REVIEW

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Recent clinical advances in PI3K inhibitors on colorectal cancer

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The PI3K/Akt/mTOR signaling pathway has the functions of regulating cell cycle, participating in tumor angiogenesis, affecting tumor invasion activity and metastasis, regulating apoptosis and autophagy, and participating in tumor drug resistance. Alpelisib (a PI3K inhibitor) has now been approved by the FDA for the treatment of PIK3CA mutant HR-positive/HER2-negative advanced/metastatic breast cancer in combination with fulvestrant which is the first PI3K inhibitor approved for breast cancer treatment. In some human colorectal cancer cells, the activation of this signal pathway is excessive and the negative regulation is impaired. Inhibitors targeting PI3K, a key protein in the PI3K/Akt/mTOR signaling pathway, have a positive effect on the treatment of colorectal cancer. Based on the role of PI3K/Akt/mTOR in the occurrence and development of colorectal cancer and its clinical application, this article reviews the PI3K inhibitors that have been on the market or are in clinical trials.

1. Introduction

Cancer has become the main cause of death in every country in the 21st century and the most important obstacle to increasing life expectancy (Bray et al. 2018). Aging of the population is a main risk factor for cancer, reflecting the changes in the prevalence and distribution of cancer. It is estimated that by 2021, there will be 1,898,160 new cancer cases and 608,570 cancer deaths in the US (Siegel et al. 2021). With the widespread adoption of colonoscopy in recent years, the incidence of colorectal cancer has experienced a rapid decline, but the overall decline in the incidence of colorectal cancer (CRC) masks the increase in the incidence of adults aged <65 years (Siegel et al. 2020). In addition, colorectal cancer is still the third most common malignant tumor in the general population without distinction of sex (Siegel et al. 2021).

The PI3K/Akt/mTOR signaling pathway has the functions of regulating cell cycle, participating in tumor angiogenesis, affecting tumor invasion activity and metastasis, regulating apoptosis and autophagy, and participating in tumor drug resistance (Polivka and Janku 2014). This diversification of functions is achieved by regulating the phosphorylation, transcription and translation of the necessary downstream targets for these processes. Phosphatidylinositol3-kinase (PI3K) are divided into three categories (I, II and III) based on its substrate preference and sequence homology. Their main function is to phosphorylate the 3'-hydroxyl group of phosphatidylinositol and phosphoinositides. The class I PI3Ks are most closely related to the occurrence and development of human cancer, and readers can refer to the comments on class I PI3Ks (Fruman et al. 2017). PI3K is located in the cytoplasm, and it is composed of two subunits, p85 (regulatory subunit) and p110 (catalytic subunit). The p85 subunit includes an SH2 domain capable of recognizing and binding to tyrosine sequences and an SH3 domain capable of recognizing and binding to rich proline. Under normal circumstances, the p110 subunit is in an inhibited state, and when the PI3K/Akt/mTOR signaling pathway receives a signal, phosphorylation of tyrosine residues activates p110 residues, thereby turning PI3K into an activated state. PI3K in the activated state converts phos-phatidylinositol 4,5-bisphosphate (PIP2) into phosphatidylinositol 3,4,5-trisphosphate (PIP3), and PIP3 continues to activate various downstream proteins. Akt (protein kinase B, PKB) is one of the key downstream proteins of PI3K and plays an important role in tumor angiogenesis, proliferation and metastasis (Alzahrani 2019; Chow and Salmena 2020; Gozzelino et al. 2020; Vanhaesebroeck et al. 2010). Ras-mediated regulation of PI3K also plays a role in many cellular processes involved in normal physiology and disease (Cuesta et al. 2021). An overview of the PI3K/AKT/mTOR signal pathway is shown in the Fig.

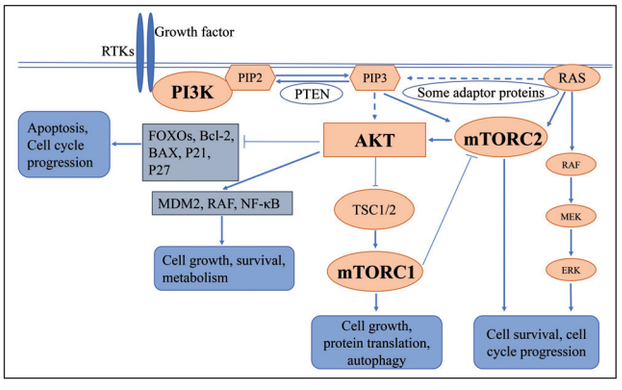

Fig.: Diagram showing the PI3K/AKT/mTOR signaling pathway. RTKs, receptor tyrosine kinases; FOXO, forkhead box protein O; MDM2, mouse double minute 2 homolog; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; PTEN, phosphatase and tensin homolog deleted on chromosome ten; TSC1, tuberous sclerosis complex 1; mTOR, mammalian target of rapamycin; RAF, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase; ERK, mitogen-activated protein kinase 1/3.

