REVIEW

Therapies targeting the signal pathways of pheochromocytoma and paraganglioma

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Abstract: Pheochromocytoma and paraganglioma (PCC/PGL) are rare tumors that originate from adrenal or extra-adrenal chromaffin cells. A significant clinical manifestation of PCC/PGL is that the tumors release a large number of catecholamines continuously or intermittently, causing persistent or paroxysmal hypertension and multiple organ functions and metabolic disorders. Though majority of the tumors are non-metastatic, about 10% are metastatic tumors. Others even have estimated that the rate of metastasis may be as high as 26%. The disease is most common in individuals ranging from 20 to 50 years old and the age of onset strongly depends on the genetic background: patients with germline mutations in susceptible genes have an earlier presentation. Besides, there are no significant differences in the incidence between men and women. At present, traditional treatments, such as surgical treatment, radionuclide therapy, and chemotherapy are still prior choices. However, they all have several deficiencies so that the effects are not extremely significant. Contemporary studies have shown that hypoxia-associated signal pathway, associated with the cluster 1 genes of PCC/PGL, and increased kinase signal pathways, associated with the cluster 2 genes of PCC/PGL, are the two major pathways involving the molecular pathogenesis of PCC/PGL, indicating that PCC/PGL can be treated with targeted therapies in emerging trends. This article reviews the progress of molecular-targeted therapies for PCC/PGL.

Keywords: pheochromocytoma, paraganglioma, targeted therapies, signal pathways

Introduction

Pheochromocytoma and paraganglioma (PCC/PGL) are neuroendocrine tumors arising from the chromaffin cells which are derived from the embryonic neural crest, including adrenal medulla PCC and extra-adrenal sympathetic and parasympathetic paraganglia (PGL). PCC/PGL often show an increase in catecholamines (adrenalin, norepinephrine, and/or dopamine), which affects the cardiovascular system and metabolic processes, thus causing high blood pressure.[1] Though hypertension is the most critical clinical symptom of PCC/PGL, this disease may also be associated with orthostatic hypotension. Besides, other common symptoms include recurrent headaches, excessive sweating, tachycardia as well as weight loss. It is reported that the features of headache, sweating, and palpitations appeared in 30–40% of the cases and could be seen as the best clue to suspect PCC/PGL.[2] There are also some clinical atypical presentations of PCC/PGL including sustained hypertension and incidental mass without associated symptoms. If PCC/PGL are not diagnosed in time, delaying in treatment can cause serious heart, brain, kidney vascular damages, and even death. In terms of catecholamines in PCC/PGL, different

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patients may have different levels. Recent researchers have found that catecholamine excretion varied according to gene mutations.[3] For example, mutations in NF1 and RET genes are almost always associated with PCC/PGL that produce catecholamine.[4,5] In opposite, some tumors due to mutations in VHL and SDHx genes lack significant excretion of catecholamine.[5] Some PCC/PGL express high levels of tyrosine hydroxylase (TH) which is the rate-limiting enzyme for catecholamine biosynthesis. For instance, the level of endogenous VHL tumor suppressor protein (pVHL) in PC12 cells expressing VHL antisense RNA reduced by 5–10 folds while the levels of TH protein and mRNA increased by 2–3 folds. Therefore, loss of pVHL function may be responsible for PCC-related hyper-catecholemia.[6]

The prevalence of PCC/PGL is estimated to be 1:6500–1:2500. Autopsy results show that the prevalence is as high as approximately 1:2000, indicating that many PCC/PGL were not diagnosed. The annual incidence rate is reported to be 2–10:1,000,000.[7] Most

PCC/PGL are discovered at 30–50 years old, and the incidence rate of males and females is basically equal.

It has been reported that PCC/PGL have the highest heritability in human tumors.[8] Furthermore, it is a kind of human tumor model that has inherited mutations in a metabolic enzyme gene, succinate dehydrogenase subunit D (SDHD). In addition to classic mutations in the genes encoding for the subunits of SDH, in the past five years more germline or somatic mutations have been found in genes encoding for other enzymes catalyzing pivotal steps of the tricarboxylic cycle acid (TCA), such as fumarate hydratase (FH), malate dehydrogenase 2 (MDH2), gluta-mic-oxaloacetic transaminase 2 (GOT2), and dihydroli-poamide S-succinyltransferase (DLST), in PCC/PGL.[9] In regard to the molecular pathogenetic mechanism of PCC/PGL, the hypoxia-related signal pathway (Figure 1) and the increased kinase signal pathways (Figure 2) are two main pathways involving the tumor.[10] It has been proved that the mutations of subunits of succinate dehydrogenase (SDH) (including SDHA, SDHB, SDHC, SDHD,
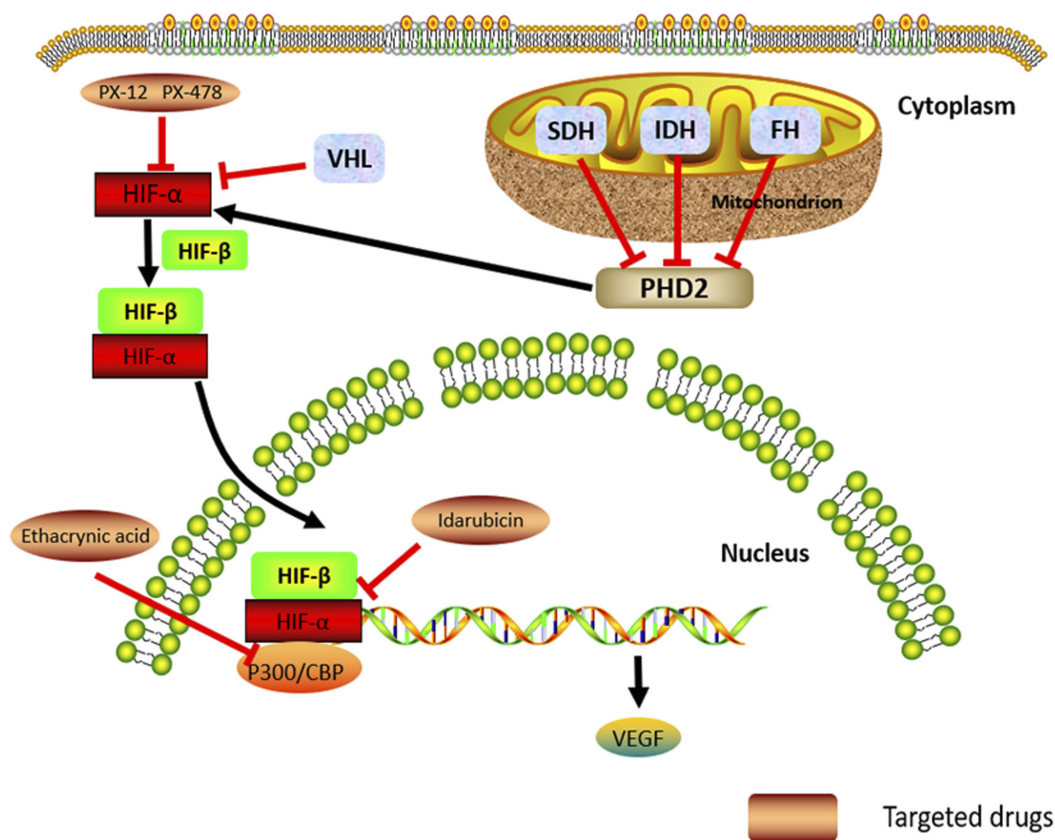

