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REVIEW

Research Progress of GPR137 in Malignant Tumors: A Review

Yangyang Li[1,*], ZhongQuan Yi[2,*], Xia Li[3,*], Rui Wang[1], Mengjie Zhao[1], Lida Mi[1], Weisong Zhang[1], Rongqi Guo[1], Song Yan[4], JianXiang Song[1]

[1]Department of Cardiothoracic Surgery, Affiliated Hospital 6 of Nantong University, Yancheng Third People's Hospital, Yancheng, 224000, People's Republic of China; [2]Department of Central Laboratory, Affiliated Hospital 6 of Nantong University, Yancheng Third People's Hospital, Yancheng, 224000, People's Republic of China; [3]Department of General Medicine, Affiliated Hospital 6 of Nantong University, Yancheng Third People's Hospital, Yancheng, 224000, People's Republic of China; [4]Department of Thoracic Surgery, Sheyang County People's Hospital, Yancheng, Jiangsu, People's Republic of China

*These authors contributed equally to this work

Correspondence: JianXiang Song, Department of Cardiothoracic Surgery, Affiliated Hospital 6 of Nantong University, Yancheng Third People's Hospital, West Xindu Road 2#, Yancheng, Jiangsu Province, 224000, People's Republic of China, Email jxsongycsy@163.com

Abstract: Receptors coupled with G proteins (GPCRs) are expressed in large numbers in multiple systems, such as endocrine, cardiovascular, digestive, immune, and reproductive systems. As an important signal transduction mediator, in recent years, the research on GPCRs has become more and more in-depth. Many articles have verified that in the gastrointestinal, reproductive, and urinary systems, GPCRs are contributed to the development and occurrence of cancerous tumors and have been associated with the infiltration of malignant tumors and metastasis. Currently, in clinical practice, GPCRs become the target of action for about 30% of drugs. However, it should be noted that there are still over 100 GPCRs collectively referred to as orphan GPCRs (OGPCRs) due to the lack of corresponding ligands. Despite the lack of known ligands, research in animals and experiments has proved that numerous OGPCRs regulate crucial physiological functions and are intriguing and undeveloped targets for therapeutics. GPR137 is a member of OGPCRS, which promotes carcinogenesis and progression of cancers, and its expression is elevated in various malignant tumor tissues. Additionally, GPR137 has been shown to play a role in promoting tumorigenesis and metastasis in colorectal, gastric, hepatocellular, ovarian and prostate cancers. Knockdown of the GPR137 leads to cell cycle arrest within cancer cells, effectively inhibiting their proliferation and colony-forming ability while promoting apoptosis. This highlights its potential therapeutic significance as a target for numerous cancers.

Keywords: malignant tumors, G protein-coupled receptor, GPR137, molecular targeting treatment

Introduction

Malignant tumors are considered a serious public health threat and are the leading cause of death worldwide.[1,2] Based on estimates of cancer incidence and mortality rates compiled by the International Agency for Research on Cancer (IARC) in GLOBOCAN 2022, roughly 20 million people were diagnosed with malignant tumors and almost 9.7 million died of malignant tumors globally in the year 2022.[3] There is evidence that the "history" of malignant tumors goes back a million years, and that cellular organisms have been afflicted by the disease for nearly 200 million years.[4] Malignant tumors differ from infectious diseases and diseases of the immune system. The pathogenesis of malignant tumors is characterized by uncontrolled cell proliferation and growth. Tumor cells undergo genetic damage while proliferating indefinitely, spreading widely and invading surrounding tissues, resulting in the loss of normal physiological and regulatory functions.[4] With advancements in modern medicine, cell and molecular studies have delved deeper into various molecules or proteins that have been employed for diagnosing and treating numerous types of malignant tumors.[5] Consequently, humanity no longer remains powerless against malignant tumors. For example, the assessment of HER2 at the diagnosis of invasive breast cancer has helped to instruct therapeutic decisions.[6,7] Similarly, the development in

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aiming at the epidermal growth factor receptor (EGFR) with erlotinib and gefitinib has greatly enhanced the therapeutic efficiency associated with non-small cell lung carcinoma.[8–10] Despite these advances, there are still insufficient molecular markers in clinical use, resulting in high morbidity and mortality from malignant tumors. Consequently, malignant tumors continue to pose a significant challenge that the medical community is unable to overcome in the short term.[5,11] Therefore, novel molecular markers are urgently needed to enhance preventive detection and early intervention strategies for patients with malignant tumors, ultimately improving their cure and survival rates.

