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GLP-1 Therapy in Cancer and Its Mechanism

Baowen Zhang[1], Jingyi Zhang[2,a,*]

[1]International School, Jinan University, Guangzhou, 510000, China
[2]School of Life Sciences, Jilin University, Jilin, 130012, China
a. zhangjy1323@jlu.edu.cn
**corresponding author*

Abstract: L-advocating cells generate the hormone glucagon-like peptide-1 (GLP-1), which is important for weight loss and the management of type 2 diabetes mellitus (T2DM).Recent studies have shown that it also reduces the risk of cardiovascular disease, reduces high blood pressure and other effects. In addition, it also has the effect of improving fatty liver, polycystic ovary syndrome. But when it comes to cancer, there are still gaps in its biological effects and mechanisms of action. In order to determine the indirect inhibitory effect of GLP-1RA on cancer as well as the metabolic regulation mechanisms of the cancer microenvironment by directly acting on the PI3K/AKT and ERK/MARK pathways, this paper analyzed studies on GLP-1 and its receptor agonist (GLP-1RA) in lowering cancer prevalence and inhibiting cancer. In turn, it effectively inhibits prostate cancer (PCa), ovarian cancer (OC) and other cancers. This study provides a reference for the indirect and direct mechanisms of GLP-1 and GLP-1RA in reducing cancer prevalence and inhibiting cancer. However, there are still gaps in other synergistic mechanisms that cannot be solved. It is hoped that future studies can focus on the anticancer mechanisms of other GLP-1 drugs.

Keywords: GLP-1 metabolism, PI3K/AKT pathway, ERK/MARK pathway, prostate cancer, ovarian cancer.

1. Introduction

Glucagon-like peptide-1 (GLP-1), an incretin secreted by intestinal L cells, consists of 30 or 31 amino acids and plays a crucial role in numerous physiological processes. Its core functions are manifested as follows: by stimulating pancreatic islet β cells to respond to glucose, it promotes insulin secretion; it delays the apoptosis process of pancreatic islet β cells, thereby enhancing islet function; it can delay gastric emptying and suppress appetite [1], which is quite effective in the treatment of diabetes and obesity; in the cardiovascular and nervous systems, it also has protective effects and can effectively prevent inflammation and the apoptosis of nerve cells. The latest research showed that GLP-1 also exhibits the functions of reducing cancer risks and inhibiting cancer [2].

The tumor immune microenvironment occupies a central position in the evolution and treatment process of cancer. This environment is a complex ecosystem covering multiple components such as tumor cells and immune cells, and the functional status of immune cells has a significant impact on tumor-related situations. GLP-1 and its receptor agonists (GLP-1RA) may have key significance in the tumor immune microenvironment. They can intervene in the energy and metabolic states of tumor cells through the regulatory effect on the metabolic process, thereby changing the growth and survival

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situations of tumor cells; they can also act on signal transduction pathways to regulate the function of immune cells and strengthen the anti-tumor immune response. This study aims to sort out and explain the regulatory mechanism of GLP-1 and its receptor agonists on the tumor immune microenvironment, specifically covering the effects on the types, functions and signal pathways of immune cells, and clarifying its action mechanism and efficacy in the treatment of cancers such as prostate cancer and ovarian cancer. With the gradual deepening of the research work, the internal mechanism of its cancer inhibition will be more thoroughly understood, providing strong support for precision treatment. It is expected to show efficacy in more cancer types and can be combined with various treatment methods to improve the treatment effect and reduce the occurrence of side effects.

2. GLP-1 drugs inhibit cancer mechanisms

Indirect mechanism: The high-fat diet of obese patients will reduce the number and function of CD8+T cells, which will lead to cancer susceptibility [3]. In addition, high Body mass index (BMI) is associated with metabolic syndrome and metabolic disorders, and is also a factor that increases the risk of cancer. According to statistics, nine different forms of cancer, including cancer of the kidney, gallbladder, and uterine, are linked to higher BMI [4]. By influencing the hypothalamic nucleus, GLP-1 can suppress hunger and postpone stomach emptying in order to aid in weight loss [5]. The first GLP/GLP-1 double receptor agonist authorized by the US Food and Drug Administration for weight loss was tesiparatide, which was sold as a GLP-1 drug in 2023 [6]. It also represents the future of widespread use of GLP-1 drugs.