Figure 1 The hypoxia-related signal pathway, Cluster 1 genes, and their potential molecular-targeted medicines.
Abbreviations: HIF, hypoxia-inducible factor; VEGF, vascular endothelial growth factor; PHD2, prolyl hydroxylase domain protein 2; SDH, succinate dehydrogenase; IDH, isocitrate dehydrogenase; FH, fumarate hydratase; VHL, von Hippel Lindau.
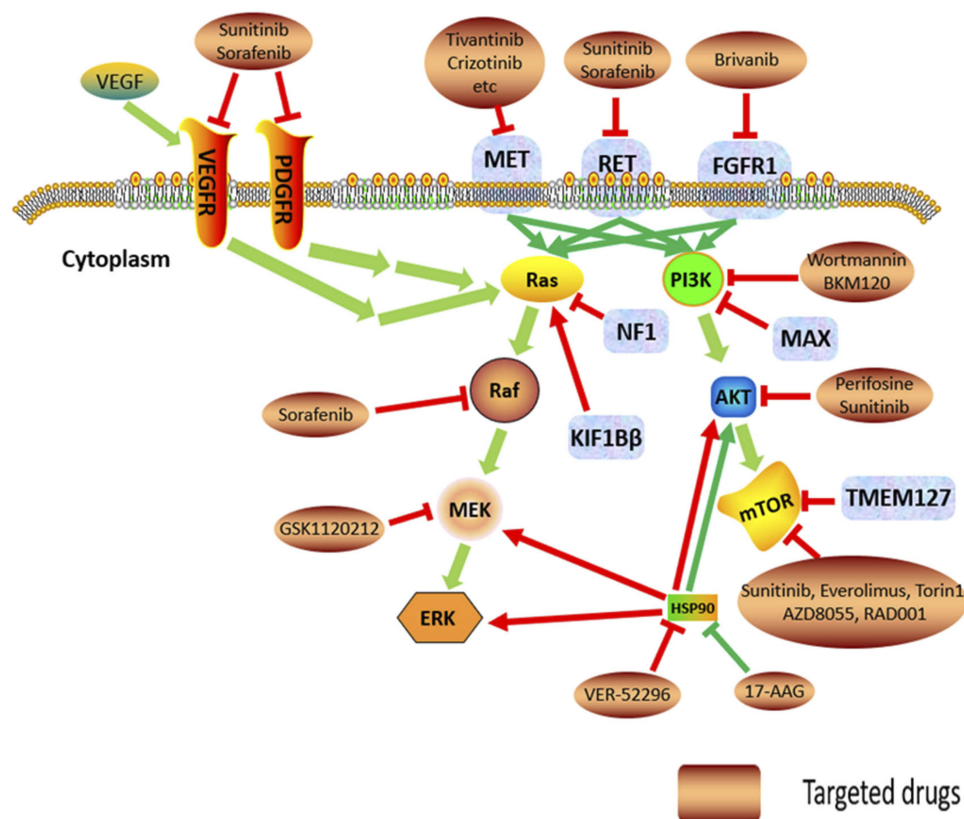
Figure 2 The increased kinase signal pathways, Cluster 2 genes, and their potential molecular-targeted medicines.
Abbreviations: VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; PDGF, platelet-derived growth factors receptor; MAX, myc-associated factor X; TMEM127, transmembrane protein 127; NF1, neurofibromin 1; KIF1Bβ, kinesin family member1B β; RET, rearranged during transfection proto-oncogene; FGFR1, fibroblast growth factor receptor 1; MET, MET proto-oncogene; PI3K, phosphatidilinositol 3-kinase; mTOR, mammalian target of rapamycin; MEK, MAPK/ERK kinase; ERK, extracellular regulated protein kinases; HSP, heat shock protein.

SDHAF2), FH, prolyl hydroxylase domain protein 2 (PHD2), von Hippel Lindau (VHL), and hypoxia-inducible factor 2A (HIF2A), which are the cluster 1 genes of PCC/PGL, influenced the hypoxia-related signal pathway, while the mutations of rearranged during transfection proto-oncogene (RET), myc-associated factor X (MAX), trans-membrane protein 127 (TMEM127), neurofibromin 1 (NF1), and kinesin family member1B β (KIF1Bβ), which are the cluster 2 genes of PCC/PGL, influenced the increased kinase signal pathways.[10]

If it were diagnosed and treated in a timely and early manner, PCC/PGL could be cured. Traditional therapies (surgical treatment, radionuclide therapy, and chemotherapy) are the most commonly used treatments for PCC/PGL nowadays, but they have shown suboptimal results in shrinking tumors and improving survival. Currently, effective molecular-targeted therapies aiming at permanent control of these highly complex neoplasms are the research hotspot and the aim of efforts and molecular

characterization of PCC/PGL suggests the targeted therapies should be optional treatments (Table 1). The current progress in the treatments of PCC/PGL is summarized as follows.