GPR137 is a novel G protein-coupled receptor identified by homology screening and is highly homologous to prostate-specific odorant orphan G protein-coupled receptor (PSGR).[12,13] It has been more than 20 years since GPR137 was discovered, and the research on its function has become more and more detailed. GPR137 has the function of regulating the localization and activity of Rag and mTORC1 and is involved in a variety of important physiological processes in the human body.[14] Previous studies have confirmed that GPR137 is overexpressed in many types of malignant tumors and promotes tumor cell proliferation, invasion and metastasis.[15] According to the latest studies on GPR137, it was reported that GPR137 showed high expression in ovarian cancer, and anisomycin could target-drive miR-134-3p and promote elevated expression of miR-134-3p, thus down-regulating the expression of GPR137 and downstream related proteins. After the downregulation of GPR137 and downstream proteins, the activity of ovarian cancer stem cells (HuOCSCs) was significantly inhibited, reducing the proliferation, migration and tumorigenicity of HuOCSCs.[16] GPR137, as a member of the G protein-coupled receptor family, is also involved in the proliferation and differentiation of human epithelial cells and plays an important role in the biology of epidermal stem cells.[17] GPR137, as a key receptor, mediates the signaling of a variety of metabolites, which enables the cells to sense extracellular signals and adapt to changes in the environment that maintain tissue homeostasis.[18]

Overall, GPR137 can function as an important signaling receptor in multiple organs and systems in the human body. Abnormalities in GPR137 metabolism may lead to a variety of diseases such as inflammation, hereditary disorders and even malignant tumors. The aim of this article is to review the development and significance of GPR137 in malignant tumors, offering potential targets for future treatment of patients with malignant tumors, and providing theoretical underpinning for the realization of more personalized and effective treatment strategies.

Structure and Function of GPR137

In terms of cell surface molecules, G protein-coupled receptors (GPCRs) are the most prevalent group and have an impact on signaling for numerous physiological and pathological functions.[19] This family comprises more than 800 individuals, each consisting of seven transmembrane alpha-helical segments linked to a common structural component by an extracellular and intracellular circuit.[20] A variety of ligands (agonists) can activate G protein-coupled receptors, including single photons, ions, amino acids, small organic molecules, lipids, peptides, and entire proteins as extracellular signals.[20] After the ligand binds, conformational change takes place in the GPCR, leading to the stimulation of specific heterotrimeric G proteins, which initiates cytoplasmic signaling networks and triggers multiple cellular responses[21,22] (Figure 1). Extensive research has demonstrated widespread expression of GPCRs in endocrine, cardiovascular, gastrointestinal, immune, and reproductive systems,[23] with implications in the development of malignant tumors across multiple organ systems[24–42] (Table 1). With the deepening of research in this field, cancer cells are observed to replicate autonomously while evading immune detection by exploiting the regular physiological function of GPCRs. In addition, they enhance oxygen and nutrient supply, promoting invasion and metastasis.[13,21] In addition, the research confirmed that many human viruses contain open reading frames encoding GPCRs. These GPCRs may have been hijacked by these viruses from host cells, and the viruses can take advantage of the replication of the GPCR family to mutate key structural motifs that are constitutively active and induce tumorigenesis.[25] For example, Epstein–Barr virus, which can encode a G protein-coupled receptor called BILF1. The receptor can upregulate NFκB activity and blocks protein kinase A (PKA) activity, which in turn affects chemokine receptor expression, leading to the development of a number of diseases associated with EBV, such as nasopharyngeal carcinoma, mononucleosis, and Burkitt's lymphoma.[43,44] Therefore, there is a widespread belief that GPCRs are a key factor leading to the proliferation and spread of cancerous growth. The identification of ligands and corresponding known receptors of most GPCRs has facilitated their clinical application.[45] It is estimated that nearly over 30% of effective drugs are currently available on the market are designed to contribute to

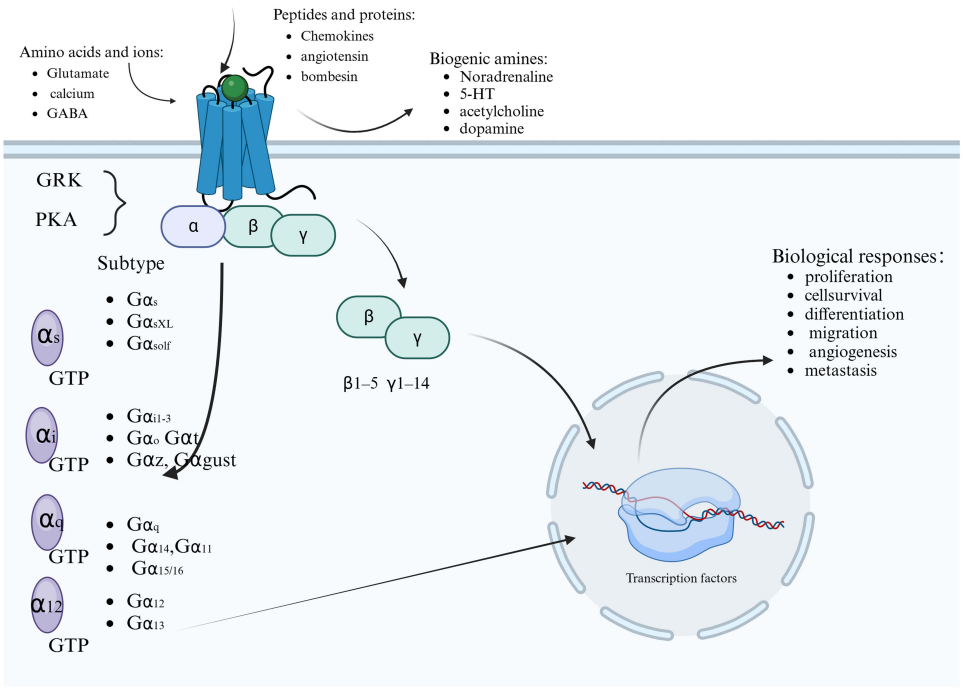

Figure 1 Ligand-activated GPCRs signal transduction.

