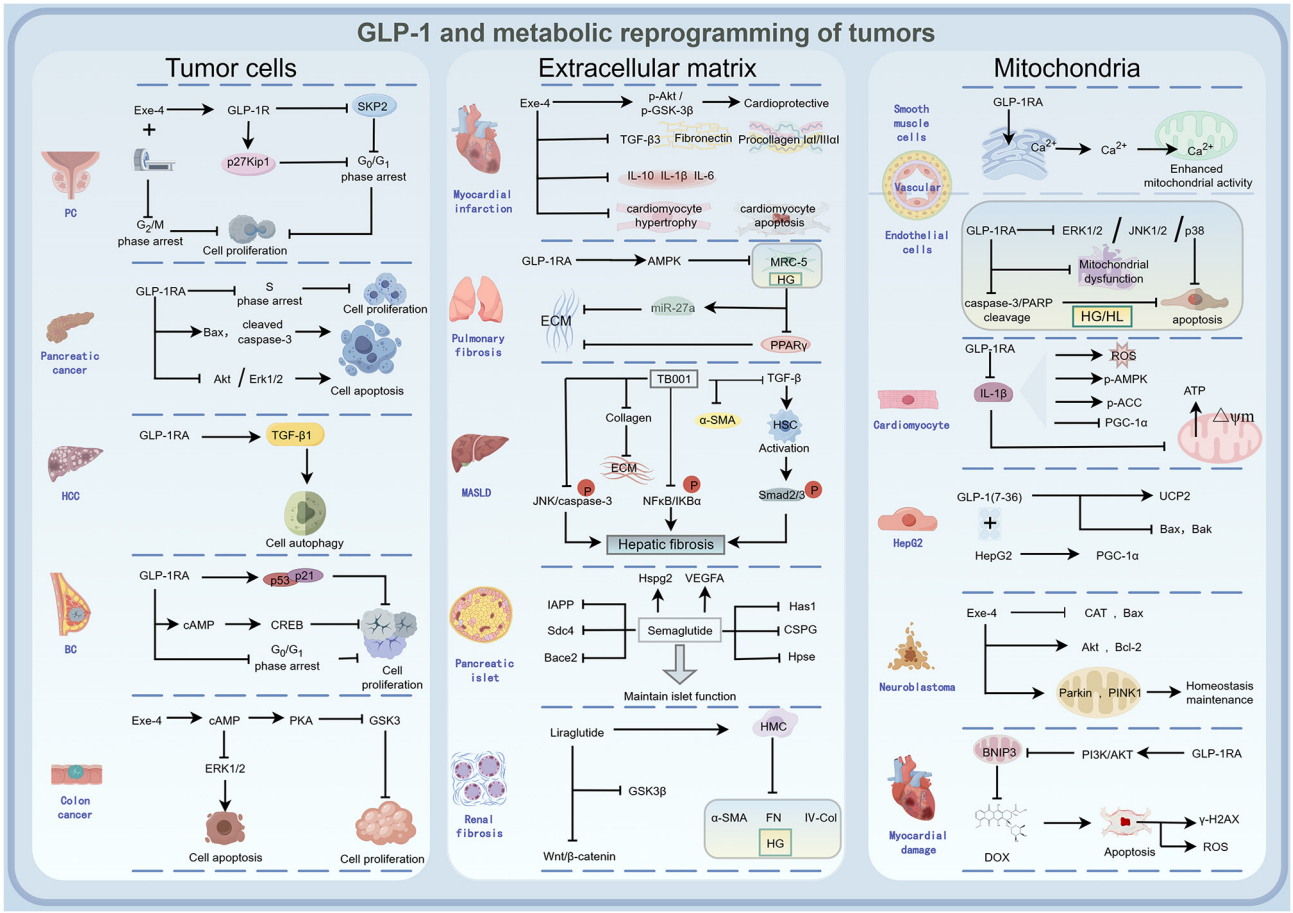

Figure 3. Multifaceted impact of GLP-1RAs on tumor metabolic reprogramming. GLP-1RAs influence three interconnected processes relevant to tumor-associated metabolic reprogramming. In tumor cells, they are shown to suppress proliferation, induce cell-cycle arrest or apoptosis, and promote autophagy in selected preclinical models. In the extracellular matrix, they attenuate profibrotic ECM remodeling and fibrosis-associated signaling, including reductions in collagen/fibronectin-related deposition and profibrotic marker expression. In mitochondria, they improve mitochondrial function by enhancing Ca^{2+}-dependent mitochondrial activity, preserving mitochondrial membrane potential, reducing oxidative stress and apoptosis, and promoting mitochondrial quality-control signaling. Created with Figdraw.com. α-SMA, α-smooth muscle actin; Δψm, mitochondrial membrane potential; ACC, acetyl-CoA carboxylase; AMPK, AMP-activated protein kinase; Bace2, β-site APP-cleaving enzyme 2; BC, breast cancer; BNIP3, BCL2 interacting protein 3; CAT, catalase; CREB, cAMP-response element-binding protein; CSPG, chondroitin sulfate proteoglycan; DOX, doxorubicin; ECM, extracellular matrix; Exe-4, exendin-4; FN, fibronectin; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; GLP-1RA, glucagon-like peptide-1 receptor agonist; Has1, hyaluronan synthase 1; HCC, hepatocellular carcinoma; HG, high glucose; HL, high lipid; HMC, human mesangial cells; Hpse, heparanase; HSC, hepatic stellate cell; Hspg2, heparan sulfate proteoglycan 2; IAPP, islet amyloid polypeptide; IV-Col, type IV collagen; MASLD, metabolic dysfunction-associated steatotic liver disease; miR, microRNA; p-, phosphorylated; PC, prostate cancer; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; PINK1, PTEN-induced kinase 1; PKA, protein kinase A; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; Sdc4, syndecan-4; SKP2, S-phase kinase-associated protein 2; UCP2, uncoupling protein 2.

immune tolerance and simultaneously activate humoral and cellular immune responses. Nevertheless, this model involved continuous, high-level transgene expression across multiple tissues, which does not reflect the pharmacokinetic profile of therapeutic GLP-1RAs. Furthermore, the functional consequences of immune activation and underlying mechanisms were not explored. However, the study implied that GLP-1 and its analogs may interact with various immune cells, warranting further investigation.

In summary, GLP-1RAs modulate the tumor immune microenvironment through multiple mechanisms. Documented antitumor mechanisms include suppression of excessive inflammation and potential functional restoration of $CD8^+$ T cells, reduction of NET formation in neutrophils to enhance $CD8^+$ T cell cytotoxicity, direct restoration of NK cell function with indirect promotion of N1-polarized neutrophils, and promotion of DC maturation and antigen presentation to reinforce T-cell activation. Conversely, potential pro-tumor effects include induction of anti-inflammatory macrophage polarization. The impact on B cells remains undetermined.

4. Tumor-associated metabolic reprogramming

Metabolic reprogramming is a hallmark of cancer, enabling rapid proliferation, survival and stress adaptation (144). GLP-1RAs influence this process through direct targeting of tumor cells, remodeling of the ECM and modulation of mitochondrial function (Fig. 3).

Metabolic reprogramming of tumor cells. Activation of GLP-1R has been reported to inhibit proliferation in several tumor models, in some cases accompanied by cell cycle arrest and apoptosis. However, these pro-apoptotic effects have thus far been demonstrated predominantly in preclinical systems

and should not be directly extrapolated to clinical antitumor efficacy or systemic toxicity (78,145).

GLP-1R expression levels exhibit an inverse association with the Gleason score in prostate cancer (146). Exendin-4 reduces S-phase kinase associated protein 2 expression and upregulates p27Kip1 in a dose-dependent manner, inducing G_0/G_1 phase arrest in ALVA-41 cells and thereby suppressing proliferation (145). Combined treatment with docetaxel and liraglutide decreases viability in the LNCaP prostate cancer cell line, leading to cell cycle arrest and apoptosis, with liraglutide enhancing chemotherapeutic efficacy and reducing drug resistance (147). Furthermore, exendin-4 potentiates the anti-proliferative effects of ionizing radiation *in vitro* and *in vivo*, and enhances radiation-induced G_2/M phase arrest in a dose-dependent manner, thereby improving radiosensitivity (148). Liraglutide reduces the proliferation of HepG2 cells by inducing TGF-β1-mediated autophagy and senescence without altering oxidative stress levels (149). GLP-1RAs and exendin-4 decrease breast cancer cell viability and promote apoptosis via activation of cAMP and CREB signaling (12). Liraglutide inhibits the proliferation of MCF-7 human breast cancer cells by ~48%, reduces colony formation, induces G_0/G_1 phase arrest and ultimately suppresses cancer cell proliferation (150). In human pancreatic cancer cells, liraglutide inhibits proliferation and promotes apoptosis accompanied by S-phase arrest through activation of cAMP-mediated Akt and ERK1/2 signaling pathways (151). Exendin-4 increases intracellular cAMP levels in colon cancer CT26 cells, activates the PKA pathway, and inhibits the activity of signaling kinases GSK3 and ERK1/2, consequently suppressing CT26 cell proliferation (152).

Through the modulation of signaling pathways such as the cAMP signaling pathway, GLP-1RAs induce cell cycle arrest and apoptosis in various cancer cells and enhance sensitivity to radiotherapy and chemotherapy. For example, exendin-4 has been shown to potentiate the antiproliferative effects of ionizing radiation and increase radiation-induced G_2/M phase arrest, whereas liraglutide enhances the effects of docetaxel in prostate cancer cells. These findings suggest that GLP-1RAs may have potential as adjuncts to radiotherapy or chemotherapy in selected tumor models (148).

Metabolic reprogramming of the ECM. The ECM provides structural and biochemical support for tumors (153). ECM remodeling within the TME facilitates tumor invasion and metastasis (154). GLP-1 and GIP-related agents serve a crucial therapeutic role in various diseases by reducing the expression and deposition of ECM proteins, such as fibronectin and type IV collagen, or by altering ECM structure (155).

GLP-1RAs have exhibited protective effects across multiple organ fibrosis and injury models. In the cardiovascular system, GLP-1RAs improve post-myocardial infarction remodeling by enhancing Akt/GSK-3 phosphorylation and downregulating profibrotic and inflammatory factors such as procollagen, TGF-β3 and interleukins (156). In diabetic kidney disease, liraglutide suppresses mesangial cell production of fibronectin and type IV collagen via activation of the Wnt/β-catenin pathway (157). In diabetic lung injury, GLP-1RAs reduce ECM accumulation and ameliorate pulmonary fibrosis via the AMP-activated protein kinase (AMPK)/microRNA-27a/peroxisome proliferator-activated receptor γ axis (158). Additionally, the GLP-1R/GCGR dual agonist TB001 alleviates liver fibrosis by inhibiting the TGF-β/Smad2/3 signaling pathway and hepatic stellate cell activation, while modulating NF-κB and JNK pathways to suppress inflammation and apoptosis (159). Semaglutide directly targets pancreatic cancer-associated fibroblasts, inhibiting the expression and activity of collagen prolyl-4-hydroxylase (P4HA1), reducing collagen hydroxylation and ECM deposition. This softens the physical barrier of the tumor stroma, promotes intratumoral infiltration of $CD3^+$ and $CD8^+$ T cells, remodels the immunosuppressive microenvironment, and suppresses pancreatic cancer progression (159).