Traditional therapies
Surgical treatments

In terms of surgical methods, laparoscopic adrenalectomy (LA) has become the choice of more and more surgeons. Open adrenalectomy (OA) has a great advantage in large tumor resection and the invention of robot-assisted adrenalectomy (RA) undoubtedly provides surgeons with more options.[11]

LA treatment of PCC is still controversial. On the one hand, laparoscopic surgery is a great advantage for adrenal tumors with deep, small, and difficult exposures. And LA is regarded as the gold standard for the treatment of non-metastatic adrenal tumors. On the other hand,

Table I Targeted drugs in PCC/PGL

Drug	Study	Targets	Efficacy	References
Sorafenib	Both sunitinib and sorafenib are effective treatments for pheochromocytoma in a xenograft model	VEGFR, PDGFR, RET	In vivo (mice)	72–74
Sunitinib	Treatment with sunitinib for patients with progressive metastatic pheochromocytomas and sympathetic paragangliomas	VEGFR, PDGFR, RET	In vivo (clinical)	75–89
Everolimus	Phase 2 study of everolimus monotherapy in patients with nonfunctioning neuroendocrine tumors or pheochromocytomas/paragangliomas	mTOR	In vivo (clinical)	90–92
AZD8055	Combined inhibition of mTORC1 and mTORC2 signaling pathways is a promising therapeutic option in inhibiting pheochromocytoma tumor growth: in vitro and in vivo studies in female athymic nude mice	mTOR	in vitro & in vivo (mice)	93–95
Torin1	Rapamycin toxicity in MIN6 cells and rat and human islets is mediated by the inhibition of mTOR complex 2 (mTORC2)	mTOR	In vitro	96, 97
17-AAG	Targeting heat shock protein 90 for the treatment of malignant pheochromocytoma	Hsp90	In vitro	98–103
VER-52296	The effects of VER-52296 targeting HSP90 in pheochromocytoma cell line PC12	Hsp90	In vitro	102, 104
Perifosine	Advances in kinase inhibitors targeting PI3K-Akt-mTOR signal transduction pathway	AKT	In vivo (clinical)	105–107
Ethacrynic acid	Menadione and ethacrynic acid inhibit the hypoxia-inducible factor (HIF) pathway by disrupting HIF-1α interaction with p300	HIF	In vitro	111
Idarubicin	Anthracycline chemotherapy inhibits HIF-1 transcriptional activity and tumor-induced mobilization of circulating angiogenic cells	HIF	In vivo (mice)	112–114
PX-12 and PX-478	Evaluation of HIF-1 inhibitors as anticancer agents	HIF	In vivo (mice)	115–117
Tivantinib	MET inhibitors for targeted therapy of EGFR TKI-resistant lung cancer	MET	In vivo (clinical)	117
Brivanib	Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: a randomized phase III trial	FGFR1	In vivo (clinical)	71, 119–122
BIBR1532	Mechanism of human telomerase inhibition by BIBR1532, a synthetic, non-nucleosidic drug candidate	TERT	In vitro	123–127

adrenal PCC is characterized by abundant blood supply and tumor volume is usually larger than other adrenal tumors.[12] Complications including uncontrolled high blood pressure, hemodynamic instability, invasion of surrounding tissues, and local recurrence are likely to occur during surgeries. It may lead to difficulties in LA, which has to be transited to OA then, not to mention that the establishment of LA itself may also stimulate the secretion of catecholamines, thereby increasing the risk of surgery.[12]

OA as a traditional surgical method has unfavorable factors such as high intraoperative blood loss, slow recovery, and long hospital stay, but it is still unable to be replaced in the resection of large tumors (>6 cm in diameter) and uncertain non-metastatic or metastatic tumors before the operation.[13] Blood supply of giant PCC is abnormal, and there is plenty of collateral circulation. Because the tumor supply vessels are ligated and blocked, the pressure inside the tumor will increase when the blood flow of the tumor blocked. Therefore, the blood will ooze more during the operation and the blood loss is greater when the tumor is isolated. At that time, timely blood transfusion is the key of guaranteed successful surgeries. The use of autologous blood recovery has the advantages of rapid, timely avoiding the loss of allogeneic blood as well as washed red blood cells are fresh thus can immediately exert oxygen-carrying function and the adverse reactions are small.[14]

Robot-assisted adrenalectomy is as safe as LA, with less bleeding, faster recovery, and shorter hospital stay. First, surgeons can adjust the angle of the endoscope to get a good view of the operation according to their own needs, allowing deep adrenal tumor surgery to achieve a better surgical field and provides protection for surgical resection. Second, the operator can use the operating tool to operate the surgical instruments freely and flexibly, making the surgery more sensitive and the operation more precise and rapid. The robotic system also allows the surgery to be performed in a relatively relaxed and comfortable environment so that the operator is less prone to be fatigue; thus, the quality of the operation is guaranteed. But it is generally believed that RA has a longer operation time and a higher cost than LA. Moreover, the operator lacks an intuitive touch to the organ during the operation, increasing the possibility of potentially damaging adjacent organs.[15–17]

In principle, the main purpose of surgical treatment is to eradicate the primary tumor and to remove local and distant metastases. However, due to the tendency of distant metastasis and recurrence of metastatic tumors, surgeries often fail to achieve the desired results. It is recommended that plasma or urinary adrenaline should be tested annually to screen for local or metastatic recurrence or new tumors and all patients undergoing PPGL surgery should be followed for at least 10 years. High-risk patients even need to receive annual follow-up during lifetime.[18]