these receptors[46,47] (Table 2). For example, the drug dulaglutide performs as a stimulator for the receptor of glucagon-like peptide-1 (GLP-1), which can initiate GLP-1 receptors on the cell surface by stimulating G-protein signaling, thereby inducing adenylyl cyclase activity.[48] This treatment effectively decreases the levels of blood glucose in

Table 1 GPCRs in Cancers

Receptor	Cancers	Ligand	Function	References
CXCR4	Breast cancer	SDF1	Metastasis; angiogenesis	[26]
	Small-cell lung cancer		Growth; metastasis	[27]
	Head and neck cancer		Metastasis	[28]
GRPR	Head and neck cancer	GRP	Growth; survival	[29]
	Small-cell lung cancer		Growth	[30, 31]
	Pancreatic cancer		Growth	[32]
CCK_1; CCK_2	Pancreatic cancer	CCK	Growth	[31]
	Small-cell lung cancer		Growth; survival	[31]
LPA_1	Colon cancer	LPA	Growth	[33]
	Ovarian cancer		Growth; metastasis; angiogenesis	[34, 35]
	Prostate cancer		Growth; invasion	[36]
EP receptors	Non-small-cell lung cancer	PGE2	Growth; metastasis; angiogenesis	[37]
	Colon cancer		Survival	[38]
MC_1R	Melanoma	MSH	Sensitivity to UV-induced DNA damage	[39, 40]
Smoothened	Basal-cell carcinoma	Sonic hedgehog	Growth	[41, 42]

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Table 2 New Molecular Entities Acting via GPCRs Approved by the FDA in Recent years

Substance	Brand Name	Indications	Targets	Approval Year
Dulaglutide	Trulicity	Type 2 diabetes	GLP1R	2014
Vorapaxar	Zontivity	Cardiovascular risk reduction	PAR1	2014
Olodaterol	Striverdi respimat	COPD	ADRB2	2014
Cariprazine	Vraylar	Schizophrenia and bipolar disorder	DRD3, DRD2	2015
Selexipag	Uptravi	Pulmonary hypertension	PI2R	2015
Pimavanserin	Nuplazid	Parkinson disease psychosis	5HT2A	2016
Naldemedine	Symproic	Opioid-induced constipation	OPRM	2017

individuals diagnosed with type 2 diabetes by minimizing the risk of hypoglycemia, weight gain, increased blood pressure, and cardiovascular events.[49] Another example, Vorapaxar, a substance that can object the activity of protease-activated receptor-1 (PAR-1) that effectively affects the thrombin-induced aggregation of platelets as well as platelets aggregation induced by the thrombin receptor agonist peptide (TRAP).[50] As an antiplatelet agent, it can be utilized to mitigate the recurrence of thrombotic cardiovascular events following myocardial infarction or peripheral arterial disease.[51]

However, there are still a number of GPCRs whose ligands have not been ascertained yet, and they are collectively described as orphan GPCRs (OGPCRs).[52] According to animal models and related studies, a large number of OGPCRs have been shown to control vital physiological functions, making them therapeutic targets with potential for further development.[53,54] A growing number of research has shown that OGPCR is also thematically linked to the growth and movement of malignant cells.[54] For instance, abnormal expressions of GPR49 have been detected in primary tumors of the colon and ovaries in humans.[55] Additionally, GPR55 has also been associated with the progression of various cancers such as cholangiocarcinoma, breast cancer, prostate cancer, ovarian cancer, and glioblastoma.[56]

GPR137 is a gene coding orphan GPCRs localized to 11cen-q13.1.[57] Gene GPR137 encodes a cytoplasmic polypeptide with four transmembrane regions. In the GPR137 protein, both the N- and the C-termini contain signaling peptides.[57,58] It was discovered that GPR137 was expressed in the human hippocampus at first,[59] and subsequent studies have found it to be widely and extensively distributed in a range of organs and tissues such as the nervous, reproductive, endocrine and digestive systems.[23] Compared with other G protein-coupled receptors, GPR137 is a relatively novel receptor protein. It is located on the lysosomal membrane and has the function of signal transduction across the lysosomal membrane.[60] It is involved in the regulation of Rag and mTORC1 localization and activity,[14] and the dysfunction of TORC1 signaling pathway can cause the occurrence of many diseases, including cancer, neurodegeneration, diabetes and so on.[61,62] It appears from these findings that GPR137 may contribute greatly to diverse physiological activities.[63] A review of prior research has confirmed that GPR137 is contributed to the growth of carcinogenic cells across different types of cancer, including colorectal cancer,[64] gastric cancer,[63] hepatocellular carcinoma,[12] bladder cancer,[65] prostate cancer,[58] medulloblastoma,[66] and malignant glioma.[21] The inhibition of the expression of GPR137 can effectively stabilize tumor cells by suppressing their proliferation and colony-forming abilities. In addition, an important function of GPR137 is to promote the reproduction, dissemination, and infiltration of tumor cells, and it could be possibly used in cancer treatments.