Through inhibition of key targets, such as TGF-β and P4HA1, GLP-1RAs exert antifibrotic and immunomodulatory effects, demonstrating protective potential in multiple organs, including the heart, kidneys, liver and lungs (160). Furthermore, their ability to remodel the pancreatic cancer ECM and enhance T-cell infiltration offers novel strategies for cancer immunotherapy (161). Future research should focus on combination therapies of GLP-1RAs with chemotherapy and immune checkpoint inhibitors, and further explore their therapeutic potential in other stroma-rich tumors.

Changes in mitochondrial function. Despite the Warburg effect, mitochondrial function remains crucial for tumor cell survival, biosynthesis and redox homeostasis (162). Mitochondrial DNA mutations or dysfunction can drive tumorigenesis (163). The aberrant proliferation of tumor cells relies on mitochondrial integrity and tricarboxylic acid (TCA) cycle activity (164). Furthermore, cancer cells exploit mutations in multiple TCA cycle enzymes to facilitate immunosuppression and immune evasion (165).

GLP-1RAs exert protective effects on mitochondrial function across multiple experimental models. GLP-1RAs enhance endoplasmic reticulum-mitochondrial coupling, promote calcium transfer from the endoplasmic reticulum to mitochondria and increase mitochondrial activity in vascular smooth muscle cells (166). Under high-glucose and high-lipid stress, GLP-1RAs reduce apoptosis and mitigate mitochondrial dysfunction in human microvascular endothelial cells by inhibiting ERK1/2, JNK and p38 pathways, while suppressing caspase-3 and PARP cleavage (167). Liraglutide treatment ameliorates IL-1β-induced ROS production in cardiomyocytes, protects against IL-1β-induced loss of mitochondrial membrane potential and decreased ATP generation, and counteracts IL-1β-induced alterations in AMPK and acetyl-CoA carboxylase phosphorylation as well as the reduction of peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), which is a key regulator whose downregulation leads to cardiac mitochondrial dysfunction (168). In hepatocytes, GLP-1 upregulates uncoupling protein 2 mRNA expression, downregulates Bax and Bak mRNA levels, enhances PGC-1α expression, improves mitochondrial antioxidant capacity, and inhibits apoptosis (169). GLP-1RAs increase mitochondrial content in the soleus muscle of SDT fatty rats by upregulating citrate synthase activity and cytochrome *c* oxidase subunit 5B protein expression (170). Additionally, in SH-SY5Y neuroblastoma cells, exendin-4 treatment upregulates the mitochondrial quality control regulators Parkin and PTEN induced kinase 1,

reduces Bax expression, enhances Akt and Bcl-2 levels, and inhibits tumor cell apoptosis (83). Through the PI3K/AKT pathway, GLP-1RAs downregulate mitochondrial BCL2 interacting protein 3 expression, reduce doxorubicin-induced ROS production and γ-H2AX elevation, and ameliorate doxorubicin-induced cardiotoxicity (171).

Evidence indicates that GLP-1RAs preserve mitochondrial function by enhancing calcium uptake, improving membrane potential, increasing ATP production, promoting mitochondrial biogenesis, and reducing oxidative stress and apoptosis (172,173). Therefore, combining conventional antitumor therapies with GLP-1RAs may not only enhance treatment efficacy and reduce drug resistance but also mitigate adverse effects.

5. Basic research and potential clinical application of incretin and GCG

The therapeutic potential of incretin and GCG-related drugs is under active investigation. In the field of oncology, GLP-1RAs have predominantly demonstrated anticancer effects, although a limited number of studies suggest potential tumor-promoting properties (13,75). However, current human evidence is derived mainly from metabolic trials and pharmacoepidemiologic studies conducted at approved therapeutic doses, rather than from oncology trials specifically designed to induce tumor apoptosis (174-176). In these clinical settings, 3.0 mg liraglutide once daily and 2.4 mg semaglutide once weekly are associated predominantly with gastrointestinal adverse events, including nausea, diarrhea, vomiting and constipation, which are generally mild-to-moderate and transient (75,177-179). Meta-analysis has not shown a significant increase in pancreatitis or pancreatic cancer with GLP-1RAs, although gallbladder-related events such as cholelithiasis warrant attention (180). Accordingly, the cancer-specific evidence discussed in the present review should be interpreted by distinguishing mechanistic findings from preclinical models and safety data derived from clinically approved regimens. Relevant evidence is summarized in Table SII (preclinical studies) (13,69,151,152,181-190) and Table SIII (clinical studies) (73,175,179,180,182,191-199). Where available, adverse effect information from cited human studies is also summarized in Table SIII and briefly noted in the corresponding cancer-specific subsections.

Thyroid cancer. The prescribing information for GLP-1RA lists MTC as a contraindication, based on a preclinical rodent study demonstrating that GLP-1R activation elevates cAMP levels in rodent thyroid C-cells, stimulates calcitonin release, and promotes C-cell hyperplasia and MTC development (200). However, in papillary thyroid carcinoma, neither insulin nor GLP-1RAs markedly influence tumor cell proliferation (201). A case report from the LY2189265 diabetes trial described a woman with previously unrecognized MTC who received dulaglutide (2.0 mg once weekly) for 6 months without a significant change in serum calcitonin levels (202). Nevertheless, this single case is insufficient to establish the safety of GLP-1RAs in human MTC. A real-world study suggested that over a 5-year period, GLP-1RAs were associated with a reduced risk of prostate, lung and colon cancer compared with metformin, but might be linked to an elevated risk of thyroid cancer (203). By contrast, a large cohort study reported that GLP-1RA use was not associated with a significant increase in thyroid cancer risk compared with dipeptidyl peptidase-4 inhibitors (191). Additionally, randomized trial data and subsequent systematic reviews have not shown a clear increase in thyroid cancer risk with GLP-1RA treatment (193,204). From a safety perspective, the available semaglutide data indicate that adverse events are predominantly gastrointestinal, most commonly nausea, diarrhea, vomiting and constipation, without a clear thyroid-specific carcinogenic signal (193).

In conclusion, current evidence has not established a causal relationship between GLP-1RAs and thyroid cancer. While rodent data support continued caution in MTC, GLP-1RAs should not be regarded as an absolute contraindication in other thyroid cancer subtypes, provided that treatment is individualized and appropriate monitoring is undertaken.

Pancreatic cancer. An early investigation indicated that GLP-1R stimulation does not affect pancreatic cancer cell proliferation (205). Liraglutide enhances chemosensitivity in pancreatic cancer: By inhibiting the NF-κB pathway, it improves the response of gemcitabine-resistanT cells to chemotherapy, and this sensitization effect has been validated in animal models (181).

A large historical cohort study of 543,595 patients demonstrated that GLP-1RA treatment over 7 years did not increase the incidence of pancreatic cancer, confirming its safety profile in this malignancy (179). Similarly, a large retrospective cohort study reported that GLP-1RAs were associated with a decreased incidence of pancreatic cancer in patients with type 2 diabetes mellitus (206). Clinically, current evidence does not indicate an increased risk of pancreatitis or pancreatic cancer with GLP-1RAs. However, gallbladder-related adverse events, particularly cholelithiasis, should be considered when interpreting their overall safety profile (180). In summary, current evidence supports the beneficial role of GLP-1RAs in both the prevention and treatment of pancreatic cancer.

Cervical cancer. A translational case-control study revealed that proteasome subunit α type-2 (PSMA2) expression was upregulated in 12 human cancer types based on The Cancer Genome Atlas database. In T2D-associated cervical cancer, GLP-1R expression was positively associated with PSMA2 levels, but this association was absent in non-T2D cervical cancer specimens (182). Subsequent preclinical experiment in the same study demonstrated that under high-glucose conditions, exendin-4 reduced phosphorylation of P65 and IκB, downregulated PSMA2 expression, inhibited the NF-κB pathway, suppressed cell proliferation, and reduced tumor volume *in vivo*. These findings suggest that hyperglycemia may promote cervical cancer progression via PSMA2 upregulation, while exendin-4 counteracts this effect (182). In conclusion, GLP-1RAs inhibit cervical cancer growth under hyperglycemic conditions. Because the current evidence in cervical cancer remains largely mechanistic and translational, to the best of our knowledge, no cancer-specific clinical adverse effect data are currently available for GLP-1RAs in this setting. Further epidemiological and clinical studies are warranted to validate these observations.

HCC. A preclinical study demonstrated that liraglutide and exenatide suppress HCC cell proliferation and induce autophagy. Compared with liraglutide, exenatide exhibits stronger inhibition of mTOR in HepG2 cells (174). In a mouse model of non-alcoholic fatty liver disease-associated HCC (207), liraglutide prevented HCC progression by modulating blood glucose levels and ameliorating steatosis and inflammation in non-tumorous liver lesions. Furthermore, liraglutide enhances NK cell-mediated cytotoxicity through suppression of the IL-6/STAT3 signaling pathway in HCC cells, thereby promoting immune surveillance (121). Multiple retrospective studies have confirmed that GLP-1RAs are associated with reduced risks of long-term adverse hepatic outcomes in patients with metabolic dysfunction-associated steatotic liver disease or T2D and cirrhosis (208), as well as lowered risks of HCC development and hepatic decompensation in patients with T2D (175,209). Notably, these studies mainly reported hepatic outcomes and cancer incidence rather than treatment-emergent adverse events, and detailed adverse effect data were not consistently available. Overall, through direct anti-proliferative effects, metabolic regulation and immunomodulation (121,174,207,209), GLP-1RAs demonstrate promising potential for clinical translation in HCC management.

CRC. Although initial hypotheses suggested that GLP-1RAs might promote CRC via the Wnt/β-catenin pathway, this was not substantiated. Nevertheless, the study by Sun *et al* (208) advised caution in using GLP-1RAs in high-risk populations. However, subsequent research has demonstrated beneficial effects of GLP-1RAs in CRC. Liraglutide inhibits CRC cell proliferation, migration and invasion by regulating the PI3K/Akt/mTOR pathway (210), and attenuates high glucose-induced proliferation by suppressing bone morphogenetic protein 4 expression (211). Cohort studies and genetic data analyses further support the preventive and therapeutic potential of GLP-1RAs against CRC (75,212). The available epidemiologic studies in CRC mainly addressed cancer incidence or risk reduction, whereas treatment-related adverse effects were not systematically reported.