Radionuclide therapy

I^{131}-metaiodoenzylguanidine (I^{131}-MIBG) is a kind of radiopharmaceutical which acts as a norepinephrine analog taken up by cells in the sympathomedullary system[19] and high doses of I^{131}-MIBG can prolong survival and relieve symptoms.[20] Since PCC expresses somatostatin receptors, radiopharmaceuticals based on the somatostatin analogs octreotide and lanreotide have also begun to be used.[21] However, these treatments are only suitable for cancer patients who have high intake of radionuclides and there is still insufficient evidence to determine radionuclide therapy doses and normal tissue tolerated doses. The dose segmentation of radionuclide therapy is also controversial and still requires a larger sample size as well as further follow-up confirmation.[22]

Chemotherapy

Since the late 1960s, a range of chemotherapies have been described as potential treatments for PCC/PGL. These include temozolomide, dacarbazine, streptozotocin, doxorubicin, vincristine, methotrexate, 5-fluorouracil, ifosfamide, cyclophosphamide, and platinum compounds. They inhibit different stages of the cell cycle, resulting in cancer cell death so they are effective in the treatment of many cancers.[23] O-6-methylguanine-DNA methyltransferase (MGMT) promoter displaying hypermethylation in SDHB-related tumors leads to the silencing of MGMT expression.[24] MGMT is at high risk of progression with DNA hypermethylation and is a prognostic factor for the response to temozolomide. When tested temozolomide in PCC/PGL patients, 67% of the patients showed clinical benefits and 80% of them showed tumors of low-level MGMT.[24] Moreover, the CVD regimen (a combination of cyclophosphamide, vincristine, and dacarbazine) recommended for chemotherapy had an effective rate of about 50%, but most of them relapsed within 2 years.[21] A meta-analysis showed that about 37% of the patients had partial response on reducing tumor volume after using chemotherapy drugs.[20] A study from Japan showed that in 17 patients with metastatic PCC, the partial response rate of chemotherapy was 47.1% and no patients were fully cured.[25] Huang et al[26] showed that in 18 metastatic PCC patients who received chemotherapy, 11% achieved complete remission and 44% had partial remission. After 22 years of follow-up, their 5-year survival was less than 50%. The study by Nomura et al[27] also showed that the survival of the chemotherapy group was not superior to the control group. Therefore, the advantage of chemotherapy is to improve symptoms, but may not extend the long-term survival time.

Signal pathways and genes associated with hereditary PCC/PGL

Before studying the targeted therapy, we try to make clear the signal pathways involving PCC/PGL in which proteins may be the selected targets for therapies. There are two kinds of signal pathways leading to PCC/PGL.[28–33] To be specific, the hypoxia-associated signal pathway, associated with the cluster 1 genes of PCC/PGL, and increased kinase signal pathways, associated with the cluster 2 genes of PCC/PGL, are the two major pathways involving the

molecular pathogenesis of PCC/PGL, proven by the Cancer Genome Atlas (TCGA) sequencing study.[34]

Hypoxia-related signal pathway and cluster 1 genes

In the process of rapid proliferation, tumor cells need to consume a large amount of oxygen, leading to the gradual formation of chronic hypoxic microenvironment in tumor tissues due to insufficient blood oxygen supply. In response to the hypoxic microenvironment, cancer cells will regulate themselves through a series of energy metabolism signal pathways, angiogenesis, proliferation, survival, invasion, and tumor metastasis. Hypoxia-inducible factor (HIF) is a kind of transcription factor that controls energy, erythropoiesis, iron metabolism, and development[29] and when dysregulated, it will result in tumorigenesis.[35] In the hypoxia-related signal pathway, the HIF is a kind of transcription factor found in mammalian cells and consists of two subunits heterodimeric, which are oxygen-sensitive HIF-α and stably expressed HIF-β. HIF-α is one of the key proteins that regulate these signal pathways in tumor cells in a hypoxic environment.[36] HIF-α has two transactivation domains at the carboxyl terminus, N-terminus and C-terminus. Under hypoxic conditions, the transactivation region at the C-terminus interacts with the transcriptional coactivator p300 and is involved in the regulation of transcriptional activation. Specifically, HIF-α has normal physiological functions after being modified by heat shock protein Hsp90 and then forms a dimer with HIF-β. After entering the nucleus, the dimer binds to the co-transcription factor p300 and cyclic AMP response element-binding protein (p300/CBP) to form HIF-p300/CBP complex which binds to a hypoxia-responsive element (HRE) of DNA and regulates transcription of downstream genes.[37] It is worth mentioning that in 2013, David et al first associated the somatic HIF2A gain-of-function mutation with PCC/PGL.[38]

What influences the hypoxia-related signal pathway is the mutations of Cluster 1 genes. In the presence of oxygen, the PHD2 catalyzes the proline hydroxylation of HIF, which is recognized and targeted to degrade by VHL that constitutes a part of the E3 ubiquitin ligase complex.[39,40] Since the discovery of VHL disease tumor suppressor gene VHL in 1993 as the genetic basis of VHL disease, VHL has been proven to have broad medical and scientific value. pVHL plays an important role in cellular oxygen sensing through targeting HIF for ubiquitination and proteasomal degradation.[41] Besides, in PCC/PGL, VHL

mutations reported were often missense mutations.[42] These mutations result in the activation of HIF signal pathways at normal oxygen levels, elevated erythropoietin levels, and overproduction of red blood cells.[43] Somatic VHL mutations in PGLs were first reported by Merlo,[44] which was tested in 53 PGL tissues through gene sequencing and other methods. The results indicated that VHL mutations could predict the clinical diagnosis of PCCs and play a crucial role in the pathogenesis of sporadic head and neck paragangliomas.