Aberrant Expression of GPR137 in Malignant Tumors

Numerous studies have illustrated that the expression of GPR137 in tumor tissue is exceptional compared to nearby healthy tissue (Table 3). The presence of GPR137 in plasma or cancer tissues was ascertained by reverse transcription polymerase chain reaction (RT-PCR). The overexpression of GPR137 has been found in various different types of cancer, including hepatocellular carcinoma,[12] renal carcinoma,[67] prostate carcinoma,[58] ovarian carcinoma,[15] colorectal

Table 3 The Biological Activity of GPR137 in Various Types of Cancer

Cancer	Cell Lines	Cell Expression	Downregulation of GPR137 Expression in vitro	Pathway	References
Colorectal cancer	HCT116, RKO, SW116, SW480, SW620, HT-29	↑	Growth↓, Invasion↓, Colony formation ability↓, Cell cycle arrest		[64]
Ovarian cancer	SKOV3, CAOV-3, COC1, OVCAR3	↑	Growth↓, Invasion↓, Colony formation ability↓, Cell cycle arrest, Apoptosis↑	PI3K/AKT	[15]
Hepatocellular carcinoma	HePG2, Bel7404, Bel7402, SK-HEP-1, Hep3B, SMMC-7721	↑	Proliferation↓, Colony formation ability↓, Cell cycle arrest, Apoptosis↑		[12]
Pancreatic cancer	BXP-3, PAN-1	↑	Proliferation↓, Colony formation ability↓, Cell cycle arrest, Apoptosis↑	PARP, Caspase3	[13]
Gastric cancer	GES-1, SGC-7901, AGS	↑	Invasion↓, Migration↓, Colony formation ability↓	Hippo signaling	[63]
Medulloblastoma	Daoy	↑	Proliferation↓, Colony formation ability↓, Cell cycle arrest, Apoptosis↑		[66]
Prostate cancer	PC-3, DU145, LN-cap	↑	Proliferation↓, Colony formation ability↓, Cell cycle arrest	Snail1, Slug, E-cadherin	[58]
Malignant glioma	U251, A172, U373, U-87MG, U-118MG	↑	Proliferation↓, Colony formation ability↓, Cell cycle arrest		[21]
Renal cancer	Caki-1, 786–0, ACHN, Osrc2, A498, 769-P	↑	Proliferation↓, Migration↓, Invasion↓	ALKBH1	[67]

carcinoma,[64] and gastric carcinoma.[63] Elevated levels of GPR137 expression have been affirmed in different types of cancerous tissues, suggesting its involvement in the pathogenesis of these malignancies.

Knockdown of GPR137 Inhibits Cell Cycle and the Proliferation of Cancer Cells

Regulating cell cycle is one function of GPR137, and the inhibition of GPR137 can lead to a halt in the cell cycle progression, thereby refraining cancer cells from multiplying and growing.[12,13,15,58] The process of cell division contributes to the progression of cancer, and the precise segregation of chromosomes during mitosis and unimpeded cell proliferation are critical events throughout the cell life cycle.[68,69] Cancer cells are characterized by their ability to evade normal lifespan limitations and exhibit aberrant proliferation.[70] In studies of hepatocellular carcinoma,[12] pancreatic cancer,[13] and ovarian cancer,[15] repressing the function of the GPR137 was observed to cause significant cell cycle sluggishness in these cancer cells. Due to this arrest, G0/G1 emerged from S phase and remained in G0/G1 for some time, thereby inducing cellular regression and inhibiting cancer cell growth. Irregular progression of cell cycle is the basic mechanism of tumorigenesis,[69] so regulators of cell cycle mechanism can be used in cancer treatment as potential targets for molecular therapy.[71] Although it is still unknown how GPR137 governs the cell cycle, it has been shown that silencing the GPR137 gene inhibits cell cycle progression, limits cancer cell proliferation, and ultimately results in cancer cell apoptosis. These findings highlight GPR137 as an optimistic target of therapeutic intervention for modulating tumor cell cycle dynamics.