In contrast to the relatively consistent beneficial profile of GLP-1RAs in CRC, the role of GCG appears to be more heterogeneous. Yagi *et al* (84) demonstrated that GCG promoted the proliferation of HT29, SW480, CT26 and CMT93 cells through GCGR-dependent AMPK deactivation and MAPK activation, using 1.0 nM GCG replenished every 24 h for up to 72 h. By contrast, Xu *et al* (213), using CT26 and SW480 models together with endothelial C166 cells and patient-derived xenografts, reported that GCG administered at 10 nM *in vitro* and 20 μg per mouse daily *in vivo* for ~14 days inhibited tumor angiogenesis and vascular mimicry and enhanced chemotherapy efficacy, without measurable differences in blood glucose levels among groups. Taken together, these discrepant findings likely reflect differences in tumor model, target cell compartment, glycemic context and exposure conditions, indicating that the effects of GCG in CRC are context-dependent. These differences suggest that GCG cannot be uniformly characterized as either pro-tumorigenic or antitumorigenic in CRC; rather, its biological effects may shift according to metabolic milieu and cellular target, which has important implications for interpreting preclinical data and for the cautious evaluation of GLP-1/GCG dual agonists in CRC.

Breast cancer. The role of GLP-1RAs in breast cancer therapy remains controversial. Exendin-4 activates the cAMP/CREB signaling pathway, thereby inhibiting cell proliferation and promoting apoptosis. This supports the view that GLP-1 acts as a potent inducer of cAMP and an inhibitor of breast cancer cell proliferation (12). However, these effects are not uniform across experimental settings, and liraglutide has also been reported to promote triple-negative breast cancer progression through the NOX4/ROS/VEGF axis when administered at 100 nM *in vitro* and 400 μg/kg *in vivo* (13). Taken together, these findings suggest that the effects of GLP-1RAs in breast cancer are context-dependent and may vary according to tumor subtype and exposure conditions, warranting caution when extrapolating high-dose preclinical observations to clinical safety. However, at present, clinical adverse effect data specific to breast cancer treatment settings remain limited, and the available human evidence is derived mainly from cancer risk analyses rather than oncology-focused intervention studies.

EC. Diabetes and obesity are established risk factors for EC, with weight loss and glycemic control representing key preventive strategies (85). Under hyperglycemic conditions, exendin-4 partially restores cisplatin sensitivity in Ishikawa and HEC1B EC cells, with treatment performed at 10 nM for 48 h and accompanied by modulation of apoptosis-related proteins (183). Semaglutide has been shown to potentiate the antitumor effect of levonorgestrel in EC models, including Ishikawa, Hec50 and KLE cells, as well as patient-derived organoids from grade 1 endometrial carcinomas. Mechanistically, this combination was associated with upregulation of nuclear and membrane progesterone receptors and produced a more pronounced reduction in viability than either agent alone; notably, the organoid experiments were performed at 100 nM for 72 h, supporting mechanistic interpretation of synergy but not direct extrapolation to clinically established exposure margins (214). The GLP-1/GIP dual agonist tirzepatide effectively reduced tumor growth in both obese and lean mice, and improved obesity-associated serum adiponectin, leptin and C-reactive protein levels in obese mice (69). Tirzepatide suppressed ErbB signaling and glycolysis/gluconeogenesis in obese mice, while enhancing O-linked glycosylation biosynthesis and phospholipase D signaling in lean mice, collectively inhibiting EC progression (69). However, not all observations support a uniformly protective role in EC. In one mechanistic study, GLP-1R expression was downregulated in EC tissues and cells, and GLP1R activation was reported to inhibit EC progression through activation of the cAMP/PKA pathway (184). Nevertheless, a later cohort study in individuals with T2D suggested a higher risk of EC with long-term use (>2 years) of GLP-1RAs (160). Thus, the role of GLP-1R signaling in EC remains context-dependent and requires further investigation.

A large cohort study of women with T2D revealed that short-term use of GLP-1RAs and dipeptidyl peptidase-4 (DPP4) inhibitors was not associated with reduced EC risk compared with sulfonylureas. However, use for >2 years was associated

with a higher risk of EC for GLP-1RAs [hazard ratio (HR), 2.47; 95% CI, 1.37-4.43] and for DPP4 inhibitors (HR, 1.63; 95% CI 1.14-2.34) (160). This observation reflects a long-term cancer risk association rather than a treatment-emergent adverse effect profile, and detailed adverse event data were not reported in the cited study.

The mechanisms underlying these contradictory effects remain unresolved. Studies on macrophages suggest that GLP-1RAs promote M2 polarization, potentially favoring tumor progression, which is a promising avenue for elucidating the dual roles of GLP-1Ras (127-131,215). Additionally, whether GIP receptor agonists can enhance the anticancer efficacy of GLP-1RAs warrants investigation in cohort and preclinical studies.

While responses to incretin-based therapies vary across cancer types, analysis of existing data reveals several shared mechanisms that may explain their particular potential in obesity-associated cancers: i) Direct metabolic intervention: Tumor cells, particularly those evolving in an obese microenvironment, may exhibit heightened sensitivity to alterations in metabolic conditions. By directly reducing circulating glucose and free fatty acid levels, and potentially enhancing hepatic fatty acid oxidation through GCGR agonism, these agents may deprive tumor cells of essential nutrients, thereby interfering with metabolic reprogramming processes (55,65,69,70). ii) Reversal of hyperinsulinemia: This represents one of the central mechanisms. Insulin and IGF-1 function as potent mitogenic signals. GLP-1RAs may counteract growth-promoting milieu through improved insulin sensitivity and reduced circulating insulin levels, which is particularly relevant in obesity- and diabetes-associated cancers, such as breast cancer, CRC and EC (75,80,81,176). iii) Attenuation of chronic inflammation: Chronic low-grade inflammation in obesity serves as a catalyst for tumorigenesis. GLP-1RAs demonstrate anti-inflammatory properties both systemically and within the TME (for example, by modulating macrophages and T cells, and reducing NETs as described in the present review), thereby suppressing the pro-tumor inflammatory milieu (105,108-110,121). iv) Modulation of adipokine secretion: Weight loss and adipose tissue reduction induced by GLP-1RAs alter adipokine secretion profiles, for example by shifting adiponectin- and leptin-related signals, which can directly influence tumor cell proliferation and invasion (69,131).

6. Conclusion

The present review systematically examines the roles of incretin and GCG signaling in tumor biology and their potential therapeutic value. By integrating fundamental research with clinical evidence, the main conclusions are summarized here.

Analysis of the basic biology of these three hormones reveals their interconnected metabolic regulatory networks mediated through shared signaling modules such as cAMP. Although the fundamental mechanisms of GLP-1, GIP and GCG are outlined in the present review, the subsequent discussion primarily focuses on GLP-1RAs, since the direct oncologic evidence for GIP and GCG remains comparatively limited.

Regarding the TME, current evidence indicates that GLP-1RAs modulate antitumor immunity through multiple cellular pathways. GLP-1RAs directly enhance NK cell cytotoxicity, promote DC antigen presentation, and ameliorate the immunosuppressive microenvironment by inhibiting NET formation and regulating macrophage polarization, thereby offering novel perspectives for combination immunotherapy. In addition, current evidence suggests that GLP-1RAs support antitumor T-cell immunity mainly through remodeling of the suppressive TME rather than through direct restoration of exhausted intratumoral $CD8^+$ T-cell function (108-111). GLP-1RAs also exert multidimensional and context-dependent effects on tumor metabolism. In addition to restraining tumor cell proliferation in selected preclinical models, they remodel the ECM through anti-fibrotic actions, thereby facilitating immune cell infiltration (156-159).

Simultaneously, their protective effects on mitochondrial function may enhance sensitivity to conventional therapy while potentially reducing treatment-related toxicity. Current human safety data obtained under approved therapeutic regimens are characterized predominantly by mild-to-moderate gastrointestinal adverse events rather than generalized cytotoxic toxicity, underscoring the need to distinguish preclinical pro-apoptotic observations from clinically established safety profiles.

Cancer-specific analyses confirm the context-dependent nature of these effects. GLP-1RAs demonstrate preventive and therapeutic potential in pancreatic cancer, hepatic cancer and CRC, require caution in MTC, and exhibit paradoxical effects in breast cancer and EC. The role of GCG further highlights the influence of metabolic context on hormone function; however, current evidence remains insufficient to support a direct antitumor effect of GCGR activation alone.

In summary, targeting GLP-1R, GIPR and GCGR signaling pathways provides novel directions for cancer therapy. Future studies should prioritize investigating GIP and GCG in oncology, while deepening the understanding of the dual effects of GLP-1RAs, establishing effective biomarker systems and ultimately enabling precise clinical applications.

Acknowledgements

The schematic figures were created by the authors using the online tool FigDraw.com.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

