

# Role of glucagon-like peptide-1 receptor in cancer: Mechanisms and pharmacologic intervention (Review)

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**Abstract.** The glucagon-like peptide-1 (GLP-1) receptor, a G-protein-coupled receptor distributed in multiple tissues, can regulate the homeostasis of blood glucose and lipids. GLP-1 receptor agonist (GLP-1RA) has been recognized as an effective hypoglycemic drug. The disruption of metabolic processes in diabetes may lead to dysregulation of numerous signaling pathways, thereby promoting the development of malignant tumors. Therefore, the activity of the GLP-1 receptor may contribute to the development of cancer. Over the years, advancements have been made in understanding the inhibitory effect of GLP-1RAs on tumorigenesis. Activation of the GLP-1 receptor can inhibit tumorigenesis by reducing neuroinflammation and oxidative stress, modulating the tumor immune microenvironment and enhancing the chemosensitivity. In addition, GLP-1RAs also regulate the activity of several related signaling pathways involved in tumorigenesis (such as the AMPK, PI3K/Akt and cAMP/PKA pathways). In the present review, a comprehensive review of the distribution of GLP-1 receptors and the pharmacological effects of GLP-1RAs is provided. The intrinsic relationship between GLP-1 receptors and cancer risk is also discussed, as well as the mechanisms of GLP-1RAs in inhibiting cancer, with the aim to provide valuable insights for the treatment of cancer using GLP-1RAs.

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## 1. Introduction

Glucagon-like peptide-1 (GLP-1) receptor is a kind of G-protein-coupled receptor that is widely distributed in multiple tissues, including the pancreas, gastrointestinal tract, brain and cardiovascular system (1-3). GLP-1, a natural agonist of GLP-1 receptor, is an endogenous insulinotropic hormone synthesized and secreted by L cells of the small intestine, which can regulate the homeostasis of insulin and blood glucose, as well as appetite (4). GLP-1 receptor agonist (GLP-1RA) has been recognized as an effective hypoglycemic drug. Various GLP-1RAs, such as semaglutide, liraglutide and exendin-4, have been applied in the clinical treatment of diabetes mellitus (DM). Moreover, studies have revealed that GLP-1RAs can not only lower glucose, but also exhibit various additional effects, including anti-inflammatory activity (5), neuroprotective effect (6), pain relief (7) and improvement of retinopathy (8). Therefore, the question has been posed: Can GLP-1RAs affect the progression of cancer?

DM is one of the most common metabolic diseases and numerous signaling pathways may dysregulate following the disruption of metabolic processes (9), thereby promoting the development of malignant tumors, such as breast and pancreatic cancer, and malignancy of the digestive system (10-12). Therefore, controlling blood glucose might be effective for the treatment of cancer. Whether GLP-1RAs play a role in inhibiting the development of tumors is worthy of investigation. Numerous clinical studies suggest the association between GLP-1RAs and cancer risk; however, the conclusions are not entirely consistent. Several results revealed that GLP-1 RAs use may be associated with an increased risk of thyroid (13), colorectal (14) and triple negative breast cancer (15); however, other findings suggested that GLP-1RAs is unlikely to be associated with an increased risk of cancers (pancreatic, thyroid and colorectal cancer) (16-18). More findings supported that GLP-1RAs can reduce the risk of cancers (19-21), and the mechanisms may relate to directly reducing tumor size and weight, suppressing the proliferation and migration of tumor

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**Key words:** glucagon-like peptide-1 receptor, agonists, pharmacological effects, cancer, high glucose

cells, inhibiting inflammation and oxidative stress, regulating tumor immune microenvironment and enhancing chemosensitivity (22-25). Although there are some limitations, notable advances have been made in understanding the mechanisms of GLP-IRAs and their application in cancer.

The present review systematically presents the distribution of GLP-1 receptors, the pharmacological effects of GLP-IRAs, the association between GLP-1 receptors and cancer risk, as well as the mechanisms of GLP-IRAs in inhibiting cancer, with the aim to provide valuable insights for the treatment of cancer using GLP-IRAs.

## 2. Distribution and expression of GLP-1 receptors in tumors

GLP-1 receptors are widely distributed in human tissues. For example, they are expressed in nerve fibers from the gastric corpus to the distal large intestine in the gastrointestinal tract of mice (3). GLP-1 receptors are notably expressed in the proximal duodenum and the distal end of the colonic segment (26), with the highest levels in the Brunner's gland of the duodenum (2,3). GLP-1 receptors may also express in the intraepithelial lymphocytes and the enteroendocrine cells of intestinal mucosa (3,27) and in the colonic smooth muscle cells (28). In the stomach, GLP-1 receptors are presented in the gastric corpus mucous neck cells, which morphologically identified as parietal cells, and in the enteroendocrine-like cells of the pyloric glands (3,29). The GLP-1 receptor protein expression was qualitatively and quantitatively investigated in gastric adenocarcinoma (n=20) and colorectal cancer (n=21) tissues with receptor autoradiography using <sup>125</sup>I-GLP-1 (7-36) amide. The result showed that no expression of GLP-1 receptor was detected (1); however, the absence of detectable receptor expression does not exclude the possibility that the GLP-1 receptor plays a role in the transformation of gastrointestinal tumors. Moreover, the study did not specify the tumor stage of the gastric/colorectal tumor tissues. It is hypothesized that GLP-1 receptor expression is downregulated or lost during malignant transformation, suggesting a negative association between GLP-1 receptor and the development of gastrointestinal tumors.

Furthermore, GLP-1 receptors are also express in other organs. In the thyroid, GLP-1 receptors are colocalized with C-cells and are more notable in neoplastic- and hyperplastic lesions of thyroid C-cells and in papillary thyroid cancer than in normal thyroid cells (30,31), suggesting the relationship between the GLP-1 receptor and neoplastic transformation in thyroid, especially papillary and medullary thyroid carcinoma. In the pancreas, GLP-1 receptors are predominantly observed in almost all  $\beta$ -cells and rarely in  $\alpha$ - and  $\delta$ -cells (23). RNA *in situ* hybridization was used to quantify GLP-1R RNA in surgically resected human pancreatic specimens (n=32), including pancreatic ductal adenocarcinoma (PDAC), pancreatic intraepithelial neoplasia (PanIN) and non-neoplastic ductal, acinar and endocrine cells. The expression of GLP-1 receptor in PanIN and PDAC was not significantly different from that in non-neoplastic cells (32). Another study using autoradiography did not detect the GLP-1 receptor protein expression in 21 cases of PDAC tissues (1). These results suggest that progression from normal pancreatic cells to

PanINs and eventually PDAC may be unrelated to changes in GLP-1R expression; however, this conclusion is not sufficiently supported by the available evidence. Since GLP-1 receptors are mainly expressed on endocrine cells in the pancreas, they may mediate the development of PDAC through indirect regulation of metabolism or immunity.