GPR137b Mediates M2 Macrophage Polarization Involved in Cancer Progression

GPR137b (TM7SF1), a widely studied isoform of GPR137, is a tissue-specific intact membrane protein localized to lysosomes, which is hypothesized to have the capacity for signal transduction across lysosomal membranes.[60] Activation

of GPR137b by various ligands (including ions, amino acids, fatty acids and hormones) leads to its interaction with effectors, which triggers a series of reactions in the downstream pathway.[60,72] Activated GPR137b performs a variety of lysosomal functions such as autophagy, product degradation, and nutrient transport. Zohirul Islam et al[73] discovered that GPR137b exhibits abundant expression in the cell line RAW264 from mouse macrophage and confirms its involvement in the IL-4-mediated assimilation of M2 macrophages by means of the PI3K/Akt pathway.[74,75] M2-polarized macrophages, often referred to as tumor-associated macrophages (TAMs), contribute greatly to the enhancement of cellular proliferation, infiltration, metastasis and formation of new blood vessels in cancer cells,[76] and are considered as an important aspect of the immune system that infiltrates tumors.[77] Relevant research has shown that TAMs are not only suitable for facilitating tumor cell initiation and metastasis but they can also restrict the immune system and aggrandize tumor angiogenesis.[78] Furthermore, the infiltration of TAMs in the tumor microenvironment has been consistently linked to unfavorable prognosis in various cancer types.[79,80] By mediating M2 macrophage polarization through specific mechanisms, GPR137b has the potential to be targeted for preventive and therapeutic interventions in controlling cancer development and progression.

Advances in the Study of GPR137 in Malignant Tumors

Colorectal Cancer

Lukas Franz Mager et al[81] demonstrated that the ESRP1-GPR137 axis is involved in intestinal pathogenesis. Literature supports ESRP1 as a tumor suppressor[82], with documented functionality in cancers of the head and neck[83] and pancreatic.[84] In their experiments, Mager affirmed that reduced intensity of ESRP1 activity led to gut barrier disruption, which increased susceptibility to inflammatory bowel disease and caused more severe cancers in transgenic mice with lower ESRP1 expression. In addition, ESRP1 has an inhibitory effect on tumor proliferation in colorectal cancer cells, and thus its absence is a poor prognostic factor for this type of cancer.[85] Meanwhile, ESRP1 regulates an additional gene encoding the protein GPR137, which promotes signal transduction in epithelial cells. Altered ESRP1 levels result in elevated GPR137 protein levels, impacting the signaling function of this protein and causing disturbances in the activity of intestinal epithelial cells. The cellular isoforms of GPR137 are greatly associated with maintaining the intestines in balance, mainly by regulating intestinal epithelial cell function, particularly from the Wnt/-catenin pathway regulation.[86] In their experiments, Zhang et al[64] demonstrated that GPR137 exhibited high expression intensities in various cells of colorectal cancer. Knockdown of this protein in colon cancer cells significantly inhibited cancer cell growth, inducing cell cycle arrest at the G0/G1 phase. In addition, the study found differences in the proportion of expression of the specific GPR137 subtype, which is dependent on ESRP1 and can be used as a potential indicator of survival outcomes among colorectal cancer patients, between intestinal tumors and normal tissues.

Gastric Cancer

Gastric cancer ranks among the top five cancers worldwide, exhibiting the third highest mortality rate globally and a notably high incidence in Asia.[87] Although the incidence of the disease has declined recently,[88] an absence of specific symptoms or diagnostic markers in the early stages prevents timely detection, resulting in many patients being diagnosed at a later stage with limited improvement in prognosis and quality of life.[89] Therefore, there is an urgent need for in-depth clinical studies on the pathogenesis of gastric cancer, as well as developing new biomarkers for early detection and improved survival rates. Notably, the existing literature has confirmed the correlation between elevated GPR137 expression levels and the cancer of the stomach.[90] Lin et al[63] demonstrated experimentally that GPR137 showed high expression levels in gastric cancer and increased AGS cell malignancy by inhibiting Hippo signaling activity, as well as conducting transcriptome analysis of regulatory genes. Furthermore, they revealed that in vitro up-regulation of GPR137 expression significantly enhances gastric cancer AGS cells proliferate, migrate, invade, form colonies, and grow as xenografts. Conversely, specific knockdown of GPR137 using targeted methods resulted in opposite effects. The researchers further elucidated the mechanism of action of GPR137 and found that it disrupts the association between MST and LATS by regulating the Hippo signaling pathway (Figure 2), particularly by binding to MST kinase. This disruption subsequently triggers YAP/TAZ-mediated transactivation of downstream target genes, ultimately leading to