MH drafted the manuscript. CJJ prepared the figures and tables. CY discussed and critically revised the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
2. Shi R, Tang YQ and Miao H: Metabolism in tumor microenvironment: Implications for cancer immunotherapy. MedComm (2020) 1: 47-68, 2020.
3. Pearson-Stuttard J, Papadimitriou N, Markozannes G, Cividini S, Kakourou A, Gill D, Rizos EC, Monori G, Ward HA, Kyrgiou M, *et al*: Type 2 diabetes and cancer: An umbrella review of observational and mendelian randomization studies. Cancer Epidemiol Biomarkers Prev 30: 1218-1228, 2021.
4. Mili N, Paschou SA, Goulis DG, Dimopoulos MA, Lambrinoudaki I and Psaltopoulou T: Obesity, metabolic syndrome, and cancer: Pathophysiological and therapeutic associations. Endocrine 74: 478-497, 2021.
5. Andersen DK, Korc M, Petersen GM, Eibl G, Li D, Rickels MR, Chari ST and Abbruzzese JL: Diabetes, pancreatogenic diabetes, and pancreatic cancer. Diabetes 66: 1103-1110, 2017.
6. Hu Y, Zeng N, Ge Y, Wang D, Qin X, Zhang W, Jiang F and Liu Y: Identification of the shared gene signatures and biological mechanism in type 2 diabetes and pancreatic cancer. Front Endocrinol (Lausanne) 13: 847760, 2022.
7. Escala-Garcia M, Morra A, Canisius S, Chang-Claude J, Kar S, Zheng W, Bojesen SE, Easton D, Pharoah PDP and Schmidt MK: Breast cancer risk factors and their effects on survival: A Mendelian randomisation study. BMC Med 18: 327, 2020.
8. Seino Y and Yabe D: Glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1: Incretin actions beyond the pancreas. J Diabetes Investig 4: 108-130, 2013.
9. Nauck MA, Quast DR, Wefers J and Meier JJ: GLP-1 receptor agonists in the treatment of type 2 diabetes-state-of-the-art. Mol Metab 46: 101102, 2021.
10. Zhao S, Yan Z, Du Y, Li Z, Tang C, Jing L, Sun L, Yang Q, Tang X, Yuan Y, *et al*: A GLP-1/glucagon (GCG)/CCK_2 receptors tri-agonist provides new therapy for obesity and diabetes. Br J Pharmacol 179: 4360-4377, 2022.
11. Bossart M, Wagner M, Elvert R, Evers A, Hübschle T, Kloeckener T, Lorenz K, Moessinger C, Eriksson O, Velikyan I, *et al*: Effects on weight loss and glycemic control with SAR441255, a potent unimolecular peptide GLP-1/GIP/GCG receptor triagonist. Cell Metab 34: 59-74.e10, 2022.
12. Ligumsky H, Wolf I, Israeli S, Haimsohn M, Ferber S, Karasik A, Kaufman B and Rubinek T: The peptide-hormone glucagon-like peptide-1 activates cAMP and inhibits growth of breast cancer cells. Breast Cancer Res Treat 132: 449-461, 2012.
13. Liu ZZ, Duan XX, Yuan MC, Yu J, Hu X, Han X, Lan L, Liu BW, Wang Y and Qin JF: Glucagon-like peptide-1 receptor activation by liraglutide promotes breast cancer through NOX4/ROS/VEGF pathway. Life Sci 294: 120370, 2022.
14. Zhang Y, Xu F, Liang H, Cai M, Wen X, Li X and Weng J: Exenatide inhibits the growth of endometrial cancer Ishikawa xenografts in nude mice. Oncol Rep 35: 1340-1348, 2016.
15. Mayendraraj A, Rosenkilde MM and Gasbjerg LS: GLP-1 and GIP receptor signaling in beta cells-a review of receptor interactions and co-stimulation. Peptides 151: 170749, 2022.
16. Baggio LL and Drucker DJ: Biology of incretins: GLP-1 and GIP. Gastroenterology 132: 2131-2157, 2007.
17. Gribble FM and Reimann F: Signalling in the gut endocrine axis. Physiol Behav 176: 183-188, 2017.
18. Rorsman P and Ashcroft FM: Pancreatic β-cell electrical activity and insulin secretion: Of mice and men. Physiol Rev 98: 117-214, 2018.
19. Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B and Creutzfeldt W: Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia 36: 741-744, 1993.
20. Drucker DJ: Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metab 27: 740-756, 2018.
21. Siraj MA, Mundil D, Beca S, Momen A, Shikatani EA, Afroze T, Sun X, Liu Y, Ghaffari S, Lee W, *et al*: Cardioprotective GLP-1 metabolite prevents ischemic cardiac injury by inhibiting mitochondrial trifunctional protein-α. J Clin Invest 130: 1392-1404, 2020.
22. Ussher JR and Drucker DJ: Glucagon-like peptide 1 receptor agonists: Cardiovascular benefits and mechanisms of action. Nat Rev Cardiol 20: 463-474, 2023.
23. Montrose-Rafizadeh C, Avdonin P, Garant MJ, Rodgers BD, Kole S, Yang H, Levine MA, Schwindinger W and Bernier M: Pancreatic glucagon-like peptide-1 receptor couples to multiple G proteins and activates mitogen-activated protein kinase pathways in Chinese hamster ovary cells. Endocrinology 140: 1132-1140, 1999.
24. Hilger D, Masureel M and Kobilka BK: Structure and dynamics of GPCR signaling complexes. Nat Struct Mol Biol 25: 4-12, 2018.
25. Holz GG: Epac: A new cAMP-binding protein in support of glucagon-like peptide-1 receptor-mediated signal transduction in the pancreatic beta-cell. Diabetes 53: 5-13, 2004.
26. Fletcher MM, Halls ML, Christopoulos A, Sexton PM and Wootten D: The complexity of signalling mediated by the glucagon-like peptide-1 receptor. Biochem Soc Trans 44: 582-588, 2016.
27. Merola A, Romagnolo A, Rosso M, Lopez-Castellanos JR, Wissel BD, Larkin S, Bernardini A, Zibetti M, Maule S, Lopiano L and Espay AJ: Orthostatic hypotension in Parkinson's disease: Does it matter if asymptomatic? Parkinsonism Relat Disord 33: 65-71, 2016.
28. Liu L, Rashid M and Wess J: Regulation of GLP-1 and glucagon receptor function by β-arrestins in metabolically important cell types. Biochemistry 64: 978-986, 2025.
29. Zaïmia N, Obeid J, Varrault A, Sabatier J, Broca C, Gilon P, Costes S, Bertrand G and Ravier MA: GLP-1 and GIP receptors signal through distinct β-arrestin 2-dependent pathways to regulate pancreatic β cell function. Cell Rep 42: 113326, 2023.
30. Holmes B, Benavides-Serrato A, Freeman RS, Landon KA, Bashir T, Nishimura RN and Gera J: mTORC2/AKT/HSF1/HuR constitute a feed-forward loop regulating rictor expression and tumor growth in glioblastoma. Oncogene 37: 732-743, 2018.
31. Zheng Z, Zong Y, Ma Y, Tian Y, Pang Y, Zhang C and Gao J: Glucagon-like peptide-1 receptor: Mechanisms and advances in therapy. Signal Transduct Target Ther 9: 234, 2024.
32. Gasbjerg LS, Helsted MM, Hartmann B, Jensen MH, Gabe MBN, Sparre-Ulrich AH, Veedfald S, Stensen S, Lanng AR, Bergmann NC, *et al*: Separate and combined glucometabolic effects of endogenous glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 in healthy individuals. Diabetes 68: 906-917, 2019.
33. Mcintosh CH, Widenmaier S and Kim SJ: Glucose-dependent insulinotropic polypeptide signaling in pancreatic β-cells and adipocytes. J Diabetes Investig 3: 96-106, 2012.
34. Ding WG and Gromada J: Protein kinase A-dependent stimulation of exocytosis in mouse pancreatic beta-cells by glucose-dependent insulinotropic polypeptide. Diabetes 46: 615-621, 1997.
35. Kagdi S, Lyons SA and Beaudry JL: The interplay of glucose-dependent insulinotropic polypeptide in adipose tissue. J Endocrinol 261: e230361, 2024.
36. Ehses JA, Pelech SL, Pederson RA and McIntosh CH: Glucose-dependent insulinotropic polypeptide activates the Raf-Mek1/2-ERK1/2 module via a cyclic AMP/cAMP-dependent protein kinase/Rap1-mediated pathway. J Biol Chem 277: 37088-37097, 2002.
37. Widenmaier SB, Ao Z, Kim SJ, Warnock G and McIntosh CH: Suppression of p38 MAPK and JNK via Akt-mediated inhibition of apoptosis signal-regulating kinase 1 constitutes a core component of the beta-cell pro-survival effects of glucose-dependent insulinotropic polypeptide. J Biol Chem 284: 30372-30382, 2009.
38. Kim SJ, Winter K, Nian C, Tsuneoka M, Koda Y and McIntosh CH: Glucose-dependent insulinotropic polypeptide (GIP) stimulation of pancreatic beta-cell survival is dependent upon phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB) signaling, inactivation of the forkhead transcription factor Foxo1, and down-regulation of bax expression. J Biol Chem 280: 22297-22307, 2005.