A study using double-labeling fluorescence detected that GLP-1 receptors are localized in myocytes of the sinoatrial node of the heart in human and monkey tissues (2). Other studies using immunohistochemistry (IHC) and immunoelectron microscopy to analyze liver biopsies obtained from rats (n=6) and patients with non-alcoholic hepatitis (n=3), the results showed that GLP-1 receptors are present in hepatocytes, some endothelial and Kupffer cells, monocytes (33,34), as well as nerve terminals of the hepatic portal system (35). The GLP-1 receptor protein expression was investigated in hepatocellular carcinomas (HCC; n=16) and intrahepatic cholangiocarcinoma (ICC) (n=17) tissues with receptor autoradiograph, and the results showed that no expression of GLP-1 receptor was detected (1). The observation that normal hepatocytes express the GLP-1 receptor while HCC does not, may suggest that changes in receptor expression are associated with the process of hepatocyte malignant transformation. However, ICC tissues and tissues around tumor from patients with ICC (n=176) were investigated for GLP-1 receptor expression by IHC and western blots in another study, and high GLP-1R expression levels were detected in tumor tissues (36). The results suggest that progression of ICC may associate with an increase in GLP-1R expression. However, this finding contradicts the previous result. The discrepancy could be due to differences in tumor stage and differentiation, or to variations in the site of tissue sampling; however, the study did not provide a detailed discussion of this issue. The inclusion criteria for future studies should be more strictly regarding the tumor stage, differentiation and specific location of the tumor tissues.

In the lung and kidney, GLP-1 receptors are only found to be expressed in arteriolar vascular smooth muscle cells (2,37). Using autoradiography did not detect the GLP-1 receptor protein expression in non-small cell lung carcinomas (n=20), small cell lung carcinomas (n=20) and renal cell carcinomas (n=20) (1). The result suggests that changes in GLP-1 receptor expression may be negatively associated with the process of lung/kidney malignant transformation. Furthermore, GLP-1 receptors have been detected in human breast cancer tissue and cell lines (38), as well as prostate cancer cell lines (39,40). In addition, GLP-1 receptors are also detected in the nervous system, including telencephalon, hypothalamus, brain stem and hippocampus (41-44), dorsal horn and dorsal root ganglia (45,46). A study revealed that GLP-1 receptors are notably expressed in brain tumors, including astrocytoma, meningioma and glioblastoma (1), suggesting the expression of GLP-1 receptors may be related to the development of tumors in nervous system. The distribution and expression of GLP-1 receptors in cancer cells is summarized in Table I.

Overall, GLP-1 receptor expression in tumors is either notable or lost, suggesting that changes in receptor expression may be associated with the process of tumor transformation.

Table I. Summary of the distribution and expression of the glucagon-like peptide-1 receptor in tissues and cancer cells.

| Tissues         | Species              | Cell localization                                                                                               | Expression in cancer cells                                                               | Methods of detection                                                                    | (Refs.)   |
|-----------------|----------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------|
| Stomach         | Human, mouse         | Gastric corpus mucous neck cells (parietal cells), enteroendocrine cells in the pyloric glands                  | Not detected in gastric adenocarcinoma                                                   | Autoradiography, IHC, RT-PCR and IHC double staining                                    | (1,3,29)  |
| Duodenum        | Human, monkey, mouse | Brunner's gland                                                                                                 | -                                                                                        | Autoradiography, IHC, double-labeling fluorescence, <i>in situ</i> hybridization        | (2,3)     |
| Intestine       | Mouse, rat           | Intraepithelial lymphocytes, enteroendocrine cells                                                              | -                                                                                        | Autoradiography, IHC, double-labeling fluorescence, <i>in situ</i> hybridization        | (3,27)    |
| Colon           | Mouse, rat           | Lymphocytes, enteroendocrine cells, smooth muscle cells                                                         | Not detected in colorectal cancer                                                        | Autoradiography, IHC, RT-PCR, western blot                                              | (1,3,28)  |
| Thyroid         | Human                | C-cells                                                                                                         | Upregulated in papillary thyroid carcinoma and medullary thyroid carcinoma               | IHC and western blot                                                                    | (30,31)   |
| Pancreas        | Human, monkey, mouse | $\beta$ -cells                                                                                                  | Not detected in pancreatic ductal adenocarcinoma                                         | Autoradiography, IHC, double-labeling fluorescence, quantitative micro-PET/CT           | (2,3,32)  |
| Heart           | Human, monkey        | Myocytes of the sinoatrial node                                                                                 | -                                                                                        | IHC, double-labeling fluorescence                                                       | (2)       |
| Liver           | Human, rat           | Hepatocytes, endothelial, and some Kupffer cells, monocytes, nerve terminals in the hepatic portal system       | Upregulated in intrahepatic cholangiocarcinoma, not detected in hepatocellular carcinoma | Autoradiography, RT-PCR, IHC, double-labeling fluorescence                              | (1,33-36) |
| Lung and Kidney | Human, monkey, mouse | Arteriolar vascular smooth muscle cells                                                                         | Not detected in lung carcinoma and renal cell carcinoma                                  | Autoradiography, IHC, double-labeling fluorescence, RT-PCR                              | (1,2,37)  |
| Breast          | Human                | -                                                                                                               | Upregulated in breast cancer                                                             | RT-PCR, immunofluorescence staining                                                     | (38)      |
| Prostate        | Human                | -                                                                                                               | Upregulated in prostate cancer                                                           | RT-PCR, western blot                                                                    | (39,40)   |
| Brain           | Human, mouse, rat    | Neuron, microglia, astrocyte in telencephalon, brain stem and hippocampus, neuron and astrocyte in hypothalamus | Upregulated in astrocytoma, meningioma, and glioblastoma                                 | Autoradiography, IHC, immunofluorescence staining                                       | (1,41-44) |
| Spinal cord     | Mouse                | Microglia in dorsal horn, neuron in dorsal root ganglia                                                         | -                                                                                        | Fluorescent <i>in situ</i> hybridization, immunofluorescence immuno-electron microscopy | (45,46)   |

RT-PCR, reverse transcription PCR; IHC, immunohistochemistry.

However, these results are mostly derived from a single study, which did not provide a detailed description of the specific tumor stage, degree of differentiation, or site of tissue sampling. Furthermore, the difference may be due to the insufficient

research on the expression of the GLP-1 receptor in various tumors. In the future, further analysis of the expression of the GLP-1 receptor in various tumors and stricter inclusion criteria should be included.

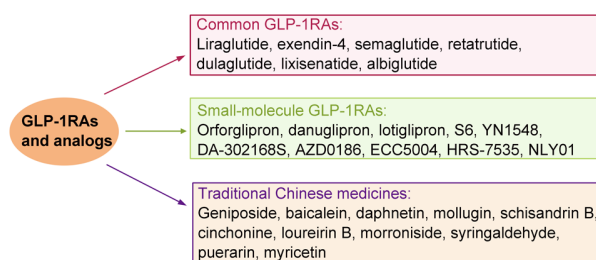


Figure 1. Compounds related with GLP-1 receptor agonistic activity. There are three major categories about the compounds with GLP-1 receptor agonistic activity, including common GLP-1RAs (such as liraglutide, exendin-4 and semaglutide), several novel small-molecule agonists (such as orforglipron, danuglipron and lotiglipron), and some traditional Chinese medicines (such as geniposide, baicalein and daphnetin). GLP-1, glucagon-like peptide-1; GLP-1RA, GLP-1 receptor agonist.

### 3. Related compounds with GLP-1 receptor agonistic activity

There are three major categories concerning the compounds with GLP-1 receptor agonistic activity, including common GLP-1RAs, several novel small-molecule agonists and some natural products. Liraglutide, exendin-4 and semaglutide are the most extensively studied drugs among GLP-1RAs and have emerged as novel effective hypoglycemic agents. Other GLP-1RAs, such as retatrutide, dulaglutide, lixisenatide and albiglutide, can also reduce the blood glucose and lipid levels (47-50). Several novel small-molecule GLP-1RAs, such as S6, orforglipron, danuglipron and lotiglipron, may be applied in oral treatment for diabetes and obesity (51-54). In addition, several traditional Chinese medicines (baicalein, cinchonine, daphnetin and geniposide) may also exhibit GLP-1 receptor agonistic activity (55-58). These reagents are summarized in Fig. 1.