Besides, SDHx genes encode succinate dehydrogenase (SDH), a mitochondrial enzyme complex, which is part of the citric acid cycle and electron transport chain.[45] SDH oxidizes succinate to fumarate in the citric acid cycle and delivers electrons to coenzyme Q in the electron transport chain.[45] Harmful mutations in SDHx lead to energy metabolism disorders and succinate accumulation, thereby inhibiting the activity of PHD2. These, in turn, lead to increased activation of HIF-α.[46] The SDHx consists of four subunits: SDHA, SDHB, SDHC, and SDHD, and germline mutations in the SDHx gene result in hereditary PCC/PGL syndrome. The discovery of SDH complex assembly in 2009 involved two factors, SDHAF1 and SDHAF2, which may play a part in the development of cancers related to this pathway.[47,48] SDHA gene acts as tumor suppressor and is considered as a new PCC/PGL susceptibility gene.[49] SDHB mutations and SDHC mutations were also proven to have relationship with PCC/PGL.[50,51] In 2000, SDHD mutations were found in sporadic and hereditary PGL/PCC.[50,52,53]

Last but not least, FH is a fumarate hydratase in the citric acid cycle, catalyzing the hydration of fumarate to malate. The mutations of FH result in the accumulation of fumarate, and thus activate the oncogenic HIF pathway through inhibiting PHD2.[54] FH mutations can be regarded as a rare source of susceptibility to PCC/PGL[32] and FH-deficient PCC/PGL have similar genetic developmental pathways to SDHB-mutated metastatic PCC/PGL. In conclusion, mutations of FH result in metastatic PCC/PGL with a great possibility.[31]

Increased kinase signal pathways and cluster 2 genes

PI3K/AKT/mTOR signal pathway is an important intracellular kinase signal pathway that regulates the cell cycle and is directly related to cell dormancy, proliferation, carcinogenesis, and longevity. PI3K is a heterodimer of

the regulatory subunit P85 and the catalytic subunit P110. Various growth factors and cytokines, such as insulin-like growth factor (IGF), nerve growth factors (NGF), and platelet-derived growth factors (PDGF), activate PI3K via tyrosine kinase and G protein-coupled receptors. Subsequently, activated PI3K catalyzes the phosphorylation of phosphatidylinositol biphosphate 2 (PIP2) to phosphatidylinositol biphosphate 3 (PIP3). On the other hand, phosphatase and tensin homolog deleted on chromosome ten (PTEN) that is a tumor suppressor gene can induce the dephosphorylation of PIP3 into PIP2, thereby antagonizing PI3K.[55] PIP3 acts as a second messenger, allowing the phosphorylation and activation of the AKT with the help of 3-phosphoinositol-dependent protein kinases (PDK1 and PDK2). Then, the activated AKT further activates the downstream mTOR which is one of the most important substrates of AKT and is closely related to the occurrence and development of tumors.[56]

Another increased kinase signal pathway of PCC/PGL is the Ras/Raf/MEK/ERK that is a typical mitogen-activated protein kinase (MAPK) pathway through which extracellular signals can be transmitted into cells to participate in physiological activities such as cell proliferation and survival. It is mainly composed of Ras (a G protein) and three bispecific protein kinases like Raf, MEK, and ERK. ERK is involved in the regulation of life activities such as cell proliferation, survival, and migration by phosphorylating downstream substrates in the cytoplasm and nucleus.

Actually, the Cluster 2 genes have fundamental impacts on PI3K/AKT/mTOR and Ras/Raf/MEK/ERK signal pathways. To begin with, RET is an oncogene in PCC/PGL susceptibility gene. In 1993, Mulligan et al found that RET was a kind of receptor tyrosine kinase gene expressed in PCC and acted as a candidate gene for multiple endocrine neoplasia type 2A (MEN 2A), a syndrome in which two or more endocrine gland neoplasms including PCC occur simultaneously or successively in the same patient.[57] The RET gene is principally expressed in the genitourinary system and neural crest precursor cells.[58] The oncogenic activation of RET has been verified to activate both PI3K/AKT/mTOR- and Raf/Raf/MEK/ERK-dependent pathways.[59]

When it comes to MAX, its mutations were first reported in susceptibility to hereditary PCC/PGL in 2011. MAX plays a crucial role in the MYC/MAX pathway, the deregulation of which contributes to activate PI3K. The isolation of MAX mutations, immunohistochemical analysis of MAX protein deletions in tumors, and loss of wild-type MAX alleles in tumors implied that MAX is a tumor suppressor gene.[60] Burnichon sequenced MAX using extracted DNA from blood leukocytes of 1694 patients with PCC/PGL, of which the MAX mutation was first discovered in PGL.[61]

As for TMEM127, it was identified as a new PCC susceptibility gene in 2010 by Yuejuan Qin et al,[62] its tumor suppressor properties cause changes in the function of endolysosomal mTOR. Therefore, mutations in TMEM127 result in an increase in the mTOR signal, which may contribute to the development of PCC/PGL.[63,64] These results suggest that abnormal activation of mTOR signal pathway may promote the occurrence of PCC, and the degree of its activation may be related to tumor invasion and metastasis.[65]

On account of KIF1Bβ, it influences Ras/Raf/MEK/ERK signal pathway by acting on the Ras. It was reported that a family with KIF1Bβ gene mutations developed neuroblastoma, ganglioneuroma, PCC, and lung cancer.[66] Similarly, in 2002, Kimura et al found that NF1 is associated with the tumorigenesis of composite PCC.[67] NF1 gene acts as a tumor suppressor gene and its main function is to inhibit the oncogenic Ras/Raf/MAPK signal pathway by converting Ras protein into an inactive form to inhibit cell proliferation. About one-fifth of sporadic PCCs may have somatic NF1 mutations and the loss of heterozygosity in NF1 suggests that loss of function may be the primary mechanism of NF1 alteration in PCC/PGL.[68,69]