39. Kim SJ, Nian C, Widenmaier S and McIntosh CH: Glucose-dependent insulinotropic polypeptide-mediated up-regulation of beta-cell antiapoptotic Bcl-2 gene expression is coordinated by cyclic AMP (cAMP) response element binding protein (CREB) and cAMP-responsive CREB coactivator 2. Mol Cell Biol 28: 1644-1656, 2008.
40. Asmar M, Asmar A, Simonsen L, Gasbjerg LS, Sparre-Ulrich AH, Rosenkilde MM, Hartmann B, Dela F, Holst JJ and Bülow J: The Gluco- and liporegulatory and vasodilatory effects of glucose-dependent insulinotropic polypeptide (GIP) are abolished by an antagonist of the human GIP receptor. Diabetes 66: 2363-2371, 2017.
41. Getty-Kaushik L, Song DH, Boylan MO, Corkey BE and Wolfe MM: Glucose-dependent insulinotropic polypeptide modulates adipocyte lipolysis and reesterification. Obesity (Silver Spring) 14: 1124-1131, 2006.
42. No authors listed: Correction to: 'Glucose-dependent insulinotropic polypeptide in incretin physiology: Role in health and disease'. Endocr Rev 46: 954, 2025.
43. Thorens B: Neuronal regulation of glucagon secretion and gluconeogenesis. J Diabetes Investig 13: 599-607, 2022.
44. Lee YH, Wang MY, Yu XX and Unger RH: Glucagon is the key factor in the development of diabetes. Diabetologia 59: 1372-1375, 2016.
45. Capozzi ME, D'Alessio DA and Campbell JE. The past, present, and future physiology and pharmacology of glucagon. Cell Metab 34: 1654-1674, 2022.
46. Li K, Qiu C, Sun P, Liu DC, Wu TJ, Wang K, Zhou YC, Chang XA, Yin Y, Chen F, *et al*: Ets1-mediated acetylation of FoxO1 Is critical for gluconeogenesis regulation during feed-fast cycles. Cell Rep 26: 2998-3010.e5, 2019.
47. Dominy JE Jr, Lee Y, Jedrychowski MP, Chim H, Jurczak MJ, Camporez JP, Ruan HB, Feldman J, Pierce K, Mostoslavsky R, *et al*: The deacetylase Sirt6 activates the acetyltransferase GCN5 and suppresses hepatic gluconeogenesis. Mol Cell 48: 900-913, 2012.
48. Gertler AA and Cohen HY: SIRT6, a protein with many faces. Biogerontology 14: 629-639, 2013.
49. Harney JA and Rodgers RL: Insulin-like stimulation of cardiac fuel metabolism by physiological levels of glucagon: Involvement of PI3K but not cAMP. Am J Physiol Endocrinol Metab 295: E155-E161, 2008.
50. Hansen LH, Gromada J, Bouchelouche P, Whitmore T, Jelinek L, Kindsvogel W and Nishimura E: Glucagon-mediated Ca2+ signaling in BHK cells expressing cloned human glucagon receptors. Am J Physiol 274: C1552-C1562, 1998.
51. Ozcan L, Wong CC, Li G, Xu T, Pajvani U, Park SK, Wronska A, Chen BX, Marks AR, Fukamizu A, *et al*: Calcium signaling through CaMKII regulates hepatic glucose production in fasting and obesity. Cell Metab 15: 739-751, 2012.
52. Liu Y, Dentin R, Chen D, Hedrick S, Ravnskjaer K, Schenk S, Milne J, Meyers DJ, Cole P, Yates J III, *et al*: A fasting inducible switch modulates gluconeogenesis via activator/coactivator exchange. Nature 456: 269-273, 2008.
53. Wondisford AR, Xiong L, Chang E, Meng S, Meyers DJ, Li M, Cole PA and He L: Control of Foxo1 gene expression by co-activator P300. J Biol Chem 289: 4326-4333, 2014.
54. Guzman CB, Zhang XM, Liu R, Regev A, Shankar S, Garhyan P, Pillai SG, Kazda C, Chalasani N and Hardy TA: Treatment with LY2409021, a glucagon receptor antagonist, increases liver fat in patients with type 2 diabetes. Diabetes Obes Metab 19: 1521-1528, 2017.
55. Shi T, Fan GQ and Xiao SD: SIRT3 reduces lipid accumulation via AMPK activation in human hepatic cells. J Dig Dis 11: 55-62, 2010.
56. Perry RJ, Zhang D, Guerra MT, Brill AL, Goedeke L, Nasiri AR, Rabin-Court A, Wang Y, Peng L, Dufour S, *et al*: Glucagon stimulates gluconeogenesis by INSP3R1-mediated hepatic lipolysis. Nature 579: 279-283, 2020.
57. Müller TD, Finan B, Clemmensen C, DiMarchi RD and Tschöp MH: The new biology and pharmacology of glucagon. Physiol Rev 97: 721-766, 2017.
58. Kim H, Mendez R, Chen X, Fang D and Zhang K: Lysine acetylation of CREBH regulates fasting-induced hepatic lipid metabolism. Mol Cell Biol 35: 4121-4134, 2015.
59. Rodgers RL: Glucagon, cyclic AMP, and hepatic glucose mobilization: A half-century of uncertainty. Physiol Rep 10: e15263, 2022.
60. Wang H, Zhao M, Sud N, Christian P, Shen J, Song Y, Pashaj A, Zhang K, Carr T and Su Q: Glucagon regulates hepatic lipid metabolism via cAMP and Insig-2 signaling: Implication for the pathogenesis of hypertriglyceridemia and hepatic steatosis. Sci Rep 6: 32246, 2016.
61. Winther JB and Holst JJ: Glucagon agonism in the treatment of metabolic diseases including type 2 diabetes mellitus and obesity. Diabetes Obes Metab 26: 3501-3512, 2024.
62. Wawrzak-Pienkowska K, Pienkowski T, Golonko A, Krupa A, Warpechowski M, Plonski AF, Mojsak P, Daniluk J, Dabrowski A and Kurek K: Incretin signaling at the crossroads of metabolism, inflammation, and tumorigenesis: Implications for obesity patients. Eur J Pharmacol 1007: 178290, 2025.
63. Miousse IR: GLP-1 receptor agonists in the context of cancer: The road ahead. Am J Physiol Cell Physiol 328: C1822-C1828, 2025.
64. Spezani R and Mandarim-de-Lacerda CA: The current significance and prospects for the use of dual receptor agonism GLP-1/Glucagon. Life Sci 288: 120188, 2022.
65. Zhou J, Cai X, Huang X, Dai Y, Sun L, Zhang B, Yang B, Lin H, Huang W and Qian H: A novel glucagon-like peptide-1/glucagon receptor dual agonist exhibits weight-lowering and diabetes-protective effects. Eur J Med Chem 138: 1158-1169, 2017.
66. Del Prato S, Gallwitz B, Holst JJ and Meier JJ: The incretin/glucagon system as a target for pharmacotherapy of obesity. Obes Rev 23: e13372, 2022.
67. Parker VER, Robertson D, Erazo-Tapia E, Havekes B, Phielix E, de Ligt M, Roumans KHM, Mevenkamp J, Sjoberg F, Schrauwen-Hinderling VB, *et al*: Cotadutide promotes glycogenolysis in people with overweight or obesity diagnosed with type 2 diabetes. Nat Metab 5: 2086-2093, 2023.
68. Sanchez-Pino MD, Gilmore LA, Ochoa AC and Brown JC: Obesity-associated myeloid immunosuppressive cells, key players in cancer risk and response to immunotherapy. Obesity (Silver Spring) 29: 944-953, 2021.
69. Kong W, Deng B, Shen X, John C, Haag J, Sinha N, Lee D, Sun W, Chen S, Zhang H, *et al*: Tirzepatide as an innovative treatment strategy in a pre-clinical model of obesity-driven endometrial cancer. Gynecol Oncol 191: 116-123, 2024.
70. Marathe SJ, Grey EW, Bohm MS, Joseph SC, Ramesh AV, Cottam MA, Idrees K, Wellen KE, Hasty AH, Rathmell JC and Makowski L: Incretin triple agonist retatrutide (LY3437943) alleviates obesity-associated cancer progression. NPJ Metab Health Dis 3: 10, 2025.
71. Huang X, Liu J, Peng G, Lu M, Zhou Z, Jiang N and Yan Z: Gut hormone multi-agonists for the treatment of type 2 diabetes and obesity: Advances and challenges. J Endocrinol 262: e230404, 2024.
72. Valencia-Rincón E, Rai R, Chandra V and Wellberg EA: GLP-1 receptor agonists and cancer: Current clinical evidence and translational opportunities for preclinical research. J Clin Invest 135: e194743, 2025.
73. Wang L, Xu R, Kaelber DC and Berger NA: Glucagon-like peptide 1 receptor agonists and 13 obesity-associated cancers in patients with type 2 diabetes. JAMA Netw Open 7: e2421305, 2024.
74. Ko A, Chang YC, Bahar F, Wang TH, Xanthavanij N, Yu CC, Hsieh RJ, See XY, Lo SW, Song J, *et al*: Risk for cancer with glucagon-like peptide-1 receptor agonists and dual agonists: A systematic review and meta-analysis. Ann Intern Med 179: 216-229, 2026.
75. Wang L, Wang W, Kaelber DC, Xu R and Berger NA: GLP-1 receptor agonists and colorectal cancer risk in drug-naive patients with type 2 diabetes, with and without overweight/obesity. JAMA Oncol 10: 256-258, 2024.
76. Silverii GA, Marinelli C, Bettarini C, Del Vescovo GG, Monami M and Mannucci E: GLP-1 receptor agonists and the risk for cancer: A meta-analysis of randomized controlled trials. Diabetes Obes Metab 27: 4454-4468, 2025.
77. Yamanouchi D: The roles of incretin hormones GIP and GLP-1 in metabolic and cardiovascular health: A comprehensive review. Int J Mol Sci 27: 27, 2025.
78. Ji L, He X, Min X, Yang H, Wu W, Xu H, Chen J and Mei A: Glucagon-like peptide-1 receptor agonists in neoplastic diseases. Front Endocrinol (Lausanne) 15: 1465881, 2024.
79. Lin A, Ding Y, Li Z, Jiang A, Liu Z, Wong HZH, Cheng Q, Zhang J and Luo P: Glucagon-like peptide 1 receptor agonists and cancer risk: advancing precision medicine through mechanistic understanding and clinical evidence. Biomark Res 13: 50, 2025.
80. Elkind-Hirsch KE, Chappell N, Shaler D, Storment J and Bellanger D: Liraglutide 3 mg on weight, body composition, and hormonal and metabolic parameters in women with obesity and polycystic ovary syndrome: A randomized placebo-controlled-phase 3 study. Fertil Steril 118: 371-381, 2022.