In addition to obesity, long-term hyperglycemia in the body will induce increased secretion of neuregulin 1 (Nrg1), which will accelerate cancer progression[7]. Studies have also shown that hyperglycemia promotes platelet activation by influencing megakaryocytes, indirectly driving tumor metastasis [8]. GLP-1 promotes insulin secretion, inhibits glucagon-like peptide secretion, lowers hyperglycemia, and prevents cancer from the start by binding with GLP-1R.

3. Direct mechanism

3.1. Action on the PIK3/AKT pathway

The PI3K/AKT pathway is an important signal transduction pathway in the human body. Its main parts are phosphatidylinositol 3-kinase (PI3K) and protein kinase B (AKT). Its main link is that when cells receive external stimuli (such as growth factors, insulin, etc.), PI3K is activated and converts phosphatidylinositol to phosphatidylinositol triphosphate (PIP3). PIP3 attracts AKT to the cell membrane and is phosphorylated and activated, thereby regulating a variety of downstream pathways, such as mTOR, GSK-2β, etc., affecting cell growth and proliferation.

Disorders in the PI3K pathway are linked to the emergence and advancement of multiple diseases, among which cancer is included. The two main mechanisms for activating the PI3K/AKT pathway are stimulation of receptor tyrosine kinases (RTKs) and somatic mutations of specific components of the pathway8]. Abnormal activation of the PI3K/AKT pathway in cancer can lead to cancer cell proliferation, angiogenesis, and longer survival of cancer cells. Therefore, inhibitors targeting the PI3K/AKT pathway have made progress in the treatment of cancer in recent years. Today, PI3Kδ inhibitors are mainly used to treat various cancers including B-cell malignancies and solid tumors [9]. PI3Kδ inhibitors combined with casein kinase-1ε are approved for follicular and marginal zone lymphomas [10].

As an incretin hormone, GLP-1 has good weight loss and blood sugar lowering effects. By binding to GLP-1R, it stimulates pancreatic cells to secrete insulin and achieves the purpose of lowering blood sugar. Long-term use of GLP-1 can improve pancreatic function. In addition, GLP-1 can affect the proliferation and growth of tumor cells by inhibiting the PI3K/AKT pathway. Studies have shown

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[11] that in OC, Exendin-4 (Ex-4), a GLP-1 drug, has the same effects on p-Akt, E-calmodulin and caspase-3 cleavage as PI3K/AKT pathway inhibitors, indicating that the inhibitory mechanism of GLP-1 on PI3K/AKT may be related to reducing the secretion of related products. In PCa [12], compared with enzalutamide alone, the combination of Ex-4 and enzalutamide has a stronger killing effect on PCa cells. Ex-4 can effectively inhibit the migration and invasion of PCa cells LNCaP and WR22RV1. At the same time, compared with enzalutamide alone, Ex-4 can effectively reduce the localization of nuclear variant AR. Most importantly, Ex-4 can effectively inhibit the PIK/AKT/mTOR pathway and its downstream effectors S6K and 4EBP-1 through the phosphorylation of AKT and mTOR.

It is worth mentioning that in addition to directly acting on the PI3K/AKT pathway to achieve cancer inhibition, GLP-1 can effectively reduce insulin-like growth factor (IGF-1) in T2DM patients. IGF-1 can activate the PI3K/AKT pathway. In other words, GLP-1 can indirectly inhibit the PI3K/AKT pathway, which is of great significance for diabetic patients with cancer [13].