There are many other recently discovered mutations that converge in this pathway, such as HRas proto-oncogene (HRAS), MET proto-oncogene (MET), and fibroblast growth factor receptor 1 (FGFR1). The first HRAS mutation found in a patient with PCC was reported by Yoshimoto in 1992.[70] Belonging to the Ras oncogene family, it is associated with Ras/Raf activation thus results in PCC/PGL. In addition, MET may also have a relationship with PCC/PGL predisposition.[71] MET is a proto-oncogene whose transmembrane receptor protein MET has tyrosine kinase activity. The binding of the MET receptor to hepatocyte growth factor induces the activation of MET dimer, which in turn phosphorylates its substrate to activate downstream signaling pathways: PI3K/AKT/mTOR and Ras/Raf/MEK. Furthermore, FGFR1 encodes FGFR1 protein, which is a kind of transmembrane protein belonging to receptor tyrosine kinase. When fibroblast growth factor binds to the extracellular segment of FGFR1, the intracellular segment of the receptor affects

the downstream kinase signaling pathway. Therefore, the dysregulation of FGFR1 signaling leads to the development, proliferation, survival, and metastasis of tumors.[71]

Targeted therapies
Multi-target inhibitors: sorafenib and sunitinib
Sorafenib
Angiogenesis, the formation of capillaries, is critical for tumor growth and metastasis, as tumors require independent blood supply with oxygen, glucose, and other nutrients to cancer cells.[72] By this token, it has already been proven that drugs blocking angiogenesis can be effective in anti-cancer therapies. In the past 10 years, a variety of drugs have been developed, including tyrosine kinase inhibitors which have anti-angiogenic activity. Vascular endothelial growth factor receptor (VEGFR) tyrosine kinases involve tumor growth, progression, metastasis as well as angiogenesis; thus, it is a suitable target for drugs. Sorafenib is a new multi-target oral anti-cancer medicine, which can inhibit serine/threonine kinase activity and tyrosine kinase activity of VEGFR-2, VEGFR-3, PDGF-β, stem cell factor receptor (KIT), and FMS-like tyrosine kinase (FLT)−3 receptors, RET, Raf.[73] Therefore, sorafenib has dual anti-tumor effects. For one thing, it can directly inhibit the proliferation of tumor cells by blocking the signal transduction pathway mediated by Raf/MEK/ERK. For another, it can also inhibit the formation of neovascularization and cut off the nutritional supply of tumor cells by acting on VEGFR, so as to achieve the purpose of restraining the growth of tumors.[74]

Sorafenib has been used to treat kidney cancer and liver cancer in the clinic. At present, sorafenib treating metastatic PCC are limited to several case reports, so more clinical studies and long-term follow-up are needed to confirm its efficacy.

Sunitinib
Sunitinib is another multi-target tyrosine kinase inhibitor with anti-angiogenic and anti-tumor effects.[75] As it has been mentioned earlier, HIF is a transcription factor responsible for regulating cellular responses to hypoxia, and its expression and regulation are influenced by intracellular oxygen tension. Both VHL mutations and SDHx mutations can cause HIF-α accumulation, leading to elevated VEGF and PDGF.[76] Targets of sunitinib are mainly VEGFR, PDGFR, and RET, and it is usually used to alleviate/treat metastatic PCC.[77,78] Experiments have

shown that knocking out VEGFR-2 attenuated the effects of sunitinib.[79] In addition, for another mechanism of PCC, the PI3K/AKT/mTOR pathway, sunitinib inhibits phosphorylation of AKT and mTOR, thereby inhibiting cell proliferation, angiogenesis, and apoptosis escaping. An important trait of metastatic PCC showed most VHL and SDHX-associated tumors are usually of high vascularization, suggesting that anti-angiogenic drugs can represent an effective treatment.[80–83] A clinical study and case report showed that oral sunitinib was effective in treating PCC/PGL.[84–86] In particular, Ayala-Ramirez et al reported some of the benefits of sunitinib in tumor shrinkage and disease stabilization in some patients with progressive metastatic PCC.[84] Several studies have also shown that can be used for the treatment of metastatic PCC, renal cell carcinoma, as well as pancreatic neuroendocrine tumors and achieved relatively good results.[75,87–89] Importantly, it has been approved in Europe and America.

mTOR inhibitor: everolimus, AZD8055, and Torin1
Everolimus
Everolimus is an mTOR inhibitor. The PI3K/AKT/mTOR pathway regulates cell growth and survival, resulting in high expression of mTOR, leading to cell proliferation, angiogenesis, and apoptosis evasion.[90] Druce et al[91] reported that 4 patients who underwent everolimus had progression and considered that everolimus was not effective in treating metastatic PCC/PGL. Oh et al[92] used everolimus to treat 5 patients with metastatic PCC and 2 patients with paraganglioma. After treatment, the patients' conditions remained stable. Though 2 patients' tumors progressed, 4 patients had significantly smaller tumor volume. It can be seen that the efficacy of everolimus in the treatment of metastatic PCC/PGL is still uncertain.

AZD8055
AZD8055 is a novel ATP-competitive mTOR inhibitor that can be administered orally and has good selectivity.[93] Furthermore, in inhibitory effects of AZD8055, mTOR is approximately 1000 times more than all class I PI3K isoenzymes and other PI3K-like kinase family members.

AZD8055 can inhibit S6K1 and 4e-bp-1 which are the downstream factors of mTOR complex 1. Besides, it can also inhibit the phosphorylation of mTOR complex 2 substrate AKT and downstream proteins. In vitro, it inhibited hyperplasia and induced autophagy in H838 and A549 cells. In a mouse xenograft model, AZD8055 inhibited

the phosphorylation of S6K1 and AKT in a concentration-dependent manner thus effectively inhibited tumor growth.[94]

Alessio Giubellino[95] found that AZD8055 could significantly reduce volume of tumor in a female athymic mouse of metastatic PCC/PGL.