81. Sandsdal RM, Juhl CR, Jensen SBK, Lundgren JR, Janus C, Blond MB, Rosenkilde M, Bogh AF, Gliemann L, Jensen JB, *et al*: Combination of exercise and GLP-1 receptor agonist treatment reduces severity of metabolic syndrome, abdominal obesity, and inflammation: A randomized controlled trial. Cardiovasc Diabetol 22: 41, 2023.
82. Muzurović EM, Volčanšek Š, Tomšić KZ, Janež A, Mikhailidis DP, Rizzo M and Mantzoros CS: Glucagon-like peptide-1 receptor agonists and dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonists in the treatment of obesity/metabolic syndrome, prediabetes/diabetes and non-alcoholic fatty liver disease-current evidence. J Cardiovasc Pharmacol Ther 27: 10742484221146371, 2022.
83. Pandey S, Mangmool S, Madreiter-Sokolowski CT, Wichaiyo S, Luangmonkong T and Parichatikanond W: Exendin-4 protects against high glucose-induced mitochondrial dysfunction and oxidative stress in SH-SY5Y neuroblastoma cells through GLP-1 receptor/Epac/Akt signaling. Eur J Pharmacol 954: 175896, 2023.
84. Yagi T, Kubota E, Koyama H, Tanaka T, Kataoka H, Imaeda K and Joh T: Glucagon promotes colon cancer cell growth via regulating AMPK and MAPK pathways. Oncotarget 9: 10650-10664, 2018.
85. Carugno J, Marbin SJ, LaganÀ AS, Vitale SG, Alonso L, DI Spiezio Sardo A and Haimovich S: New development on hysteroscopy for endometrial cancer diagnosis: State of the art. Minerva Med 112: 12-19, 2021.
86. Kundu M, Butti R, Panda VK, Malhotra D, Das S, Mitra T, Kapse P, Gosavi SW and Kundu GC: Modulation of the tumor microenvironment and mechanism of immunotherapy-based drug resistance in breast cancer. Mol Cancer 23: 92, 2024.
87. De Visser KE and Joyce JA: The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. Cancer Cell 41: 374-403, 2023.
88. Li Z, Pai R, Gupta S, Currenti J, Guo W, Di Bartolomeo A, Feng H, Zhang Z, Li Z, Liu L, *et al*: Presence of onco-fetal neighborhoods in hepatocellular carcinoma is associated with relapse and response to immunotherapy. Nat Cancer 5: 167-186, 2024.
89. Ward PS and Thompson CB: Metabolic reprogramming: A cancer hallmark even warburg did not anticipate. Cancer Cell 21: 297-308, 2012.
90. Ghesquière B, Wong BW, Kuchnio A and Carmeliet P: Metabolism of stromal and immune cells in health and disease. Nature 511: 167-176, 2014.
91. Jing X, Yang F, Shao C, Wei K, Xie M, Shen H and Shu Y: Role of hypoxia in cancer therapy by regulating the tumor microenvironment. Mol Cancer 18: 157, 2019.
92. Colegio OR, Chu NQ, Szabo AL, Chu T, Rhebergen AM, Jairam V, Cyrus N, Brokowski CE, Eisenbarth SC, Phillips GM, *et al*: Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. Nature 513: 559-563, 2014.
93. Gabrilovich DI, Ostrand-Rosenberg S and Bronte V: Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol 12: 253-268, 2012.
94. Macintyre AN, Gerriets VA, Nichols AG, Michalek RD, Rudolph MC, Deoliveira D, Anderson SM, Abel ED, Chen BJ, Hale LP and Rathmell JC: The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. Cell Metab 20: 61-72, 2014.
95. van Vlerken-Ysla L, Tyurina YY, Kagan VE and Gabrilovich DI: Functional states of myeloid cells in cancer. Cancer Cell 41: 490-504, 2023.
96. You S, Li S, Zeng L, Song J, Li Z, Li W, Ni H, Xiao X, Deng W, Li H, *et al*: Lymphatic-localized Treg-mregDC crosstalk limits antigen trafficking and restrains anti-tumor immunity. Cancer Cell 42: 1415-1433.e12, 2024.
97. Zheng Y, Yao Y, Ge T, Ge S, Jia R, Song X and Zhuang A: Amino acid metabolism reprogramming: Shedding new light on T cell anti-tumor immunity. J Exp Clin Cancer Res 42: 291, 2023.
98. Lucente D, Bellino S and La Salvia A: GLP-1 receptor agonists in solid tumour therapy: Exploring their anticancer potential and underlying molecular pathways. Genes (Basel) 16: 1352, 2025.
99. Kounatidis D, Vallianou NG, Karampela I, Rebelos E, Kouveletsou M, Dalopoulos V, Koufopoulos P, Diakoumopoulou E, Tentolouris N and Dalamaga M: Anti-diabetic therapies and cancer: From bench to bedside. Biomolecules 14: 1479, 2024.
100. Ostroumov D, Fekete-Drimusz N, Saborowski M, Kühnel F and Woller N: CD4 and CD8 T lymphocyte interplay in controlling tumor growth. Cell Mol Life Sci 75: 689-713, 2018.
101. Farhood B, Najafi M and Mortezaee K: $CD8^+$ cytotoxic T lymphocytes in cancer immunotherapy: A review. J Cell Physiol 234: 8509-8521, 2019.
102. Wei J, Zheng W, Chapman NM, Geiger TL and Chi H: T cell metabolism in homeostasis and cancer immunity. Curr Opin Biotechnol 68: 240-250, 2021.
103. Deng S, Chen Z and Shi Y: Roles of glucagon-like peptide 1 receptor agonists in immune cell biology and autoimmune/autoinflammatory diseases. Cell Biosci 15: 137, 2025.
104. Ben Nasr M, Usuelli V, Dellepiane S, Seelam AJ, Fiorentino TV, D'Addio F, Fiorina E, Xu C, Xie Y, Balasubramanian HB, *et al*: Glucagon-like peptide 1 receptor is a T cell-negative costimulatory molecule. Cell Metab 36: 1302-1319.e12, 2024.
105. Moschovaki Filippidou F, Kirsch AH, Thelen M, Kétszeri M, Artinger K, Aringer I, Schabhüttl C, Mooslechner AA, Frauscher B, Pollheimer M, *et al*: Glucagon-like peptide-1 receptor agonism improves nephrotoxic serum nephritis by inhibiting T-cell proliferation. Am J Pathol 190: 400-411, 2020.
106. Wong CK, Yusta B, Koehler JA, Baggio LL, McLean BA, Matthews D, Seeley RJ and Drucker DJ: Divergent roles for the gut intraepithelial lymphocyte GLP-1R in control of metabolism, microbiota, and T cell-induced inflammation. Cell Metab 34: 1514-1531.e7, 2022.
107. Wong CK and Drucker DJ: Antiinflammatory actions of glucagon-like peptide-1-based therapies beyond metabolic benefits. J Clin Invest 135: e194751, 2025.
108. Stanisavljevic I, Pavlovic S, Simovic Markovic B, Jurisevic M, Krajnovic T, Mijatovic S, Spasojevic M, Mitrovic S, Corovic I and Jovanovic I: Semaglutide decelerates the growth and progression of breast cancer by enhancing the acquired antitumor immunity. Biomed Pharmacother 181: 117668, 2024.
109. Chen D, Li Q, Liang H, Huang L, Zhou H, Zheng X and Wang Z: Exenatide enhanced the antitumor efficacy on PD-1 blockade by the attenuation of neutrophil extracellular traps. Biochem Biophys Res Commun 619: 97-103, 2022.
110. Chen D, Liang H, Huang L, Zhou H and Wang Z: Liraglutide enhances the effect of checkpoint blockade in lung and liver cancers through the inhibition of neutrophil extracellular traps. FEBS Open Bio 14: 1365-1377, 2024.
111. Pachimatla AG, Fitzgerald B, Ogidigo J, Bhatia M, Smith RJ Jr, Ratnakaram K, Kalvapudi S, Vedire Y, Washington D, Vethanayagam Rr R, *et al*: Glucagon-like peptide-1 receptor agonism improves lung cancer outcomes and tumor growth control. JCI insight 10: e195484, 2025.
112. Fridlender ZG, Sun J, Kim S, Kapoor V, Cheng G, Ling L, Worthen GS and Albelda SM: Polarization of tumor-associated neutrophil phenotype by TGF-beta: 'N1' versus 'N2' TAN. Cancer Cell 16: 183-194, 2009.
113. Teijeira Á, Garasa S, Gato M, Alfaro C, Migueliz I, Cirella A, de Andrea C, Ochoa MC, Otano I, Etxeberria I, *et al*: CXCR1 and CXCR2 chemokine receptor agonists produced by tumors induce neutrophil extracellular traps that interfere with immune cytotoxicity. Immunity 52: 856-871.e8, 2020.
114. Kaltenmeier C, Yazdani HO, Morder K, Geller DA, Simmons RL and Tohme S: Neutrophil extracellular traps promote T cell exhaustion in the tumor microenvironment. Front Immunol 12: 785222, 2021.
115. Guo J, Shu T, Zhang H, Huang N, Ren J, Lin L, Wu J, Wang Y, Huang Z, Bin J, *et al*: A combined model of serum neutrophil extracellular traps, $CD8^+$ T cells, and tumor proportion score provides better prediction of PD-1 inhibitor efficacy in patients with NSCLC. FEBS J 291: 3403-3416, 2024.
116. Coënon L, Geindreau M, Ghiringhelli F, Villalba M and Bruchard M: Natural Killer cells at the frontline in the fight against cancer. Cell Death Dis 15: 614, 2024.
117. Chen S, Zhu H and Jounaidi Y: Comprehensive snapshots of natural killer cells functions, signaling, molecular mechanisms and clinical utilization. Signal Transduct Target Ther 9: 302, 2024.
118. De Barra C, Khalil M, Mat A, O'Donnell C, Shaamile F, Brennan K, O'Shea D and Hogan AE: Glucagon-like peptide-1 therapy in people with obesity restores natural killer cell metabolism and effector function. Obesity (Silver Spring) 31: 1787-1797, 2023.
119. Ogura K, Sato-Matsushita M, Yamamoto S, Hori T, Sasahara M, Iwakura Y, Saiki I, Tahara H and Hayakawa Y: NK cells control tumor-promoting function of neutrophils in mice. Cancer Immunol Res 6: 348-357, 2018.