It is noteworthy that these natural medicines possess anti-tumor effects. For example, baicalein can inhibit the proliferation, migration and invasion of cancer cells in various tumors (59-61). These mechanisms are related to inducing apoptosis, autophagy and ferroptosis (62,63), enhancing the sensitivity to cisplatin (64) and suppressing some pathways (such as the PI3K/Akt, TGF- $\beta$ /FTO/ZEB1, Wnt/ $\beta$ -catenin and STAT3 pathways) (65-68). Myricetin can also inhibit the progression of gastric cancer (69) and HCC (70,71), by suppressing the PI3K/Akt pathway, thereby stimulating autophagy and apoptosis (72). Furthermore, other studies revealed that other natural products, such as daphnetin, geniposide, puerarin and schisandrin B, may also exert anti-cancer effects by regulating GLP-1 receptor activation. Daphnetin can suppress the survival of lung adenocarcinoma, hepatic and ovarian cells by reducing antioxidant and inflammatory reactions and regulating the JNK/STAT3/NF- $\kappa$ B, Wnt/ $\beta$ -catenin and AMPK/Akt/mTOR pathways (73-77). Geniposide may inhibit colorectal cancer and HCC by inducing ferroptosis, reducing inflammation and downregulating the PI3K/Akt pathway (78-81). Puerarin can reduce the proliferation and migration of colorectal and lung cancer cells by suppressing the PI3K/Akt pathway and enhancing the sensitivity to cisplatin, 5-FU and oxaliplatin (82-85). In addition, schisandrin B can ameliorate the

viability of HCC, colorectal and breast cancer cells, possibly related to decreasing the expression of IL-1 $\beta$ , STAT3, SIRT1 and exosomal fibronectin 1 (86-90). However, only a single study has identified that cinchonine, loureirin B, mollugin, morroniside and syringaldehyde may have anti-cancer effects, and their mechanisms remain unclear.

These mechanisms of natural products in inhibiting cancer are summarized in Table II. The functions of these GLP-1RA analogs provide new research directions for future exploration in treating cancer, such as the anti-cancer effects of several natural medicines (Cinchonine, loureirin B, mollugin, morroniside and syringaldehyde), the related mechanisms including inflammation, ferroptosis, and oxidative stress, as well as some key signaling pathways (such as PI3K/Akt, Wnt/ $\beta$ -catenin and AMPK/Akt/mTOR pathways).

### 4. Protective effects of GLP-1RAs on multiple tissues: Implications for cancer inhibition

GLP-1RAs exhibit a variety of effects beyond lowering blood glucose and lipids, including cardiopulmonary protection, hepatoprotection, eye protection, anti-cancer and others. Here, the protective effects of GLP-1RAs in multiple tissues are summarized to provide assistance in exploring the anti-tumor mechanisms of GLP-1RAs.

In the heart, geniposide and exendin-4 have been found to suppress myocardial inflammation and myocyte apoptosis in obese mice (91), reduce cardiac interstitial fibrosis in mice with myocardial infarction (92) and decrease the recurrence of arrhythmia following atrial fibrillation ablation in patients who are obese (93) possibly related to activating the MKK3 and Akt-1 pathways (92). Exendin-4 are also effective in treating vascular diseases, such as vascular calcification and thrombus formation (94,95). The mechanisms are related to suppressing the proliferation and migration of vascular smooth muscle cells, decreasing reactive oxygen species (ROS) levels (95) and inhibiting M1 macrophage polarization (96). In the lung, liraglutide can ameliorate fibrosis by increasing the surfactant proteins and decreasing the collagen levels in bleomycin-induced rats (97) and can also alleviate acute lung injury by maintaining endothelial barrier function and modulating pyroptosis in lipopolysaccharide-induced mice and ischemia-reperfusion rats (98,99).

In the liver, liraglutide plays a role in improving hepatic steatosis in diabetic fatty rats and reducing hepatotoxicity in valproic acid- and atorvastatin-treated rats, the mechanisms are related to decreasing oxidative stress (100), reducing the expression of liver enzymes, attenuating histopathological alterations and suppressing inflammation and necroptosis (101,102). In the kidney, semaglutide and liraglutide can inhibit glomerular hypertrophy and renal fibrosis in diabetic mice by suppressing inflammatory responses, normalizing mitochondrial morphology and function and downregulating the TLR4/MyD88/NF- $\kappa$ B pathway (103,104). In the muscle and bone, semaglutide has been found to improve skeletal muscle atrophy in mice (105). In addition, exendin-4 has been shown to enhance bone volume and collagen quality to improve bone strength and structure in mice (106).

As a therapeutic agent for diabetes, geniposide and dulaglutide also exhibit beneficial effects on diabetic retinopathy

Table II. Mechanisms of several glucagon-like peptide-1 receptor agonist-like natural compounds in cancer.

| Name          | Molecular weight, kDa | Models                                                                                               | Biological activities                                                                                                                                                                                                       | (Refs.) |
|---------------|-----------------------|------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Baicalein     | 270.24                | MCF-7 cell, HGC-27 and AGS cells, HCT116 and DLD1 cells, colorectal and gastric cancer mice          | Inhibits the proliferation, migration and invasion of cancer cells, induces apoptosis, autophagy and ferroptosis, enhances the sensitivity to cisplatin, blocks the PI3K/Akt, JAK2/STAT3 and Wnt/ $\beta$ -catenin pathways | (62-68) |
| Daphnetin     | 178.14                | A549 cell, hepatocellular carcinoma rat                                                              | Inhibits the proliferation, migration, invasion of cancer cells and colony formation, reduces inflammation and oxidative stress, suppresses the JNK/STAT3/NF- $\kappa$ B pathway                                            | (73-77) |
| Geniposide    | 388.37                | Colorectal cancer mouse, Huh7 and HepG2 cells                                                        | Attenuates the proliferation, invasion and migration of cancer cells, induces ferroptosis, reverses oxaliplatin resistance, inhibits the PI3K/Akt pathway                                                                   | (78-81) |
| Myricetin     | 318.24                | Huh7, HepG2 and Hep3B cells, HepG2 cell xenografted mouse                                            | Inhibits proliferation, invasion, metastasis of cancer cells, stimulates autophagy, suppresses the PI3K/Akt/mTOR, p38 MAPK and STAT3 pathways                                                                               | (69-72) |
| Puerarin      | 416.38                | Colorectal cancer cells and mouse                                                                    | Reduces the proliferation and migration of cancer cells, promotes apoptosis, enhances the sensitivity to 5-FU and oxaliplatin, suppresses the PI3K/Akt pathway                                                              | (82-85) |
| Schisandrin B | 400.48                | HepG2, HCCLM3, MDA-MB-231, and Hs-578T cells, HCCLM3 cell xenografted mouse, colorectal cancer mouse | Suppresses the proliferation, invasion, migration and colony formation of cancer cells, reduces the expression of exosomal fibronectin 1, SIRT1 and IL-1 $\beta$                                                            | (86-90) |

and dry eye, the mechanisms may relate to improving retinal thickness, morphology and vascular ultrastructure in diabetic mice (48), reducing ROS accumulation and inflammatory cytokines and activating the Nrf2 pathway (58). In a mouse model of hypertensive glaucoma, NLY01 can rescue retinal ganglion cells and inhibit the activation of microglia/macrophage and A1 astrocyte (107,108). In the nervous system, GLP-1 levels are decrease in mice with Alzheimer's disease (109), and lixisenatide can protect against memory impairment through the activation of the PKA/CREB pathway and the inhibition of the p38 MAPK pathway (110). Furthermore, semaglutide and exendin-4 have been found to mitigate brain injury in middle cerebral artery occlusion-induced rats (111), improve depression in repeated restraint stress-induced mice (42), alleviate pain (112) and suppress nerve fiber injury and demyelination in mice (113). The mechanisms are related to inhibiting inflammation, autophagy, neuronal apoptosis and ferroptosis, improving mitochondrial function (42,111,114), reversing glial activation (113) and activating the pAMPK pathway and inhibiting the NLRP3 pathway (115). Moreover, semaglutide and liraglutide may have other uncommon effects, such as improving testicular injury (116), facilitating wound healing (117) and reducing alcohol intake (118). A brief description is listed in Fig. 2.