Torin1

Torin1 is one of mTOR kinase inhibitors and others including Torin2, PP242, PP30, KU0063794, WAY-600, WYE-687, WYE-354, OSI-027, AZD-8055, KU-BMCL-200908069–1, Wyeth-BMCL- 200908069–2, XL-388, INK-128he, and AZD-2014 and some have entered different clinical trials.[96] In addition, Torin1 can also inhibit glycolysis of tumor cells in hypoxic and energy-poor environments, thereby making tumor cells starved and further enhancing their anti-tumor effects.[97]

H90 inhibitors: 17-AAG and VER-52296

HSP90 has turned out to be involved in the maturation and stable folding of a variety of proteins, which are critical for tumor cell growth and metastasis. Therefore, HSP90 may be a potential for tumor therapies.[98,99] Several Hsp90 inhibitors have been developed in the past few years and several clinical trials are in progress. Geldanamycin (17-AAG) is one of the most widely studied HSP90 inhibitors in cancer treatment in recent years. One study has demonstrated that 17-AAG reduced the expression of Hsp90-dependent phospho-AKT.[100,101] Moreover, experiments have proven that 17-AAG can affect client proteins of Hsp90 in MTT (a kind of metastatic mouse PCC cell-derived cell line) cells and inhibit metastasis of PCC/PGL.[102] They have a significant anti-tumor activity against both subcutaneous and metastatic tumor growth. However, its clinical application is restricted by adverse liver toxicity and adverse effects such as resistance.[103]

Another Hsp90 inhibitor VER-52296 can be used as a better small molecule inhibitor that is toxic to tumor cells while avoiding adverse effects of 17-AAG medicines.[104] VER52296 mainly inhibits the activity of HSP90 protein by binding to the N-terminal domain of HSP90 protein and promotes the anti-tumor effect of its client protein activity. In addition, Xu et al[102] found that VER-52296 can effectively inhibit the growth of tumors and the effects of inducing apoptosis on metastatic PCCs are shown both in vitro. Therefore, VER-52296 will be a very reasonable and effective option for the treatment of metastatic PCCs, either alone or in combination with other medicines. Cell

experiments showed that VER-52296 significantly inhibited the proliferation and migration of PC12 cells in a time- and dose-dependent manner, and apoptosis and cell cycle arrest were observed in cells exposed to VER-52296. Therefore, it was speculated that VER-52296 might play a regulatory role by phosphorylation of HSP90-specifically related client proteins. Noteworthily, exposure of HSP70 to VER-52296 for 24 hrs showed a relationship with upregulation of dose-dependent expression, which is a typical marker for HSP90 inhibition. In sharp contrast, phosphorylated AKT, MEK, and ERK were significantly downregulated after exposure to VER-52296 while the expression of total protein of these three signal proteins did not change significantly. The study indicated that the inhibition of PI3K/AKT and MEK/ERK signal pathways produced by VER-52296 could provide a reasonable explanation for its obvious promotion in apoptosis and significant promotion in cell cycle quiescence.[102]

AKT inhibitor: perifosine

Perifosine is a class of phosphatidylinositol analogs developed by Aeterna Zentaris and it is the first AKT inhibitor. It prevents the recruitment and activation of AKT on cell membrane, thereby inhibiting the activation of AKT. Studies have shown that perifosine inhibits AKT-mediated cellular signal pathways. In preclinical studies, perifosine inhibits the proliferation of immortalized keratinocytes (HaCaT cells) and squamous cell carcinoma of the head and neck. Also, it significantly reduces AKT phosphorylation and cell cycle arrest in G1 and G2. Besides, it causes dose-dependent growth inhibition of mouse glial progenitor cells.[105] In addition, perifosine exhibits good anti-tumor activity against mouse neuroblastoma.

Perifosine has shown excellent efficacy and tolerability in clinical phase II studies of recurrent breast, pancreatic, prostate, head and neck, and lung cancer.[106] Unlike the majority of kinase inhibitors that target the adenosine triphosphate-binding region, perifosine targets the homeodomain of AKT, preventing its transport to the plasma membrane. Additionally, the efficacy of perifosine has been observed in patients with sarcoma. However, the response rate of common solid tumors to perifosine as a single medicine has been disappointing, lowering expectations and prompting further research into its mechanism of action. Although many preclinical studies have documents on AKT inhibition by perifosine, clinical validation of these findings is still lacking.[107]

PI3K inhibitor: wortmannin

For PI3K inhibitors, the present clinical evidence is more limited due to their early stages of development. In most phase I studies, the quantity of responses was too small to determine any clear association with the candidate PI3K/AKT/mTOR pathway biomarkers currently.[108,109]

Wortmannin is an inhibitor of the PI3K's catalytic subunit. Although wortmannin has a good anti-tumor effect, it is poorly water-soluble and highly toxic, which limits its further development into clinical use. Although PI3K inhibitors can avoid activation of AKT, they do not show significant clinical advantages which may be related to the early stage of PI3K inhibitor development.[110]

HIF inhibitors: ethacrynic acid, idarubicin, PX-12, and PX-478

Ethacrynic acid

Na et al[111] found that ethacrynic acid has a blocking effect on HIF-α/p300 protein–protein interaction. Ethacrynic acid is a diuretic that increases urination mainly by inhibiting the active reabsorption of NaCl in thick sections of the renal tubules. It does not affect the expression of HIF-1α but can reduce the transcriptional expression of downstream VEGF. As a commonly used diuretic, the safety of ethacrynic acid has been clinically proven. Whereas, the structure–activity relationship and target selectivity need to be further studied to increase protein–protein interaction blocking activity and decrease diuretic activity.

Idarubicin

Idarubicin is one of the anthracyclines, which is a well-known class of chemotherapy medicines mainly including daunorubicin, doxorubicin, epirubicin, and idarubicin. When administered to mice at low doses, it had been shown to inhibit tumor growth and angiogenesis by blocking the HIF signal pathway.[112,113] Anthracyclines' effects on the progression of metastatic PCC have been explored in vitro and in vivo.[114] It has been demonstrated that anthracyclines, particularly idarubicin, could suppress hypoxia signaling by preventing the binding of HIF to the hypoxia response element sites on DNA. This contributed to reduced transcriptional activation of HIF target genes, including vascular endothelial growth factor A (VEGFA), erythropoietin (EPO), kinase 1 (PGK1), lactate dehydrogenase A (LDHA), endothelin 1 (EDN1), and phosphoglycerate glucose transporter 1 (GLUT1), and consequently it inhibited the growth of metastatic PCC. What's more, idarubicin interferes with the transcriptional

activation of HIF-α to downregulate hypoxia signaling. Moreover, the animal model demonstrates the dose-dependent inhibition of idarubicin on metastatic PCC growth in vivo. Thus, anthracyclines are promising candidates for inclusion in metastatic PCC therapies, especially for patients who have gene mutations in the hypoxia signal pathway.[114]