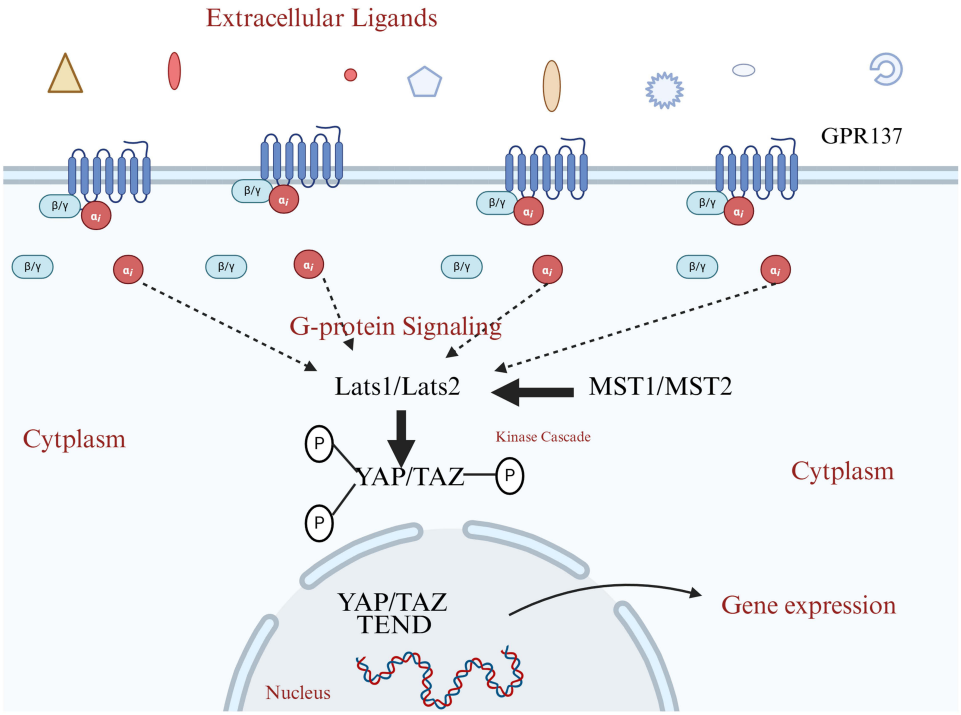

Figure 2 GPR137 regulates Lats and YAPTAZ activity in the HIPPO pathway.

malignant enhancement of cancer cells.[91] In summary, these observations highlight the involvement of GPR137 in gastric cancer carcinogenesis and metastatic invasion while suggesting its utilization potential as an emerging tumor biomarker for gastric cancer. Targeting GPR137 could offer a promising therapeutic approach for gastric cancer treatment.

Hepatocellular Carcinoma and Pancreatic Cancer

Hepatocellular carcinoma is a heterogeneous disease that still leads to the top five deadliest cancers, with a rising incidence each year.[43] The prognosis of hepatocellular carcinoma is unfavorable, as only 10–20% of patients can undergo complete resection through surgical intervention. In stages II and III, the median survival rate stands at a mere 1.6–3.5 months.[92] With the advent of targeted therapies, more and more molecules are being used for cancer treatment, and the widespread expression of GPR137 in the digestive system has garnered significant interest from multiple researchers. To investigate the roles and functions of GPR137 in hepatocarcinogenesis and progression, Shao et al[12] conducted knockdown experiments targeting GPR137 in two cell lines of hepatocellular carcinoma, HepG2 and Bel7404. The findings demonstrated that hepatocellular carcinoma cells were inhibited in their ability to proliferate and form colonies after the downregulation of GPR137. In addition, flow cytometry analyses manifested that knocking down GPR137 by lentivirus significantly increased cell proliferation in the G0/G1 and G2/M phases. In contrast, cell proliferation in the S phase is considerably decreased. These findings indicate that knockdown of GPR137 can arrest cell cycle progression at the G0/G1 phase, preventing entry into S phase and leading to tumor cell cycle arrest. This subsequently triggers apoptosis, ultimately inhibiting cell proliferation. The experimental results showed that GPR137 could function as an oncogene and inspire cell proliferation in hepatocellular carcinoma, thus promoting hepatocarcinogenesis. Cui et al[13] conducted a similar experiment to investigate how GPR137 affects pancreatic cancer. Using a lentivirus system, they knocked down GPR137 in two types of pancreatic cancer cell lines (BXPC-3 and PANC-1). When GPR137 was inhibited, a clear diminution in the growth and ability of cancer cells to form colonies was observed. Analyses by flow cytometry indicated that downregulation of GPR137 caused the arrest of the cell cycle in the sub-G1 phase and substantially increased apoptosis rate. Knocking down GPR137 resulted in activation of apoptosis and arrest of cell cycle through PARP fragmentation and up-regulation of Caspase3 expression levels, as confirmed by Western blotting. Conversely,

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overexpression of GPR137 mediated by lentivirus in PANC-1 cells promoted cellular proliferation. These experimental findings collectively underscore an integral part of the regulatory process of GPR137 in controlling the growth and apoptosis of cancer cells, thereby suggesting that it is a potential oncogene in cancers such as hepatocellular carcinoma and pancreatic cancer.