In summary, these findings demonstrate that GLP-1RAs exert protective effects on multiple tissues, with mechanisms involving the inhibition of inflammatory responses, glial activation and oxidative stress, as well as the regulation of multiple signaling pathways (Akt-1, PKA/CREB, p38, NF- $\kappa$ B,). Since cancer occurs in multiple tissues, these mechanisms may also contribute to the alleviation of cancer by GLP-1Ras; however, most of these results are from *in vivo* studies. Although the majority of animal studies did not find side effects of GLP-1RA, a handful of preclinical studies showed that GLP-1RAs increase heart rate, induce gastrointestinal disturbances (nausea, vomiting and diarrhea) and pancreatitis (119). GLP-1RAs may also lead to an increased risk of biliary disease (119), thyroid (13) and colorectal cancer (14). Since patients receiving GLP-1RA therapy often have concomitant risk factors for diseases (notably obesity, longer diabetes duration and co-medication), future clinical studies should more strictly control the inclusion criteria to clarify the side effects of GLP-1RAs. Furthermore, liraglutide has been on the market for >10 years, but some real-world data on the association between liraglutide and cancer have been available for only 6 years (13,20); therefore, the longer-term studies are also a welcome direction.

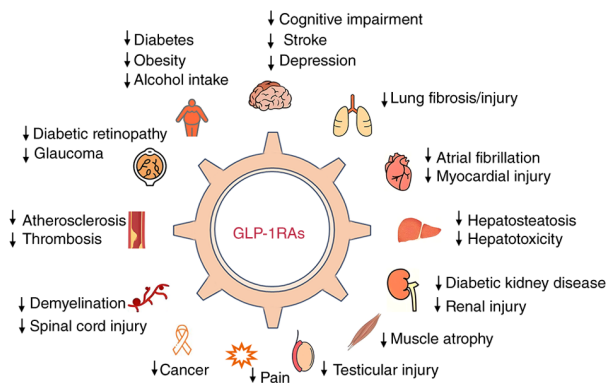


Figure 2. Effects of GLP-1Rs on different tissues. GLP-1Rs exhibit a variety of effects beyond lowering blood glucose and lipids, including alleviating neurological diseases (such as cognitive impairment, stroke, depression, demyelination and spinal cord injury), inhibiting the formation of atherosclerosis and thrombosis, improving diabetic retinopathy and glaucoma, relieving cardiac and pulmonary injuries (such as myocardial infarction, atrial fibrillation and lung fibrosis), reducing hepatosteatosis and hepatotoxicity, alleviating diabetic kidney disease and renal injury, improving muscle atrophy and testicular injury, relieving pain and treating cancer. GLP-1RA, glucagon-like peptide-1 receptor agonist.

## 5. Potential pathways of GLP-1RAs in cancer treatment: Lowering glucose

Activation of the GLP-1 receptor plays a role in regulating glucose homeostasis, and GLP-1RAs have been applied in the treatments for DM. Therefore, questions have been raised such as are there correlations between high glucose (HG) and cancer, and can the inhibition of GLP-1RAs on HG affect the development of cancer?

HG is a risk factor for cancer, a study obtained female breast cancer burden attributable to HG from 1990 to 2021 showed that 4.62% of female breast cancer deaths (30,000) globally is attributed to HG (10), a prospective cohort study among 53,747 participants suggested that HG is an independent factor in malignancy of the digestive system (12), another case-control study revealed that the risk of pancreatic cancer increases with rising blood glucose levels (11). Studies in various types of cancer have further confirmed that HG can promote tumor progression. For example, HG can promote the invasion/migration of PDAC cells, possibly through the upregulation of hypoxia inducible factor 1 $\alpha$  (120) and activation of ROS/MMP-3 (121), as well as by contributing to gemcitabine resistance (121). Studies in HCC and cholangiocarcinoma (CCA) suggest that HG can promote cell proliferation by increasing IL-1 $\beta$  (122) and ROS expression (123). Furthermore, the high expression of NCAPD2 (124), forkhead box protein M1 (FOXM1) (125) and ribosome binding protein 1 (RRBP1) (126) may also associate with the progression of HCC. In breast cancer specimens and cells, HG can enhance tumor proliferation by stimulating angiogenesis, increasing inflammatory factors and tumor associated macrophage infiltration and decreasing thrombospondin-1 levels (127,128). In addition, HG can enhance colorectal cancer cell proliferation and migration by activating the PI3K/AKT/mTOR pathway (129). HG may also play a role in the development of lung adenocarcinoma by activating the epidermal growth factor receptor/signal transducer and

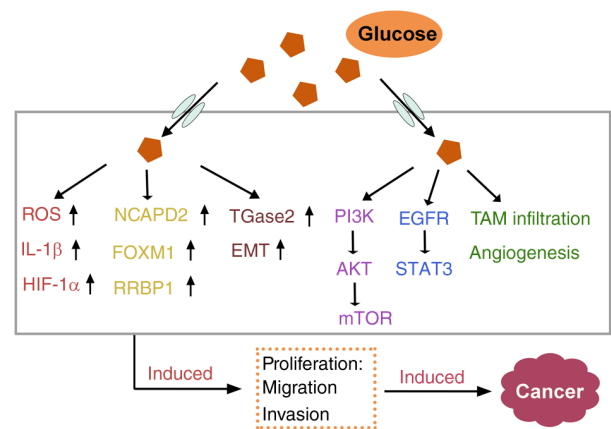


Figure 3. Potential pathways of high glucose involvement in the development of cancer. High glucose can promote proliferation, invasion and migration of cancer cells. The mechanisms are related to the increase of ROS, IL-1 $\beta$  and HIF1 $\alpha$ , the upregulation of NCAPD2, FOXM1, RRBPI and TGase2, the promotion of EMT and TAM infiltration, the stimulation of angiogenesis and the activation of PI3K/AKT/mTOR and EGFR/STAT3 pathways. NCAPD2, non-smc condensin I complex subunit D2; ROS, reactive oxygen species; HIF-1 $\alpha$  hypoxia inducible factor-1 $\alpha$ ; FOXM1, forkhead box protein M1; RRBPI, ribosome-binding protein 1; TGase2, transglutaminase 2; EMT, epithelial-mesenchymal-transition; TAM, tumor associated macrophage.

activator of transcription 3 (EGFR/STAT3) pathway (130). Furthermore, HG can increase the activation of ROS and transglutaminase 2 and promote epithelial-mesenchymal transition (EMT) to facilitate tumor development in ovarian and prostate cancer (131,132). These possible mechanisms by which HG induces tumorigenesis are summarized in Fig. 3. Therefore, controlling blood glucose may be a useful way to inhibit tumor development.