PX-12 and PX-478

HIF is a key regulator of tumor environment, so some agents like PX-12and PX-478 play a role in inhibiting tumor activity by inhibiting HIF. Although there is no reported data on metastatic PCC, these medicines have shown significant antineoplastic activity in mouse xenografts of various human tumors and appear to be promising for metastatic PCC, but there is no conclusive data.[115–117]

Inhibitors of MET, FGFR1, and TERT

MET inhibitors have three categories: the small molecule MET receptor inhibitors such as tivantinib, crizotinib, tepotinib, savolitinib, cabozantinib, and foretinib; MET receptor monoclonal antibodies such as onartuzumab; antibodies against its ligand. They have shown survival benefit in the treatment of PCC/PGL.[118]

As for FGFR1, in the past few years, there has been considerable progress in the development of selective FGFR1 inhibitors for use.[71] At present, more than 10 FGFR1 inhibitors have been in clinical trials. Under the experimental conditions, several agents have achieved encouraging results.[119] The use of clinical grade tyrosine kinase inhibitors targeting FGFR1, as well as agents for chromatin modifications may extend the number of experimental treatment regimens to malignant or inoperable PCC/PGL.[120,121] Brivanib is a kind of FGFR1 inhibitor developed as therapeutics and has already been in clinical phrase III.[122]

Last but not least, telomerase reverse transcriptase (TERT) activation is also a potential target, particularly for metastatic tumors,[123] because immortalization in primary PCC/PGL could be an important risk factor for metastasis. Immortalization is achieved by a recombination-based alternative lengthening of telomeres (ALT) pathway[124] which can be assessed by evaluation of TERT expression.[125] BIBR1532 is one of the most promising TERT-specific active site inhibitors to date. It is a synthetic compound of non-nucleotide small molecules

that inhibits telomere extension by noncompetitive binding to the active site of TERT.[126,127]

Combined medicine therapies

The growth-inhibiting effects of AZD8055 and Torin-1 that are the inhibitors of mTOR were evaluated in human primary cells derived from PCC/PGL patients' donated tumor tissue. Combined use of AZD8055 with Torin-1 reduced the number of tyrosine hydroxylase positive cells to 50% compared with the control cells, confirming the cytotoxic effect on human PCC/PGL cells. In addition, they can inhibit the glycolysis of tumor cells and further enhance its anti-tumor effect. Some have entered different clinical trials.[96]

Additionally, activation of ERK contributes to the acquired resistance and poor prognosis in everolimus-treated renal cell carcinoma (RCC) patients. The combination of SCH772984, an ERK inhibitor, with everolimus, an mTOR inhibitor, inhibited the proliferation of RCC cells synergistically by blocking the G1 phase cell cycle. Meanwhile, the combined therapy significantly downregulated the transcription of ribonucleotide reductase M1 (RRM1) and ribonucleotide reductase M2 (RRM2) by weakening the expression of E2F. Overexpression of E2F1 or supplementation of dNTP saved the anti-proliferative activity of Ivermos-SCH772984 combination.[128]

What's more, PI3K/AKT/mTOR signal pathway has cross-talking with Ras/Raf/MEK/ERK signal pathway. To be specific, the PI3K/AKT/mTOR and Ras/Raf/ERK signal pathways are not independent of each other in transducing survival signals and there are many interactions between them.[129] As a result, inhibiting both these signal pathways at the same time may be a promising strategy for treating PCC/PGL. For instance, the combination of BKM120 (a selective inhibitor of PI3K) and GSK1120212 (a MEK inhibitor) has entered the clinical trial phase I.[130]

Last but not least, combination of olaparib and temozolomide can reduce the tumor burden and metastatic lesions of SDHB mutant PCC/PGL.[131,132] Olaparib is a kind of poly ADP-ribose polymerase (PARP) inhibitor and temozolomide is a kind of chemotherapeutic agent which triggers tumor cell apoptosis through damaging genomic DNA.[133,134] The PCC/PGL with SDHB mutants exhibited a reprogrammed mitochondrial complex I. Elevation of NAD^+ is an important cofactor that supports the PARP DNA repair pathway, leading to resistance to SDHB-related PCC/PGL. The use of olaparib and temozolomide to target the NAD^+/PARP DNA repair pathway not only makes cluster I PCC/PGL cells sensitive to genotoxic drugs but also inhibits metastatic xenograft damage and improves overall survival.[135]

Expectations and conclusion

In this review, we introduced the genes associated with PCC/PGL and summarized two types of signal pathways about their composition and roles. Besides, how these two types of signal pathways lead to the onset of PCC/PGL was also detailedly described. For the relevant targets in these two signal pathways, we introduced the targeted medicines and their mechanism as comprehensively as possible. Therefore, our review would provide a reference for clinical targeted therapy on PCC/PGL.

Targeted therapy has many advantages, such as less toxic and side effects, longer survival time, and better quality of life. The molecular pathogenetic mechanism of PCC/PGL shows that the mutations of SDHx, FH, PHD2, VHL, and HIF influenced the hypoxia-related signaling, while the mutations of RET, MAX, TMEM127, NF1, KIF1Bβ, HRAS, MET, and FGFR1 influenced the increased kinase signaling. The review provides new ideas for targeted therapies of PCC/PGL by acting on the signal pathway of PCC. In a word, valuable progress has been achieved.

However, despite many new treatments for PCC/PGL have appeared, these data are still limited or experimental. Though molecular-targeted therapy is a promising strategy, but due to the complexity of the pathogenesis of tumors, further research on PCC/PGL tumor biology is needed to discover new targeting genes and targeted medicines to develop more effective treatments, optimize clinical trial designs as well as improve the prognosis and survival of patients with PCC/PGL.

Acknowledgment

Disclosure

The authors declare no conflicts of interest in this work.

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