120. Wang Y, Guo Z, Xu A, Fu Z, Hou Y, Tang K, Li J, Zhao F and Chen L: Mechanistic insights into IL-6-mediated NK cell dysfunction in NSCLC via the IRE1α-XBP1s-STAT3-UBE2S axis. NPJ Precis Oncol 9: 361, 2025.
121. Lu X, Xu C, Dong J, Zuo S, Zhang H, Jiang C, Wu J and Wei J: Liraglutide activates nature killer cell-mediated antitumor responses by inhibiting IL-6/STAT3 signaling in hepatocellular carcinoma. Transl Oncol 14: 100872, 2021.
122. Li S, Yu J, Huber A, Kryczek I, Wang Z, Jiang L, Li X, Du W, Li G, Wei S, *et al*: Metabolism drives macrophage heterogeneity in the tumor microenvironment. Cell Rep 39: 110609, 2022.
123. Laoui D, Van Overmeire E, Di Conza G, Aldeni C, Keirsse J, Morias Y, Movahedi K, Houbracken I, Schouppe E, Elkrim Y, *et al*: Tumor hypoxia does not drive differentiation of tumor-associated macrophages but rather fine-tunes the M2-like macrophage population. Cancer Res 74: 24-30, 2014.
124. Li M, Yang Y, Xiong L, Jiang P, Wang J and Li C: Metabolism, metabolites, and macrophages in cancer. J Hematol Oncol 16: 80, 2023.
125. Cassetta L and Pollard JW: Targeting macrophages: Therapeutic approaches in cancer. Nat Rev Drug Discov 17: 887-904, 2018.
126. Basak U, Sarkar T, Mukherjee S, Chakraborty S, Dutta A, Dutta S, Nayak D, Kaushik S, Das T and Sa G: Tumor-associated macrophages: An effective player of the tumor microenvironment. Front Immunol 14: 1295257, 2023.
127. Meurot C, Martin C, Sudre L, Breton J, Bougault C, Rattenbach R, Bismuth K, Jacques C and Berenbaum F: Liraglutide, a glucagon-like peptide 1 receptor agonist, exerts analgesic, anti-inflammatory and anti-degradative actions in osteoarthritis. Sci Rep 12: 1567, 2022.
128. Vinué Á, Navarro J, Herrero-Cervera A, García-Cubas M, Andrés-Blasco I, Martínez-Hervás S, Real JT, Ascaso JF and González-Navarro H: The GLP-1 analogue lixisenatide decreases atherosclerosis in insulin-resistant mice by modulating macrophage phenotype. Diabetologia 60: 1801-1812, 2017.
129. Shiraishi D, Fujiwara Y, Komohara Y, Mizuta H and Takeya M: Glucagon-like peptide-1 (GLP-1) induces M2 polarization of human macrophages via STAT3 activation. Biochem Biophys Res Commun 425: 304-308, 2012.
130. Yang L, Chen L, Li D, Xu H, Chen J, Min X, He M, Wu T, Zhong J, Yang H and Chen J: Effect of GLP-1/GLP-1R on the polarization of macrophages in the occurrence and development of atherosclerosis. Mediators Inflamm 2021: 5568159, 2021.
131. Hogan AE, Gaoatswe G, Lynch L, Corrigan MA, Woods C, O'Connell J and O'Shea D: Glucagon-like peptide 1 analogue therapy directly modulates innate immune-mediated inflammation in individuals with type 2 diabetes mellitus. Diabetologia 57: 781-784, 2014.
132. Wang S, Wang J, Chen Z, Luo J, Guo W, Sun L and Lin L: Targeting M2-like tumor-associated macrophages is a potential therapeutic approach to overcome antitumor drug resistance. NPJ Precis Oncol 8: 31, 2024.
133. Bruen R, Curley S, Kajani S, Crean D, O'Reilly ME, Lucitt MB, Godson CG, McGillicuddy FC and Belton O: Liraglutide dictates macrophage phenotype in apolipoprotein E null mice during early atherosclerosis. Cardiovasc Diabetol 16: 143, 2017.
134. Salkeni MA and Naing A: Interleukin-10 in cancer immunotherapy: From bench to bedside. Trends Cancer 9: 716-725, 2023.
135. Bułdak Ł, Bołdys A, Skudrzyk E, Machnik G and Okopień B: Liraglutide therapy in obese patients alters macrophage phenotype and decreases their tumor necrosis factor alpha release and oxidative stress markers-a pilot study. Metabolites 14: 554, 2024.
136. Rannikko JH and Hollmén M: Clinical landscape of macrophage-reprogramming cancer immunotherapies. Br J Cancer 131: 627-640, 2024.
137. Heras-Murillo I, Adán-Barrientos I, Galán M, Wculek SK and Sancho D: Dendritic cells as orchestrators of anticancer immunity and immunotherapy. Nat Rev Clin Oncol 21: 257-277, 2024.
138. Xiao Z, Wang R, Wang X, Yang H, Dong J, He X, Yang Y, Guo J, Cui J and Zhou Z: Impaired function of dendritic cells within the tumor microenvironment. Front Immunol 14: 1213629, 2023.
139. Liu Z, Dai H, Cui X, Liu Y and Dong Z: Importance of B cells (review). Int J Mol Med 57: 2, 2026.
140. Fridman WH, Meylan M, Petitprez F, Sun CM, Italiano A and Sautès-Fridman C: B cells and tertiary lymphoid structures as determinants of tumour immune contexture and clinical outcome. Nat Rev Clin Oncol 19: 441-457, 2022.
141. Yang Y, Chen X, Pan J, Ning H, Zhang Y, Bo Y, Ren X, Li J, Qin S, Wang D, *et al*: Pan-cancer single-cell dissection reveals phenotypically distinct B cell subtypes. Cell 187: 4790-4811. e22, 2024.
142. Sakimura C, Tanaka H, Okuno T, Hiramatsu S, Muguruma K, Hirakawa K, Wanibuchi H and Ohira M: B cells in tertiary lymphoid structures are associated with favorable prognosis in gastric cancer. J Surg Res 215: 74-82, 2017.
143. Baggio LL, Holland D, Wither J and Drucker DJ: Lymphocytic infiltration and immune activation in metallothionein promoter-exendin-4 (MT-Exendin) transgenic mice. Diabetes 55: 1562-1570, 2006.
144. Jin HR, Wang J, Wang ZJ, Xi MJ, Xia BH, Deng K and Yang JL: Lipid metabolic reprogramming in tumor microenvironment: From mechanisms to therapeutics. J Hematol Oncol 16: 103, 2023.
145. Moiz A, Filion KB, Tsoukas MA, Yu OHY, Peters TM and Eisenberg MJ: The expanding role of GLP-1 receptor agonists: A narrative review of current evidence and future directions. EClinicalMedicine 86: 103363, 2025.
146. Shigeoka T, Nomiyama T, Kawanami T, Hamaguchi Y, Horikawa T, Tanaka T, Irie S, Motonaga R, Hamanoue N, Tanabe M, *et al*: Activation of overexpressed glucagon-like peptide-1 receptor attenuates prostate cancer growth by inhibiting cell cycle progression. J Diabetes Investig 11: 1137-1149, 2020.
147. Eftekhari S, Montazeri H and Tarighi P: Synergistic anti-tumor effects of Liraglutide, a glucagon-like peptide-1 receptor agonist, along with Docetaxel on LNCaP prostate cancer cell line. Eur J Pharmacol 878: 173102, 2020.
148. He W and Li J: Exendin-4 enhances radiation response of prostate cancer. Prostate 78: 1125-1133, 2018.
149. Krause GC, Lima KG, Dias HB, da Silva EFG, Haute GV, Basso BS, Gassen RB, Marczak ES, Nunes RSB and de Oliveira JR: Liraglutide, a glucagon-like peptide-1 analog, induce autophagy and senescence in HepG2 cells. Eur J Pharmacol 809: 32-41, 2017.
150. Alanteet AA, Attia HA, Shaheen S, Alfayez M and Alshanawani B: Anti-proliferative activity of glucagon-like peptide-1 receptor agonist on obesity-associated breast cancer: The impact on modulating adipokines' expression in adipocytes and cancer cells. Dose Response 19: 1559325821995651, 2021.
151. Zhao H, Wei R, Wang L, Tian Q, Tao M, Ke J, Liu Y, Hou W, Zhang L, Yang J and Hong T: Activation of glucagon-like peptide-1 receptor inhibits growth and promotes apoptosis of human pancreatic cancer cells in a cAMP-dependent manner. Am J Physiol Endocrinol Metab 306: E1431-E1441, 2014.
152. Koehler JA, Kain T and Drucker DJ: Glucagon-like peptide-1 receptor activation inhibits growth and augments apoptosis in murine CT26 colon cancer cells. Endocrinology 152: 3362-3372, 2011.
153. Yuan Z, Li Y, Zhang S, Wang X, Dou H, Yu X, Zhang Z, Yang S and Xiao M: Extracellular matrix remodeling in tumor progression and immune escape: From mechanisms to treatments. Mol Cancer 22: 48, 2023.
154. Saatci O, Kaymak A, Raza U, Ersan PG, Akbulut O, Banister CE, Sikirzhytski V, Tokat UM, Aykut G, Ansari SA, *et al*: Targeting lysyl oxidase (LOX) overcomes chemotherapy resistance in triple negative breast cancer. Nat Commun 11: 2416, 2020.
155. Scavo MP, Lisco G, Depalo N, Rizzi F, Volpe S, Arrè V, Carrieri L, Notarnicola M, De Nunzio V, Curri ML, *et al*: Semaglutide modulates extracellular matrix production of LX-2 cells via exosomes and improves metabolic dysfunction-associated steatotic liver disease (MASLD). Int J Mol Sci 25: 1493, 2024.
156. Robinson E, Cassidy RS, Tate M, Zhao Y, Lockhart S, Calderwood D, Church R, McGahon MK, Brazil DP, McDermott BJ, *et al*: Exendin-4 protects against post-myocardial infarction remodelling via specific actions on inflammation and the extracellular matrix. Basic Res Cardiol 110: 20, 2015.
157. Huang L, Lin T, Shi M, Chen X and Wu P: Liraglutide suppresses production of extracellular matrix proteins and ameliorates renal injury of diabetic nephropathy by enhancing Wnt/β-catenin signaling. Am J Physiol Renal Physiol 319: F458-F468, 2020.
158. Liu J, Li X, Lu S, Zheng X, Zhang X and Zhao W: Glucagon-like peptide-1 (GLP-1) improved diabetic lung fibrosis via AMPK and microRNA-27a (miR-27a). Ann Transl Med 9: 492, 2021.

159. Song N, Xu H, Liu J, Zhao Q, Chen H, Yan Z, Yang R, Luo Z, Liu Q, Ouyang J, *et al*: Design of a highly potent GLP-1R and GCGR dual-agonist for recovering hepatic fibrosis. Acta Pharm Sin B 12: 2443-2461, 2022.
160. Yang F, Luo X, Li J, Lei Y, Zeng F, Huang X, Lan Y and Liu R: Application of glucagon-like peptide-1 receptor antagonists in fibrotic diseases. Biomed Pharmacother 152: 113236, 2022.
161. Cardoso LEM, Marinho TS, Martins FF, Aguila MB and Mandarim-de-Lacerda CA: Treatment with semaglutide, a GLP-1 receptor agonist, improves extracellular matrix remodeling in the pancreatic islet of diet-induced obese mice. Life Sci 319: 121502, 2023.
162. Du H, Xu T, Yu S, Wu S and Zhang J: Mitochondrial metabolism and cancer therapeutic innovation. Signal Transduct Target Ther 10: 245, 2025.
163. Patel PS, Castelow C, Patel DS, Bhattacharya SK, Kuscu C, Kuscu C, Makowski L, Eason JD and Bajwa A: Mitochondrial role in oncogenesis and potential chemotherapeutic strategy of mitochondrial infusion in breast cancer. Int J Mol Sci 23: 12993, 2022.
164. Zhang Y, Yan H, Wei Y and Wei X: Decoding mitochondria's role in immunity and cancer therapy. Biochim Biophys Acta Rev Cancer 1879: 189107, 2024.
165. Kiweler N, Delbrouck C, Pozdeev VI, Neises L, Soriano-Baguet L, Eiden K, Xian F, Benzarti M, Haase L, Koncina E, *et al*: Mitochondria preserve an autarkic one-carbon cycle to confer growth-independent cancer cell migration and metastasis. Nat Commun 13: 2699, 2022.
166. Morales PE, Torres G, Sotomayor-Flores C, Peña-Oyarzún D, Rivera-Mejías P, Paredes F and Chiong M: GLP-1 promotes mitochondrial metabolism in vascular smooth muscle cells by enhancing endoplasmic reticulum-mitochondria coupling. Biochem Biophys Res Commun 446: 410-416, 2014.
167. Liao P, Yang D, Liu D and Zheng Y: GLP-1 and ghrelin attenuate high glucose/high lipid-induced apoptosis and senescence of human microvascular endothelial cells. Cell Physiol Biochem 44: 1842-1855, 2017.
168. Zhang L, Tian J, Diao S, Zhang G, Xiao M and Chang D: GLP-1 receptor agonist liraglutide protects cardiomyocytes from IL-1β-induced metabolic disturbance and mitochondrial dysfunction. Chem Biol Interact 332: 109252, 2020.
169. Wang C, Li Q, Wang W, Guo L, Guo C, Sun Y and Zhang J: GLP-1 contributes to increases in PGC-1α expression by down-regulating miR-23a to reduce apoptosis. Biochem Biophys Res Commun 466: 33-99, 2015.
170. Yamada S, Ogura Y, Inoue K, Tanabe J, Sugaya T, Ohata K, Nagai Y, Natsuki Y, Hoshino S, Watanabe S, *et al*: Effect of GLP-1 receptor agonist, liraglutide, on muscle in spontaneously diabetic torii fatty rats. Mol Cell Endocrinol 539: 111472, 2022.
171. Li X, Luo W, Tang Y, Wu J, Zhang J, Chen S, Zhou L, Tao Y, Tang Y, Wang F, *et al*: Semaglutide attenuates doxorubicin-induced cardiotoxicity by ameliorating BNIP3-mediated mitochondrial dysfunction. Redox Biol 72: 103129, 2024.
172. Old VJ, Davies MJ, Papamargaritis D, Choudhary P and Watson EL: The effects of glucagon-like peptide-1 receptor agonists on mitochondrial function within skeletal muscle: A systematic review. J Cachexia Sarcopenia Muscle 16: e13677, 2025.
173. Luna-Marco C, de Marañon AM, Hermo-Argibay A, Rodriguez-Hernandez Y, Hermenejildo J, Fernandez-Reyes M, Apostolova N, Vila J, Sola E, Morillas C, *et al*: Effects of GLP-1 receptor agonists on mitochondrial function, inflammatory markers and leukocyte-endothelium interactions in type 2 diabetes. Redox Biol 66: 102849, 2023.
174. Krause GC, Lima KG, Levorse V, Haute GV, Gassen RB, Garcia MC, Pedrazza L, Donadio MVF, Luft C and de Oliveira JR: Exenatide induces autophagy and prevents the cell regrowth in HepG2 cells. EXCLI J 18: 540-548, 2019.
175. Wang L, Berger NA, Kaelber DC and Xu R: Association of GLP-1 receptor agonists and hepatocellular carcinoma incidence and hepatic decompensation in patients with type 2 diabetes. Gastroenterology 167: 689-703, 2024.
176. Rothman SM, Yin H, Yu OHY, Pollak M and Azoulay L: Incretin-based drugs and the incidence of endometrial cancer among people with type 2 diabetes: Active comparator new-user design. Drug Saf 48: 1023-1033, 2025.
177. Kolotkin RL, Fujioka K, Wolden ML, Brett JH and Bjorner JB: Improvements in health-related quality of life with liraglutide 3.0 mg compared with placebo in weight management. Clin Obes 6: 233-242, 2016.
178. Wharton S, Calanna S, Davies M, Dicker D, Goldman B, Lingvay I, Mosenzon O, Rubino DM, Thomsen M, Wadden TA and Pedersen SD: Gastrointestinal tolerability of once-weekly semaglutide 2.4 mg in adults with overweight or obesity, and the relationship between gastrointestinal adverse events and weight loss. Diabetes Obes Metab 24: 94-105, 2022.
179. Dankner R, Murad H, Agay N, Olmer L and Freedman LS: Glucagon-like peptide-1 receptor agonists and pancreatic cancer risk in patients with type 2 diabetes. JAMA Netw Open 7: e2350408, 2024.
180. Monami M, Nreu B, Scatena A, Cresci B, Andreozzi F, Sesti G and Mannucci E: Safety issues with glucagon-like peptide-1 receptor agonists (pancreatitis, pancreatic cancer and cholelithiasis): Data from randomized controlled trials. Diabetes Obes Metab 19: 1233-1241, 2017.
181. Zhao HJ, Jiang X, Hu LJ, Yang L, Deng LD, Wang YP and Ren ZP: Activation of GLP-1 receptor enhances the chemosensitivity of pancreatic cancer cells. J Mol Endocrinol 64: 103-113, 2020.
182. Mao D, Cao H, Shi M, Wang CC, Kwong J, Li JJX, Hou Y, Ming X, Lee HM, Tian XY, *et al*: Increased co-expression of PSMA2 and GLP-1 receptor in cervical cancer models in type 2 diabetes attenuated by exendin-4: A translational case-control study. EBioMedicine 65: 103242, 2021.
183. Zhang Y, Cheng J, Li J, He J, Li X and Xu F: The GLP-1R agonist exendin-4 attenuates hyperglycemia-induced chemoresistance in human endometrial cancer cells through ROS-mediated mitochondrial pathway. Front Oncol 11: 793530, 2021.
184. Li W, Gu Y, Liu S, Ruan F and Lv W: GLP1R inhibits the progression of endometrial carcinoma through activation of cAMP/PKA pathway. J Clin Lab Anal 36: e24604, 2022.
185. Byrd RA, Sorden SD, Ryan T, Pienkowski T, LaRock R, Quander R, Wijsman JA, Smith HW, Blackbourne JL, Rosol TJ, *et al*: Chronic toxicity and carcinogenicity studies of the long-acting GLP-1 receptor agonist dulaglutide in rodents. Endocrinology 156: 2417-2428, 2015.
186. Mao T, Zhang C, Yang S, Bi Y, Li M and Yu J: Semaglutide alters gut microbiota and improves NAFLD in db/db mice. Biochem Biophys Res Commun 710: 149882, 2024.
187. Chen BD, Zhao WC, Jia QA, Zhou WY, Bu Y, Wang ZZ, Wang F, Wu WJ and Wang Q: Effect of the GLP-1 analog exendin-4 and oxaliplatin on intrahepatic cholangiocarcinoma cell line and mouse model. Int J Mol Sci 14: 24293-24304, 2013.
188. Kissow H, Hartmann B, Holst JJ, Viby NE, Hansen LS, Rosenkilde MM, Hare KJ and Poulsen SS: Glucagon-like peptide-1 (GLP-1) receptor agonism or DPP-4 inhibition does not accelerate neoplasia in carcinogen treated mice. Regul Pept 179: 91-100, 2012.
189. Iwaya C, Nomiyama T, Komatsu S, Kawanami T, Tsutsumi Y, Hamaguchi Y, Horikawa T, Yoshinaga Y, Yamashita S, Tanaka T, *et al*: Exendin-4, a glucagonlike peptide-1 receptor agonist, attenuates breast cancer growth by inhibiting NF-κB activation. Endocrinology 158: 4218-4232, 2017.
190. Ligumsky H, Amir S, Arbel Rubinstein T, Guion K, Scherf T, Karasik A, Wolf I and Rubinek T: Glucagon-like peptide-1 analogs activate AMP kinase leading to reversal of the Warburg metabolic switch in breast cancer cells. Med Oncol 41: 138, 2024.
191. Dai H, Li Y, Lee YA, Lu Y, George TJ, Donahoo WT, Lee KP, Nakshatri H, Allen J, Guo Y, *et al*: GLP-1 receptor agonists and cancer risk in adults with obesity. JAMA Oncol 11: 1186-1193, 2025.
192. Pasternak B, Wintzell V, Hviid A, Eliasson B, Gudbjörnsdottir S, Jonasson C, Hveem K, Svanström H, Melbye M and Ueda P: Glucagon-like peptide 1 receptor agonist use and risk of thyroid cancer: Scandinavian cohort study. BMJ 385: e078225, 2024.
193. Bezin J, Gouverneur A, Pénichon M, Mathieu C, Garrel R, Hillaire-Buys D, Pariente A and Faillie JL: GLP-1 receptor agonists and the risk of thyroid cancer. Diabetes Care 46: 384-390, 2023.
194. Feier CVI, Vonica RC, Faur AM, Streinu DR and Muntean C: Assessment of thyroid carcinogenic risk and safety profile of GLP1-RA semaglutide (ozempic) therapy for diabetes mellitus and obesity: A systematic literature review. Int J Mol Sci 25: 4346, 2024.
195. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, Sanyal AJ, Sejling AS and Harrison SA; NN9931-4296 Investigators: A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 384: 1113-1124, 2021.
196. Abrahami D, Yin H, Yu OHY, Pollak MN and Azoulay L: Incretin-based drugs and the incidence of colorectal cancer in patients with type 2 diabetes. Epidemiology 29: 246-253, 2018.