## 6. Intrinsic link between GLP-1 receptors and cancer

Numerous studies in patients with diabetes and/or obesity have demonstrated that activation of GLP-1 receptor may reduce cancer risk. Subsequently, experiments have discovered the potential mechanisms of GLP-1RAs in suppressing cancer. The present section summarizes these findings to elucidate the relationship between GLP-1 receptors and cancer, with the aim to be helpful for the treatment of cancer.

**Pancreatic cancer.** A retrospective cohort study included 167,091 patients with diabetes who were prescribed GLP-1RAs found that GLP-1RAs may reduce the risk of pancreatic cancer (20). Another multicenter, retrospective cohort study included 492,760 patients with diabetes and/or who were overweight or obese who were newly treated with GLP-1As (exenatide, liraglutide and dulaglutide) or metformin for the first time between 2006 and 2021. The result showed that taking GLP-1As was associated with a lower risk of pancreatic cancer compared with taking metformin (133). In mice with pancreatic cancer and fibroblasts isolated from patients with PDAC, the GLP-1RA semaglutide can inhibit stromal deposition in PDAC and allow T lymphocyte infiltration, thereby reducing tumor development (134). Exendin-4 can also inhibit tumor proliferation, migration and invasion, lead to the inactivation of pancreatic stellate cells and suppress the

deposition of extracellular matrix in PANC-1 cells and xenografted mice (135). Data from MIA PaCa-2 and PANC-1 cells revealed that activation of the GLP-1 receptor by liraglutide can increase the sensitivity to gemcitabine (25) and suppress cell metastasis by inhibiting the PI3K/Akt pathway (136). These animal/cellular results suggest that GLP-IRAs may indirectly inhibit tumor progression by regulating immunity, improving stromal effects or modulating signaling pathways. Alternatively, another study showed that GLP-1R expression (semi-quantitatively evaluated by IHC) in 48 PDAC samples, demonstrated positive expression in 23 tumors and negative expression in 25 tumors; no correlations were found between GLP-1R expression and clinicopathological characteristics of PDAC (137). This contrary conclusion may be due to the insufficient sample size ( $n=48$ ). Moreover, the study suggested that GLP-1 receptor knockdown may reduce the proliferation, migration and invasion of CFPAC-1 cells (137). The discrepancy may be due to variations in research models and experimental methods, and *in vivo* experiments may be necessary for further validation. More large-sample, long-term clinical studies should be conducted to further clarify the correlation between GLP-IRAs and pancreatic cancer, and animal/cell experiments should be carried out to determine whether GLP-IRAs act directly on tumor cells.

**Breast cancer.** Some *in vitro* and *in vivo* research has demonstrated that GLP-IRAs can inhibit breast cancer. In mice with 4T1 breast cancer, semaglutide can decelerate the growth of breast cancer and enhance the acquired anti-tumor immune response by increasing the accumulation and maturation of CD11c(+) dendritic cells and stimulating the cytotoxic capacity of CD8(+) T cells (22). Exendin-4 and liraglutide can also inhibit the proliferation and migration of breast cancer cells by activating the cAMP and AMPK pathways (138). Studies in human breast cancer cell lines and xenograft breast cancer mice demonstrate that exendin-4 can markedly decrease cancer cell number, tumor weight and size (38,139) by inhibiting the activation of NF- $\kappa$ B and decreasing the phosphorylation of Akt and I $\kappa$ B (38). Moreover, treatment with GLP-1 or exendin-4 can enhance the apoptosis of breast cancer cells by elevating the cAMP and CREB levels (140). In addition, studies in Ehrlich's ascitic carcinoma-treated mice and MCF-7 cells suggest that liraglutide can inhibit cell growth (24,141) by decreasing the levels of inflammatory mediators (24) and promote the apoptosis of MCF-7 cells by inhibiting the expression of miR-27a and increasing the expression of AMP-activated protein kinase catalytic subunit  $\alpha$ 2 protein (142). However, a study presented contrary result that liraglutide can accelerate the progression of cancer in human triple negative breast cancer cells (MDA-MB-231 and MDA-MB-468, 100 nM), which was replicated *in vivo* (400  $\mu$ g/kg) (143). Furthermore, another study suggested that liraglutide can stimulate the growth of triple negative cell line MDA-MB-231 (15). Both results were derived from highly invasive triple negative breast cancer cells, suggesting that GLP-IRAs may have no protective effect against triple-negative breast cancer. However, there are few clinical studies on the correlation between GLP-1 receptors and breast cancer. It is recommended that more clinical trials and *in vivo* experiments focused on the correlation between GLP-IRAs and breast cancer should be conducted in the

future. In addition, cancer tissues of different histological types and different clinical stages should be included.

**Thyroid cancer.** A retrospective cohort study among 98,142 patients with thyroid nodules treated with GLP-1 analogues (ATC A10BJ) from 1995 to 2024 revealed that there is a low incidence of thyroid cancer compared with those on metformin (19). However, another retrospective cohort study involving 7,746 patients with diabetes treated with GLP-IRAs for 6 years showed an increased risks of thyroid cancer compared with 124,371 metformin-only users and 36,146 insulin-only users (13). Similarly, a nested case-control analysis also suggested that GLP-IRAs increase the risk of thyroid cancer (144); however, these two studies did not analyze whether the patients had thyroid nodule, which can affect the incidence of thyroid cancer. In addition, the studies did not distinguish which type of GLP-IRAs were involved, such as liraglutide, semaglutide or exendin-4, nor did they describe the dosage used. These factors may lead to the differences in the results.

Several *in vitro* and *in vivo* research has explored the effects of GLP-IRAs in inhibiting thyroid cancer. For example, in papillary thyroid carcinoma mice and THP-1 cells, semaglutide and liraglutide can reduce tumor size and inhibit the proliferation and migration of cancer cells (145,146). The related mechanisms may involve the inhibition of the PI3K/Akt/mTOR pathway (146), the upregulation of M1 macrophages and the reduction in M2 macrophages through the regulation of the PPARG/ACSL1 signaling pathway (145). Furthermore, GLP-1 receptors are expressed in medullary thyroid cancer tissues (31), but the underlying mechanism of the effect of GLP-1 receptors on medullary thyroid cancer has not been fully investigated. Overall, research on the role and specific mechanisms of the GLP-1 receptor in thyroid cancer remains limited, and the results are not entirely consistent. In the future, more clinical studies and various thyroid cancer animal models should be included. The patient inclusion criteria, drugs, doses and study design should be more strictly controlled.