Ovarian Cancer

The reproductive system cancer is a significant contributor to mortality due to cancer among women, because of its lack of specificity, most patients with ovarian cancer are diagnosed at an advanced stage.[93] Current treatment modalities for ovarian cancer encompass surgical intervention, radiation therapy, and chemotherapy.[94] Despite this, it is still important to point out, after surgery many patients will relapse or become resistant to chemotherapy drugs.[95,96] Therefore, identifying effective therapeutic targets has become a prominent focus with expertise in ovarian cancer treatment. Zhang et al[15] devised a series of studies to elucidate the function of GPR137 in regulating the development of ovarian cancer and spread to other parts of the body. They investigated the gene expression of GPR137 in ovarian cancer tissue samples and demonstrated its high expression levels in clinical samples. Subsequently, they performed knockdown experiments targeting the GPR137 gene in two cell lines of this tumor, SKOV3 and OVCAR3. In the results, it was found that in SKOV3 and OVCAR3 cells, knocking down GPR137 caused different degrees of limitations of cell activity, migration ability and invasion. Flow cytometry analysis further revealed that the number of cells in the G2/M phase decreased substantially and an increase in the population of cells in the S phase after knocking down GPR137 in SKOV3 cells. In summary, these observations suggest that the knockdown of GPR137 effectively reduces the cell proliferation rate and clone-forming ability and inhibits xenograft tumor formation from SKOV3 and OVCAR3 cells. Additionally, the researchers observed the occurrence of transition from epithelium to mesenchyme (EMT) in NC or cells lacking GPR137. The findings demonstrated that following the knockout of GPR137 in SKOV3 and OVCAR3 cells, mesenchymal markers Snail, N-cadherin, and Vimentin expression continuously declined, while it was found that epithelial marker E-cadherin was expressed at higher levels. An immunofluorescence analysis targeting Vimentin confirmed a strong staining takes place in the cytoplasm and nucleus of SKOV3 cells that have been treated with NC, and cells treated with shRNA exhibited reduced intensity and lower levels of Vimentin expression. Conversely, E-calmodulin expression increased in shRNA-treated cells but was barely detectable in NC-treated cells. Based on these results, it appears that the knockdown of the GPR137 gene led to a reversal of EMT. Furthermore, an investigation into the signaling pathway associated with GPR137 gene action revealed its promotion of PI3K/AKT activation within the population of individuals with ovarian cancer. Thus, it is suggested the PI3K/AKT pathway may represent a potential mechanism by which GPR137 functions the development of reproductive system cancer. These findings offer novel insights into potential strategies aimed at preventing and treating ovarian cancer.

Medulloblastoma

There has been evidence that GPR137 is expressed in the nervous system, indicating that as part of the nervous system, it takes part in a wide range of processes linked to physiological and pathological changes. According to the evidence provided by Zong et al,[21] proliferation of glioma cells is regulated by GPR137, and the inhibition of GPR137 expression leads to reduced colony growth and proliferation. Wang et al[66] probed the roles and responsibilities of GPR137 in medulloblastoma by employing knockdown techniques in medulloblastoma cell line of Daoy cells. The experimental findings demonstrated that silencing GPR137 considerably inhibited cell proliferation and colony formation in Daoy cells. Based on flow cytometry, when GPR137 expression was knocked down, the percentage of cells in the G0/G1 phase increased, while the proportion of cells in the S phase exhibited a significant decrease. Moreover, there was a notable elevation in sub-G1 phase cells indicative of apoptotic cells following GPR137 knockdown in Daoy cells. Upon double staining with annexin V-APC/7-AAD, silencing GPR137 gene expression led to robust pro-apoptotic effects in Daoy cells. Therefore, we suggest that inhibition of GPR137 gene expression may hinder medulloblastoma cell growth and survival by reversing cell cycle progression and inducing arrest in the G0/G1 phase and enhancing apoptosis.

Other Malignancies

Moreover, GPR137 has been extensively investigated across various cancer types. For instance, an increasing expression of ALKBH1 (AlkB homologue 1) was ascertained in renal cancer tissues, which was associated with the expression of GPR137.[67] Based on earlier research, the aberrant expression of ALKBH1 has been linked to various malignant tumors such as gastric cancer,[97] hepatocellular carcinoma,[98] lung cancer[99] and head and neck cancer.[100] According to the study by Li et al, elevated ALKBH1 expression is involved with malignant features of renal cancer cells, including enhanced cell proliferation, migratory and invasion movements. Investigations of mechanisms further revealed that ALKBH1 regulates the expression of GPR137 through m6A-dependent mRNA demethylation. Specifically, ALKBH1 reduces the m6A level of GPR137 in renal cancer cells, which resulted in upregulation of GPR137 mRNA and protein levels, and thus enhanced the physiological activities of renal carcinoma cells. Conversely, the inhibition of GPR137 effectively attenuated the ALKBH1-induced malignant transformation in renal cancer cells. Another example is the study of GPR137 within the neural system by Kensuke Iwahara et al, which showed that down-regulation of the GPR137 gene promotes Neuro2a cell proliferation and impedes the process of neuronal differentiation. These results indicate that GPR137 has a substantial impact on regulating neuronal differentiation and the cessation of cell cycle in nerve cells.[101] The authors speculate that the differential effects of GPR137 observed between tumors and neuronal cells may stem from differences in GPR137-mediated signaling pathways. Ren et al[58] researched the function of GPR137 in prostate cancer. According to the demonstration, the level of GPR137 expression is elevated in prostate cancer tissues, and by targeted silencing the GPR137 gene, prostate cancer PC-3 and DU145 cells are efficaciously prevented from proliferating and colonizing, inducing a halt in the cell cycle at the G0/G1 phase. Suppression of GPR137 gene expression in prostate cancer cells caused a downregulation of snail1 and slug, while an upregulation of E-cadherin, which inhibits the migration and invasion of prostate cancer cells. The results highlight the oncogenic function of GPR137 in prostate cancer pathogenesis, indicating its potential to be a therapeutic target for advanced diseases.