3.2. Acting on the ERK/MARK pathway

GLP - 1 binds to the glucagon-like peptide-1 receptor (GLP - 1R) and subsequently activates GLP - 1R. This binding can trigger the initiation of the intracellular ERK pathway. Exenatide-4 (Ex - 4) is a peptide agonist of GLP - 1R and has the ability to promote insulin secretion. The ERK - MAPK pathway is one of the key signal transduction pathways that stimulate the proliferation of prostate cancer cells. However, Ex - 4 inhibits the proliferation of prostate cancer cells through the activation of GLP - 1R. Relevant studies have shown that Ex - 4 can significantly reduce the activation of ERK - MAPK. The application of Ex - 4 can remarkably reduce the proliferation of prostate cancer cells (LNCap) by inhibiting the activation of ERK - MAPK. Compared with other cell lines, due to the abundant expression of GLP - 1R in the prostate cancer cell line LNCap, the inhibitory effect of Ex - 4 on cell proliferation observed in LNCap cells is more pronounced. Moreover, the GLP - 1R antagonist can eliminate the proliferation inhibitory effect of Ex-4 [14].

Ex-4 primarily suppresses the ERK-MAPK pathway through the cyclic adenosine monophosphate-protein kinase A (cAMP-PKA) signaling cascade, thereby hindering the proliferation of prostate cancer cells without causing apoptosis. Specifically, Ex-4 dose-dependently decreases DNA synthesis in LNCap cells. The inhibitory effect of Ex-4 on ERK-MAPK activation can be fully abolished by a protein kinase inhibitor (PKI). Similarly, forskolin also exhibits inhibitory effects on ERK-MAPK phosphorylation in LNCap cells. When combined with a mitogen-activated protein kinase kinase (MEK) inhibitor, Ex-4 further dampens the proliferation of LNCap cells. However, a higher dose of the MEK inhibitor completely halts the proliferation of LNCap cells, suggesting that the ERK-MAPK inhibition induced by Ex-4 operates independently of MEK inhibition [15].

In summary, glucagon-like peptide-1 receptor agonists (GLP-1RAs), including Ex-4, exhibit promising anti-cancer activity against prostate cancer by inhibiting ERK-MAPK activation both in vitro and in vivo.

3.3. Acting on the NF-Kβ pathway

Preclinical research has shown that MCF-7, MDA-MB-231, and KPL-1 cell lines, as well as human breast cancer tissues, express the GLP-1 receptor. In vivo, Ex-4 can shrink MCF-7 tumors in size. Ex-4 can dramatically suppress target gene expression and nuclear factor κB (NF-κB) nuclear translocation in MCF-7 cells. Furthermore, Ex-4 decreases Akt and IκB phosphorylation. Following receptor activation, GLP-1 can prevent NF-κB activation, which will reduce the growth of breast cancer cells. In athymic mice, exendin-4 can increase the death of breast cancer cells and decrease

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the development of mammary tumors, indicating that GLP1-As may have an inhibitory effect on breast cancer [16].

3.4. Acting on the GLP-1R/SIRT3 pathway

SIRT3 is an NAD+-dependent deacetylase in mitochondria that has the ability to widely regulate mitochondrial morphology and function. It has a profound impact on cancer, cardiovascular disease, aging, and metabolic control. 8-Oxoguanine DNA glycosylase 1 (OGG1) is an enzyme that repairs mitochondrial DNA damage. SIRT3 can inhibit tumors by mediating the deacetylation of OGG1. At the same time, SIR3 can inhibit the energy metabolism of tumor cells by inhibiting glycolysis [17]. In gliomas, Ex-4 increases SIR3 expression through high levels of GLP-1R, thereby inhibiting the energy metabolism, migration and invasion of glioma cells [18].

4. Current applications of GLP-1 drugs in the treatment of cancer

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4.1. Ovarian cancer

He.et al. found that when the concentration of Ex-4 increased from 0-100 nmol/L, the proliferation of SKOV3 and A2780 cell lines slowed down [11]. And compared with the control group, the number of cells invading through the matrix in the membrane permeability and pore migration experiments in the Ex-4-treated subgroup was significantly reduced, indicating that Ex-4 has better invasion and metastasis of OC cells. inhibitory effect.