**HCC and CCA.** GLP-1 receptors are widely expressed in the liver (hepatocytes, endothelial cells and Kupffer cells) (33,34), but are not detected in HCC (1), suggesting that GLP-1 receptor activity may be negatively associated with liver cancer. Activation of the GLP-1 receptor may exert a protective effect on the liver. A large population-based matched cohort study of patients with diabetes treated with GLP-IRAs (exenatide, liraglutide, dulaglutide, lixisenatide, albiglutide and semaglutide) showed a reduced risk of CCA development (147). Similarly, another retrospective cohort included 47,578 patients with diabetes treated with semaglutide also showed a reduced risk of HCC (148). Some animal studies have explored the inhibitory effects and mechanisms of GLP-IRAs, liraglutide and exendin-4, in HCC and CCA. For example, a study in CCA mice suggested that liraglutide can reduce tumor volume and weights and suppress the migration of cancer cells by inhibiting the EMT and Akt/STAT3 signaling pathway (149). Moreover, liraglutide can suppress HCC by downregulating neutrophil extracellular traps (NETs) and ROS of neutrophils in Hepa1-6 tumor-bearing mice (23), enhancing NK-mediated

cytotoxicity, and inhibiting the IL-6/STAT3 pathway in HCC cells (150). A study in diabetic mice revealed that liraglutide can ameliorate steatosis, inflammation and hepatocyte swelling to suppress the development of HCC (151). In addition, GLP-1 can reduce HCC cell migration through inhibition of the SAPK/JNK pathway (18). Studies in HCC and CCA mice showed that exendin-4 can inhibit tumor cell proliferation and promote apoptosis (152,153) by activating the cAMP/PKA pathway and downregulating the expression of EGFR and STAT3 (152). These *in vivo* results suggest that GLP-1RAs indirectly inhibits HCC through immune modulation, inflammatory and stromal regulation. Whether GLP-1RAs have direct effect on HCC cells still lacks in-depth cellular evidence. An *in vitro* experiment provides evidence that GLP-1RAs have no direct effect on hepatocytes, hepatic stellate cells or Kupffer cells (154), which also supports that the protective effect of GLP-1RAs may be secondary to the improvement in glucose metabolism. These findings providing a foundation for further investigation into GLP-1RAs as therapeutic targets for cancers.

**Colorectal cancer.** GLP-1 receptors are not detected in colorectal cancer (1); therefore, this poses the question are GLP-1 receptors related to the development of colorectal cancer? Studies have shown that the expression of GLP-1, the natural agonist of the GLP-1 receptors, was lower in patients with colorectal cancer than age-matched healthy controls (155). The GLP-1R expression was absent in both human colon cancer tissues and colon cancer cell lines, as determined by IHC analysis (156). These results suggest a negative association between the activity of the GLP-1 receptor and the development of colorectal cancer. A cohort study suggested that the use of GLP-1RAs (exenatide, liraglutide, dulaglutide, lixisenatide and semaglutide) in patients with obesity and diabetes is associated with a lower risk for colorectal cancer (21). Since GLP-1 receptors are expressed in the colonic lymphocytes, enteroendocrine cells and smooth muscle cells (28), the protective effect of GLP-1RAs maybe not a direct action on tumor cells but rather secondary to improve metabolism. Several *in vitro* and *in vivo* studies have explored the mechanisms by which GLP-1RAs inhibit colon cancer. For example, in colorectal cancer cell lines, semaglutide can impair the migration of cells (157). Studies in colorectal cancer mice and cell lines have shown that liraglutide can suppress the growth and promote the apoptosis of cancer cells by downregulating bone morphogenetic protein 4 (BMP4) (158), activating the TGF- $\beta$ /Smad3 pathway (159) and inhibiting the PI3K/Akt/mTOR pathway (160). Exendin-4 can increase fibroblast growth factor 7 (Fgf7) levels in colonic polyps to regulate gut growth and intestinal tumorigenesis in mice (161), induce apoptosis and inhibit the proliferation of CT26 colon cancer cells by increasing intracellular cAMP expression and inhibiting glycogen synthase kinase 3 and ERK1/2 signaling activity (162). Moreover, the reduction of colonic energy metabolism, and the upregulation of endoplasmic reticulum-stress and oxygen levels have been revealed in GLP-1R knockout mice (163). These findings suggest that GLP-1RAs may indirectly inhibit tumor progression by regulating immunity, modulating signaling pathways and improving colonic energy metabolism.

However, current findings are inconsistent, and evidence suggest that the risk of colorectal cancer is elevated among patients treated with GLP-1RAs compared with other drugs such as DPP-4 or metformin (164). Patients receiving GLP-1RA therapy often accompanied by obesity, which is a direct risk factor for colorectal cancer. This factor may be contributed to the bias in the result. In the future, inclusion criteria should be more strictly controlled, and long-term studies are also a welcome direction to further clarify the effect of GLP-1RAs on colorectal cancer.

**Endometrial cancer.** Several studies have demonstrated the mechanisms of GLP-1RAs in inhibiting endometrial cancer. For example, a study in mice with endometrial cancer and endometrial cancer derived cells (Ishikawa and RL95-2) suggested that the expression of the GLP-1 receptor is decreased and that activation of the GLP-1 receptor following vector-mediated transfection can hinder cancer cell proliferation, invasion, migration and promote apoptosis by activating the cAMP/PKA signaling pathway (165). Studies in endometrial cancer cell lines also showed that semaglutide and exendin-4 can enhance the anti-cancer activity of levonorgestrel (166) and attenuate the sensitivity to cisplatin (167). In addition, exendin-4 can attenuate the growth of cancer cells and promote cell apoptosis in mice with endometrial cancer, and the mechanism may be related to an increase in p-AMPK expression and a decrease in p-mTOR expression (168). In addition, the cell viability of Ishikawa cells treated with 1, 10 and 100 nM of exendin-4 was markedly lower at 24, 48, 72 and 96 h compared with 0 nM (168). Liraglutide can suppress the proliferation of endometrial cancer cells by promoting autophagy, elevating the p-AMPK levels (169,170) and decreasing the p-P70S6K levels (169). However, another *in vitro* study suggested that exendin-4 (100 nM) may enhance the survival, migration and invasion of endometrial cancer cell lines (AN3CA cells) at 24 h (171). The discrepancy may be due to the differences in cancer cell lines and the short observation period. The inhibitory effect of exendin-4 on the viability of endometrial cancer cells is more pronounced at 96 h compared with 24, 48 and 72 h (168). Long-term observation and *in vivo* experiments may further clarify the effect of GLP-1RAs on endometrial cancer. Furthermore, there is limited clinical research on the association between GLP-1 receptor and endometrial cancer. Future clinical studies should be conducted to evaluate the efficacy of GLP-1RAs in patients with endometrial lesions (including endometrial hyperplasia and endometrial cancer).

**Prostate cancer.** A total of two cohort studies have revealed that treatment with GLP-1RAs is inversely associated with prostate cancer risk (172,173). Subsequently, study in prostate cancer cell lines showed that activation of the GLP-1 receptor by using a lentiviral vector can attenuate cell proliferation by inhibiting the progression of cell cycle (174). Administration of exendin-4 in prostate cancer cells can also attenuate cancer cell growth (40,175,176), which is possibly associated with downregulation of the Akt and mTOR expression (175), inhibition of the ERK/MAPK pathway (176) and activation of the p38 pathway (40). Moreover, exendin-4 can radiosensitize prostate cancer cells through activation of the p-AMPK

pathway and inhibition of the p-mTOR, cyclin B and CDK1 expression (177). In addition, liraglutide can decrease the viability of LNCaP cells and induce apoptosis (178) by activating the p38 pathway (40). Although these findings have clarified the inhibitory effect of GLP-1RAs on prostate cancer, they are mostly limited to *in vitro* experiments. A greater variety of GLP-1RAs, more clinical and *in vivo* studies should be conducted in the future.