197. Figlioli G, Piovani D, Peppas S, Pugliese N, Hassan C, Repici A, Lleo A, Aghemo A and Bonovas S: Glucagon-like peptide-1 receptor agonists and risk of gastrointestinal cancers: A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 208: 107401, 2024.
198. Piccoli GF, Mesquita LA, Stein C, Aziz M, Zoldan M, Degobi NAH, Spiazzi BF, Lopes Junior GL, Colpani V and Gerchman F: Do GLP-1 receptor agonists increase the risk of breast cancer? A systematic review and meta-analysis. J Clin Endocrinol Metab 106: 912-921, 2021.
199. Sun Y, Liu Y, Dian Y, Zeng F, Deng G and Lei S: Association of glucagon-like peptide-1 receptor agonists with risk of cancers-evidence from a drug target Mendelian randomization and clinical trials. Int J Surg 110: 4688-4694, 2024.
200. Wang L, Wang Q, Li L, Kaelber DC and Xu R: Glucagon-like peptide-1 receptor agonists and pancreatic cancer risk: Target trial emulation using real-world data. J Natl Cancer Inst 117: 476-485, 2025.
201. Bjerre Knudsen L, Madsen LW, Andersen S, Almholt K, de Boer AS, Drucker DJ, Gotfredsen C, Egerod FL, Hegelund AC, Jacobsen H, *et al*: Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology 151: 1473-1486, 2010.
202. He L, Zhang S, Zhang X, Liu R, Guan H and Zhang H: Effects of insulin analogs and glucagon-like peptide-1 receptor agonists on proliferation and cellular energy metabolism in papillary thyroid cancer. Onco Targets Ther 10: 5621-5631, 2017.
203. Sherman SI, Kloos RT, Tuttle RM, Pontecorvi A, Völzke H, Harper K, Vance C, Alston JT, Usborne AL, Sloop KW and Lakshmanan M: No calcitonin change in a person taking dulaglutide diagnosed with pre-existing medullary thyroid cancer. Diabet Med 35: 381-385, 2018.
204. Wang J and Kim CH: Differential risk of cancer associated with glucagon-like peptide-1 receptor agonists: Analysis of real-world databases. Endocr Res 47: 18-25, 2022.
205. Espinosa De Ycaza AE, Brito JP, McCoy RG, Shao H and Singh Ospina N: Glucagon-like peptide-1 receptor agonists and thyroid cancer: A narrative review. Thyroid 34: 403-418, 2024.
206. Koehler JA and Drucker DJ: Activation of glucagon-like peptide-1 receptor signaling does not modify the growth or apoptosis of human pancreatic cancer cells. Diabetes 55: 1369-1379, 2006.
207. Kojima M, Takahashi H, Kuwashiro T, Tanaka K, Mori H, Ozaki I, Kitajima Y, Matsuda Y, Ashida K, Eguchi Y and Anzai K: Glucagon-like peptide-1 receptor agonist prevented the progression of hepatocellular carcinoma in a mouse model of nonalcoholic steatohepatitis. Int J Mol Sci 21: 5722, 2020.
208. Sun Y, Fan L, Meng J, Zhang F, Zhang D and Mei Q: Should GLP-1 receptor agonists be used with caution in high risk population for colorectal cancer? Med Hypotheses 82: 255-256, 2014.
209. Elsaid MI, Li N, Firkins SA, Rustgi VK, Paskett ED, Acharya C, Reddy KR, Chiang CW and Mumtaz K: Impacts of glucagon-like peptide-1 receptor agonists on the risk of adverse liver outcomes in patients with metabolic dysfunction-associated steatotic liver disease cirrhosis and type 2 diabetes. Aliment Pharmacol Ther 59: 1096-1110, 2024.
210. Tong G, Peng T, Chen Y, Sha L, Dai H, Xiang Y, Zou Z, He H and Wang S: Effects of GLP-1 receptor agonists on biological behavior of colorectal cancer cells by regulating PI3K/AKT/mTOR signaling pathway. Front Pharmacol 13: 901559, 2022.
211. Ma B, Wang X, Ren H, Li Y, Zhang H, Yang M and Li J: High glucose promotes the progression of colorectal cancer by activating the BMP4 signaling and inhibited by glucagon-like peptide-1 receptor agonist. BMC Cancer 23: 594, 2023.
212. Zhu C, Lai Y, Liu C, Teng L, Zhu Y, Lin X, Fu X, Lai Q, Liu S, Zhou X and Fang Y: Comprehensively prognostic and immunological analyses of GLP-1 signaling-related genes in pan-cancer and validation in colorectal cancer. Front Pharmacol 15: 1387243, 2024.
213. Xu Y, Ni F, Sun D, Peng Y, Zhao Y, Wu X, Li S, Qi X, He X, Li M, *et al*: Glucagon enhances chemotherapy efficacy by inhibition of tumor vessels in colorectal cancer. Adv Sci (Weinh) 11: e2307271, 2024.
214. Hagemann AR, Hagemann IS, Mutch DG, Devor EJ, Malmrose PK, Zhang Y, Morrison AM, Thiel KW and Leslie KK: Enhancing progestin therapy with a glucagon-like peptide 1 agonist for the conservative management of endometrial cancer. Cancers (Basel) 17: 598, 2025.
215. Bułdak Ł, Machnik G, Bułdak RJ, Łabuzek K, Bołdys A, Belowski D, Basiak M and Okopień B: Exenatide (a GLP-1 agonist) expresses anti-inflammatory properties in cultured human monocytes/macrophages in a protein kinase A and B/Akt manner. Pharmacol Rep 68: 329-337, 2016.