Discussion

The G protein-coupled receptor family is the largest family of cell surface molecules involved in signaling identified to date. The family has a large number of members, accounting for more than 2% of the total number of genes encoded in the human genome.[25] These receptors are involved in the regulation of many key physiological functions, such as contraction and diastole of smooth and cardiac muscle, neurotransmitter release and blood pressure regulation.[102] Smoothened, for example, is a member of the G protein-coupled receptor (GPCR) frizzled (FzD) class. Smoothened has an extracellular cysteine-rich domain (CRD), which is involved in the regulation of the Hedgehog signaling pathway.[103] Similarly, GPCRs are expressed in proliferating cells versus differentiated mitotic cells and are involved in important physiological processes such as embryogenesis, normal cell growth, angiogenesis and tissue repair and remodeling.[104,105] Overexpression of GPCRs can lead to disruption of physiological processes and thus cause diseases such as inflammation and even tumors.[106,107] In fact, numerous basic studies have confirmed that many GPCRs are overexpressed in various types of cancers.[107] When GPCRs are activated by ligands, tumor cells will hijack their normal physiological functions, proliferate autonomously, evade immune detection, and thus invade surrounding tissues and organs or undergo distant metastasis. GPCRs are also targets of key mediators of inflammation,[25] and Marco De Giovanni[108] found that the G protein-coupled receptor, GPR35, is up-regulated in activated neutrophils and can act as a pro-migratory and pro-adhesion receptor in mobilized neutrophils, thus promoting inflammation. GPR35 is upregulated in activated neutrophils and can function as a pro-migratory and pro-adhesion receptor in mobilized neutrophils to promote neutrophil recruitment to inflammatory sites.

As a member of GPCRs, GPR137 has been increasingly studied in recent years. In this paper, we reviewed the progress of GPR137 in malignant tumors, which are overexpressed in various types of malignant tumors, such as hepatocellular carcinoma and pancreatic cancer.[12,13] Knockdown of GPR137 expression by shRNA can effectively inhibit tumor cell proliferation, migration, and invasion, and significantly increase the rate of apoptosis of tumor cells. However, there are still serious shortcomings in the current research on GPR137. Firstly, GPR137 has a trans-lysosomal membrane signaling function,[60] which can regulate the localization and activity of Rag and mTORC1,[14] and it should be

involved in the occurrence of neurodegeneration, diabetes mellitus, and many other diseases.[61,62] However, the current research on this gene is mostly limited to malignant tumors, and its mechanism of action in various malignant tumors has not been confirmed. Secondly, most of the studies on this gene still remain at the level of in vitro cellular experiments, without further in vivo experiments and clinical trials. As a next step, we should strengthen the research on GPR137, verify the specific signaling pathway of GPR137 in inflammation or malignant tumors through a series of basic experimental techniques, establish in vivo experimental models, and carry out clinical trials or drug tests at an early date, so as to use the results of the research in the clinic and serve the clinic.

Conclusion

Malignant tumors have long been a major concern for human well-being and survival. While the concept of prevention and modern medical technologies have helped people avoid suffering and death from certain types of cancer, effective diagnostic and therapeutic options are still needed for those who already have the disease. GPR137, a ubiquitously expressed orphan GPCR gene, has shown encouraging discoveries in a variety of cancer studies, and may be a potential therapeutic target. Future studies should focus on the molecular mechanisms of GPR137 in tumors or other diseases, especially the downstream signaling pathways (eg, PI3K/AKT, MAPK, etc.) that it regulates. Screening proteins interacting with GPR137 to reveal its functional network in cells. Explore the regulatory role of miRNAs, lncRNAs and other non-coding RNAs on GPR137 and monitor the dynamic changes of GPR137 expression in disease progression and assess its potential as a marker for dynamic monitoring. Early screening or design of small molecule inhibitors or agonists targeting GPR137 and use the research results targeting GPR137 in the clinic to provide patients with more effective and safer individualized therapeutic strategies.

Abbreviations

GPCR, G protein-coupled receptor; OGPCRs, Orphan GPCRs; GPR137, G Protein-Coupled Receptor 137; IARC, International Agency for Research on Cancer; PSGR, Prostate-specific odorant-like GPCR-encoding gene; HuOCSCs, Human ovarian cancer stem cells; GLP-1, Glucagon-like peptide-1; PAR-1, Protease-activated receptor-1; TRAP, Thrombin receptor agonist peptide; TAMs, Tumor-associated macrophages; ESRP1, Epithelial splicing regulator protein 1; ALKBH1, AlkB homologue 1; ShRNA, Short hairpin RNA.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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