**Other cancers.** Studies have also analyzed the role of GLP-1RAs in other cancers, including lung cancer, ovarian cancer and glioma. In mice with lung cancer and Lewis cells, liraglutide can suppress the proliferation and migration of cancer cells by downregulating NETs and ROS of neutrophils (23) and suppressing the process of EMT (179). Administration of exendin-4 in ovarian cancer cells can inhibit cell growth, migration and invasion and enhance apoptosis through activation of the caspase-3/7 signaling (180) and inhibition of the PI3K/Akt pathway (181). Moreover, exendin-4 can also suppress the survival and proliferation of glioma cells by inhibiting EMT and elevating sirt3 expression (182). A study in oral squamous cell carcinoma demonstrated that semaglutide can inhibit cancer cell proliferation, migration and invasion and promote apoptosis by activating the p38 MAPK pathway (183).

These mechanisms of GLP-1RAs in inhibiting cancer have been summarized in Table III, with the aim to provide experimental basis for the future application of GLP-1RAs in the treatment of cancer. In the future, continued investigations should incorporate more clinical and animal experiments, as well as a wider variety of GLP-1RAs.

## 7. Discussion

The aforementioned studies suggest that activation of the GLP-1 receptor may inhibit cancer progression, and the detailed mechanisms are summarized in Fig. 4. Through systematic analysis, it is hypothesized that these mechanisms can be classified into the following categories. i) Direct regulation of cell proliferation, migration, invasion and apoptosis. In various types of tumors, GLP-1RAs and several natural compounds directly inhibit tumor cell proliferation, migration and invasion, reduce tumor size and weight, and induce tumor apoptosis. ii) Increased chemosensitivity, various natural compounds including baicalein, myricetin and puerarin, have been shown the ability to enhance sensitivity of ovarian (64,184), colorectal (83) and lung cancer cells (85) to cisplatin, 5-FU and oxaliplatin. The effects of classic GLP-1RAs on chemotherapy efficacy have rarely been studied. Currently, liraglutide is the only GLP-1RA that has been reported to enhance the sensitivity of pancreatic cancer cells to gemcitabine (25). iii) Regulation of inflammation and immune responses. Numerous studies have shown that GLP-1RAs can exhibit anti-inflammatory effects in various diseases. Levels of inflammatory factors, including IL-1, IL-6 and TNF- $\alpha$ , are elevated in colorectal, breast cancer and HCC. Treatment with liraglutide, geniposide and schisandrin B reduces inflammation and then alleviates tumor progression (24,79,89). Furthermore, GLP-1RAs enhance the antitumor immune response by increasing the infiltration of T cells, neutrophils

and dendritic cells to reduce tumor development in pancreatic, breast and hepatic cancer (22,59,134). Liraglutide is capable of downregulating NETs and ROS of neutrophils (23). Overall, inflammation and immune function are key factors in tumorigenesis and are also important directions for studying the antitumor effects of GLP-1RAs. iv) Regulation of the PI3K/Akt signaling pathway. Liraglutide and semaglutide suppress cell growth and metastasis by inhibiting the PI3K/Akt pathway in pancreatic, thyroid and colorectal cancer cells (136,146,175). Similarly, several natural GLP-1RA-like compounds (geniposide, baicalein and daphnetin) also effectively suppress the growth of various cancer cells via inhibition of the same pathway (67,82,185). Thus, regulating the function of the PI3K/Akt pathway plays a crucial role in the antitumor activity of GLP-1RAs. v) Regulation of the cAMP-dependent pathway. Activation of the GLP-1 receptor can inhibit cancer cell proliferation, invasion, migration and promote apoptosis by increasing the intracellular cAMP expression (150,162,165). Elevated cAMP levels activate PKA and subsequently induce the activation of AMPK. GLP-1RAs inhibit tumor growth through the suppression of cAMP/PKA and AMPK pathway activity in various cancers (138,152,165). Furthermore, elevated cAMP can also exert its effect by inhibiting the ERK pathway. Exendin-4 can induce apoptosis and inhibits proliferation of colon/prostate cancer cells by downregulating the ERK1/2 signaling pathway (162,176). Therefore, elevated cAMP may regulate tumorigenesis via the following molecular pathways: activation of the PKA-AMPK-mTOR pathway and inhibition of the ERK pathway. The cAMP-dependent pathway is critical for the anticancer effect of GLP-1RAs. vi) Regulation of other molecules. Liraglutide and exendin-4 can reduce the levels of ROS, EGFR and STAT3 in HCC and lung cancer cells (23,152). Exendin-4 can also suppress the survival and proliferation of glioma cells by elevating the expression of sirt3 (182). The inhibitory effect of liraglutide on BMP4 has been shown to suppress the growth of colorectal cancer cells (158). Treatment with exendin-4 increases Fgf7 levels in colonic polyps to regulate gut growth and intestinal tumorigenesis (161).

Furthermore, high blood glucose can increase cancer risk. As a new hypoglycemic drug, GLP-1RA may potentially lower cancer risk by controlling glycemic levels and enhancing insulin sensitivity. The effects of GLP-1 signaling on autophagy, angiogenesis and ferroptosis during tumorigenesis revealed in some studies are also future directions for the anti-cancer effects of GLP-1RAs.

## 8. Conclusion

Cancer is one of the main threats to human health, and it is essential to find effective methods for treating cancer. Notable progress has been made in understanding the association between GLP-1RAs and cancer (such as pancreatic, thyroid, breast and colorectal cancer). Activation of GLP-1 receptor by GLP-1RAs and some compounds with GLP-1 receptor agonistic activity can inhibit tumorigenesis by reducing neuroinflammation and oxidative stress, modulating tumor immune microenvironment, enhancing chemosensitivity and regulating related signaling pathways (such as the AMPK, PI3K/Akt and cAMP/PKA pathways). Although these findings suggest the potential effects of GLP-1RAs on cancer, there are

Table III. Mechanisms of GLP-1RAs in cancer.

| Cancer type                 | GLP-1RA     | Models                                                   | Bioactivities                                                                                                                                                                           | (Refs.)      |
|-----------------------------|-------------|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| Pancreatic cancer           | Exendin-4   | PANC-1 cell xenografted mice; PANC-1 cells               | Inhibits cell proliferation, migration and invasion by attenuating the activation of pancreatic stellate cells and the deposition of extracellular matrix.                              | (135)        |
|                             | Liraglutide | MIA PaCa-2 and PANC-1 cells                              | Suppresses cell metastasis by inhibiting the PI3K/Akt pathway, increases the chemosensitivity to gemcitabine.                                                                           | (25,136)     |
|                             | Semaglutide | Patients and xenografted mice                            | Prevents stromal deposition and allows T lymphocyte infiltration.                                                                                                                       | (134)        |
| Breast cancer               | Exendin-4   | MCF-7, MDA-MB-231 and KPL-1 cells; xenograft mice        | Suppresses tumor weight, size and proliferation, and promotes apoptosis by activating AMPK and cAMP/CREB pathway, inhibiting NF- $\kappa$ B and Akt/I $\kappa$ B pathway.               | (38,138-140) |
|                             | Liraglutide | Ehrlich's ascitic carcinoma-treated mice; MCF-7 cells    | Inhibits cell viability, proliferation, migration, and promotes apoptosis by activating AMPK, reducing the colony formation and the levels of inflammatory mediators.                   | (24,141,142) |
|                             | Semaglutide | 4T1 xenografted mice                                     | Increases CD11c+ dendritic cells and enhances the cytotoxic capacity of CD8+ T cells.                                                                                                   | (22)         |
| Papillary thyroid carcinoma | Liraglutide | TT and TPC-1 cells                                       | Suppresses cell proliferation and migration by inhibiting the PI3K/Akt/mTOR pathway.                                                                                                    | (146)        |
|                             | Semaglutide | THP-1 cells, xenografted mice.                           | Reduces tumor size and inhibits cell proliferation.                                                                                                                                     | (145)        |
| Hepatocellular carcinoma    | Exendin-4   | Diethylnitrosamine-treated mice                          | Inhibits cell proliferation and induces apoptosis by activating cAMP/PKA pathway, reducing EGFR and STAT3 levels.                                                                       | (152)        |
|                             | Liraglutide | Hepa1-6 bearing mice; HCC-LM3 and Hepa1-6 cells          | Reduces NETs and ROS of neutrophils, enhances NK-mediated cytotoxicity by inhibiting the IL-6/STAT3 pathway.                                                                            | (23,150)     |
| Cholangiocarcinoma          | Liraglutide | KKU-213A xenografted mice                                | Reduces tumor volumes and weights, suppresses the migration of cancer cells by inhibiting EMT and Akt/STAT3 pathway.                                                                    | (149)        |
| Colorectal cancer           | Exendin-4   | Glp1r -/- mice, CT26 cells                               | Increases fibroblast growth factor 7, inhibits cell proliferation and induces apoptosis.                                                                                                | (161,162)    |
|                             | Liraglutide | MC38 cell xenografted mice; colorectal cancer cell lines | Reduces cell proliferation, migration and invasion, promotes apoptosis by inhibiting the PI3K/Akt/mTOR pathway, activating the TGF- $\beta$ /Smad3 pathway, and decreasing BMP4 levels. | (158-160)    |
|                             | Semaglutide | Colorectal cancer cell lines                             | Inhibits cell migration.                                                                                                                                                                | (157)        |