More important, metalloproteinases (MMP-2 and MMP-9) and their inhibitors (TIMP-1 and TIMP-2) that are pertinent to tumor development are also expressed in relation to Ex-4. By controlling the production of these proteins, Ex-4 can prevent the growth and metastasis of cancer cells [19]. According to the experimental findings, treatment with Ex-4 or GLP-1 somewhat decreased the protein levels of all MMPs following TNF-α incubation. Ex-4 or GLP-1 decreased MMP-1 by 14% and 19%, respectively, following TNF-α incubation; MMP-2 fell by 23% and 47%, respectively; MMP-7 declined by 22% and 32%, respectively; MMP-9 decreased by 15% and 21%, respectively; and MMP-10 decreased by 16% and 37%, respectively.

4.2. Prostatic cancer

He. et al. experimentally demonstrated that in PCa, enzalutamide alone did not have any significant effects on tumors formed by CWR22Rv1 cells. Ex-4 singly slowed down the rate of growth of tumors, while the combined use of enzaglutide and Ex-4 resulted in a further reduction in the size and the weight of prostate tumor t than Ex-4 singly [12]. This suggests that the combined use of these drugs has a more pronounced and effective inhibitory effect on tumors. At the same time, after Ex-4 was combined with enzaglutide, it was observed that the number of PCa cell lines LNCaP and CWR22Rv1 cell lines sown in Matrigel and Transwell chambers moved to the base of the filter membrane, indicating that Ex-4 can compare with Good at combating tumor invasion and metastasis caused by enzaglutide alone.

Another study also showed that the combination of docetaxel and liraglutide (a GLP-1 analogue) can be more effective in inhibiting the cell line LNCaP. The MTT assay showed that docetaxel and liraglutide each had an inhibitory effect on the growth of LNCaP cells when used alone, but when used in combination, a more significant inhibitory effect appeared [20].

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4.3. Other cancers

Other researches have shown that another GLP-1 analog, Liraglutide, can effectively raise the sensitivity of the drug-resistant pancreatic cancer cell line PANC-GR to the chemotherapy drug guitarxibine and effectively reduce its sensitivity. proliferation [21]. In addition, for another cell line of pancreatic cancer , MiaPaCa-2/MiaPaCa-2-GR, liraglutide can effectively reduce the expression of NF-κB and ABCG2 in cancer cells. In addition, GLP-1 also has good effects on the treatment of cancers such as breast cancer [22].

5. Conclusion

GLP - 1 exhibits remarkable efficacy in the treatment process of T2DM and weight regulation. In terms of cancer prevention, it can reduce the cancer incidence risk through two indirect approaches, namely weight regulation and hyperglycemia improvement. In cancer treatment, GLP - 1 mainly reduces the growth and proliferation rate of cancer cells and hinders their metastasis and invasion process by inhibiting metabolic pathways such as the PI3K/AKT pathway and the ERK/MARK pathway. In the treatment scenarios of cancers such as ovarian cancer and prostate cancer, whether GLP - 1 is administered alone or in combination, it can effectively limit the development trend of cancer. GLP - 1 drugs have shown considerable potential in the field of cancer treatment. With the continuous deepening of the exploration of their action mechanisms, there are sufficient grounds to expect that in the future comprehensive cancer treatment system, GLP - 1 drugs are expected to become a key component.

Firstly, continuously and deeply analyzing the specific action mechanisms of GLP - 1 and its receptor agonists in different cancer types, especially their efficacy in metabolic regulation of the cancer microenvironment, will build a more solid theoretical foundation for precision treatment. By further optimizing the drug formulation and administration mode, the targeting accuracy and treatment efficacy of the drug can be improved, and potential adverse reactions can be reduced. Secondly, combining GLP - 1 drugs with other cancer treatment methods such as surgery, radiotherapy, and chemotherapy, and carrying out clinical research on multimodal treatment, so as to fully release the indirect inhibition and direct regulation efficacy of GLP - 1 drugs. At the same time, strengthening the monitoring of the long-term efficacy and safety of the drug, to create a more reliable treatment plan for patients.

Future research can further explore its action mechanism, optimize treatment strategies, open up new treatment paths and bring hope for cancer patients, improve the effectiveness of cancer treatment and the quality of life of patients. In addition, more clinical research is needed to verify its safety and reliability, and lay a solid foundation for its wide clinical application. Overall, GLP - 1 drugs have a bright prospect in the field of cancer treatment and are expected to open a new door of hope for cancer patients.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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