Table III. Continued.

| Cancer type                  | GLP-1RA     | Models                                                        | Bioactivities                                                                                                              | (Refs.)      |
|------------------------------|-------------|---------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|--------------|
| Endometrial cancer           | Exendin-4   | Ishikawa xenografted mice;<br>Ishikawa and HEC-1B cells       | Reduces cell growth and cisplatin chemoresistance, promotes apoptosis, upregulates p-AMPK and downregulates p-mTOR levels. | (167,168)    |
|                              | Liraglutide | Ishikawa and HEC-1B cells                                     | Inhibits cell proliferation and induces autophagy by upregulating p-AMPK and downregulating p-P70S6K expression.           | (169,170)    |
|                              | Semaglutide | Patient-derived organoids;<br>Hec50co, KLE and Ishikawa cells | Enhances the anticancer activity of levonorgestrel.                                                                        | (166)        |
| Prostate cancer              | Exendin-4   | LNCaP, PC3, DU145 and CWR22RV1 cells                          | Suppresses cell proliferation, promotes apoptosis by activating p38 pathway, inhibiting ERK/ MAPK, Akt and mTOR levels     | (40,175-177) |
|                              | Liraglutide | LNCaP cells                                                   | Inhibits cell viability and promotes apoptosis.                                                                            | (178)        |
| Lung cancer                  | Liraglutide | A549 cells xenografted mice, Lewis cell                       | Suppresses cell proliferation and migration, reduces NETs and ROS.                                                         | (23,179)     |
| Ovarian cancer               | Exendin-4   | SKOV-3 and CAOV-3 cells                                       | Inhibits cell growth, migration and invasion, and enhances apoptosis by inhibiting the PI3K/Akt pathway.                   | (180,181)    |
| Glioma                       | Exendin-4   | U87, U251, U373 and A172 cells                                | Suppresses the survival and proliferation of cells by inhibiting EMT and elevating sirt3 expression.                       | (182)        |
| Oral squamous cell carcinoma | Semaglutide | Cal27 cell xenografted mice; Cal27 and HSC4 cells             | Inhibits cell proliferation, migration and invasion, and promotes apoptosis.                                               | (183)        |

GLP-1RA, glucagon-like peptide-1 receptor agonist; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; NETs, neutrophil extracellular traps; ROS, reactive oxygen species.

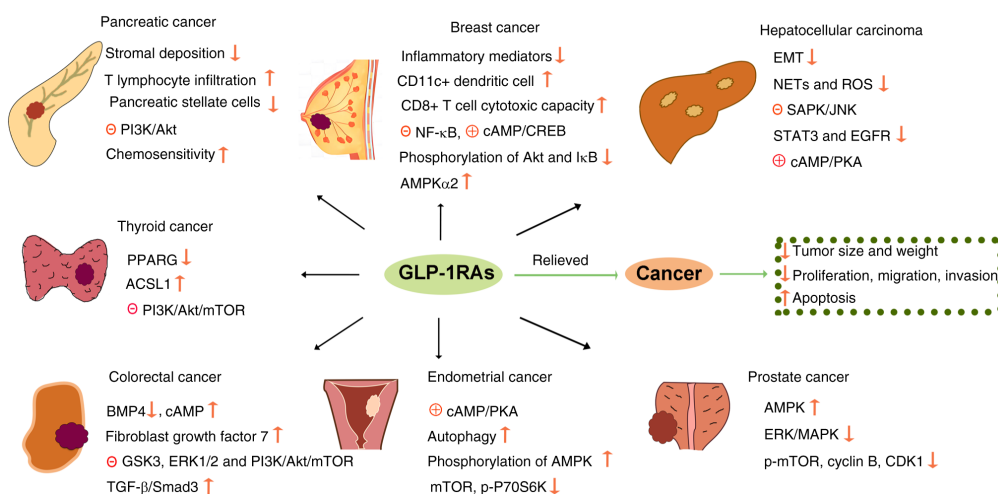


Figure 4. Schematic diagram of the mechanisms GLP-1RAs in relieving cancer. Activation of GLP-1 receptor by GLP-1RAs can reduce tumor size and weight, suppress the proliferation, invasion and migration of cancer cells, and promote cell apoptosis to relieve cancer (such as pancreatic-, thyroid-, breast-, colorectal-, endometrial-, prostate cancer and hepatocellular carcinoma). The mechanisms are associated with decreasing inflammatory mediators and ROS, promoting autophagy, modulating tumor immune microenvironment, enhancing chemosensitivity and regulating related signaling pathways (such as AMPK, PI3K/Akt and cAMP/PKA pathways). GLP-1RA, glucagon-like peptide-1 receptor agonist; EMT, epithelial-mesenchymal-transition; ROS, reactive oxygen species; NETs, neutrophil extracellular traps; ACSL1, acyl-CoA synthetase long-chain family member 1; PPARγ, peroxisome proliferator-activated receptor gamma; BMP4, bone morphogenetic protein 4; GSK3, glycogen synthase kinase 3; SAPK, stress activated protein kinase; CDK1, cyclin dependent kinase 1.

still numerous limitations. For instance, only three types of GLP-1RAs, including exendin-4, semaglutide and liraglutide, have been studied in cancer. There are insufficient *in vivo* studies and limited *in vitro* research. Additionally, clinical investigations are almost focused on patients with diabetes and/or obesity complicated by cancer. Therefore, continued *in vivo* research and rigorous clinical trials are needed to confirm the effects of the GLP-1 receptor in cancer. In addition, GLP-1RAs may be a novel effective approach for patients with the medical triad of diabetes, obesity and cancer in the future.

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### Authors' contributions

FJ was involved in the conception and design of the study. FJ wrote the first draft of the review, while QLY and CJF were involved in the acquisition and analysis of data. YZ revised the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

### Ethics approval and consent to participate

Not applicable.

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### Competing interests

The authors declare that they have no competing interests.

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