Scientists are actively developing PI3K inhibitor drugs and have achieved gratifying results in breast cancer, prostate cancer, colorectal cancer and other solid tumors. In a randomized phase 3 trial, PI3Kα specific inhibitor alpelisib plus fulvestrant was used to treat HR-positive, HER2-negative advanced breast cancer that had previously received endocrine therapy. The results show that alpelisib-fulvestrant treatment can prolong the progression-free survival of patients with PIK3CA mutation, HR-positive, and HER2-negative advanced breast cancer who have previously received endocrine therapy (11.0 months vs. 5.7 months, the progression-free survival in the alpelisib-fulvestrant group vs. the placebo-fulvestrant group). Alpelisib has now been approved by the FDA for the treatment of PIK3CA mutant HR-positive/

HER2-negative advanced/metastatic breast cancer in combination with fulvestrant which is the first PI3K inhibitor approved for breast cancer treatment (Markham 2019). In addition, idelalisib, a PI3K inhibitor, is also approved for the treatment of recurrent follicular B-cell non-Hodgkin's lymphoma, recurrent small lymphocytic lymphoma, or chronic lymphocytic leukemia (Zirlik and Veelken 2018).

2. PI3K in colorectal cancer

Overexpression of insulin-like growth factor, KRAS mutations, reduced or mutated PTEN function, and PI3K mutations are often found in colorectal cancer. Ekstrand et al. (2010) found that there are obvious mutations of PI3KCA and KRAS genes, overexpression of PI3KCA and Akt, and deletion of PTEN tumor suppressor genes in hereditary non-polyposis colorectal cancer. The activation of PI3K/AKT/mTOR pathway is an important link in the occurrence and development of colorectal cancer, which promotes protein synthesis and affects cell proliferation. PI3K inhibitors can inhibit the activity of mTOR, arrest the cell cycle in the G1 phase, and block cell growth. Whitehall et al. (2012) found that the activation of PI3K/AKT signaling pathway caused by PI3KCA gene mutation can significantly promote the proliferation of colorectal cancer cells. Akt can phosphorylate mTOR and downstream molecules to transmit survival signals, inhibit cell apoptosis, and promote the survival of colorectal cancer cells. Promoting cell proliferation, prolonging cell survival, and inhibiting cell apoptosis are the ways that PI3K axis participates in the progression of colorectal cancer.

2.1. Preclinical studies of PI3K inhibitors in colorectal cancer cells

Because of the multifaceted roles of this signaling pathway in tumors, it has become a research hotspot. Published reports indicate that this pathway is related to the occurrence of colorectal cancer (Engelman 2009). Akt signaling activation and impaired negative regulation happened in 60-70% of human colon cancer cells (Colakoglu et al. 2008). Numerous preclinical studies have shown that inhibition of the PI3K pathway can inhibit the proliferation, invasion and metastasis of colorectal cancer cells. Natural products often have multi-target anti-cancer effects, and can inhibit the proliferation of colorectal cancer cells by inhibiting the PI3K signaling pathway. Li confirmed that the *Selaginella doederleinii* Hieron ethyl acetate (SDEA) extract can inhibit the growth of colorectal cells (HT29 and HCT116) *in vivo* and *in vitro* by inducing apoptosis and inhibiting the PI3K-Akt-mTOR signaling pathway (Li et al. 2020). Myricetin extracted from berries can also inhibit the growth of colon cancer cells by inhibiting the PI3K signaling pathway (Zhu et al. 2020). Wang reported a new PI3K/Akt/mTOR signaling inhibitor W922, which can inhibit tumor growth by promoting the apoptosis of colorectal cancer cells and controlling the cell cycle (Wang et al. 2020). MK-2206 and afuresertib can effectively inhibit PI3K/Akt signal to inhibit colorectal tumor growth. However, in *in vitro* experiments, these inhibitors show strong adverse activity or toxicity, which has become an obstacle to their clinical application (Agarwal et al. 2014; Mundi et al. 2016; Tolcher et al. 2015). Despite the limiting factors, the research on PI3K inhibitors has never stopped.

A variety of common drugs or newly synthesized compounds can regulate the PI3K/Akt/mTOR signaling pathway. For example, the hypoglycemic drug metformin has been shown to inhibit the proliferation of CRC cells by inhibiting Myc protein synthesis through the mTOR-4EBP-eIF4E axis (Shen et al. 2018). Both the Cox2 inhibitors indomethacin and nimesulide reduced the mTOR signaling activity of colorectal cancer cells and reduced the mTOR signaling activity after COX-2 silence in CRC cells, thereby inhibiting the growth of CRC cells (Zhang et al. 2011). According to different mechanisms of action, synthetic PI3K inhibitors can be divided into three major categories, including pan-PI3K inhibitors, selective-PI3K inhibitors, which can act on specific subtypes of PI3K, and dual PI3K/mTOR inhibitors. In Table 1 we summarized the preclinical studies of synthetic PI3K inhibitors in colorectal cancer cells.

2.2. Clinical studies of PI3K inhibitors in colorectal cancer cells

In order to provide clinicians with the latest clinical research progress of PI3K inhibitors in colorectal cancer, this article reviews the relevant clinical trials.

2.2.1. Pan-PI3K inhibitors

2.2.1.1. PX-866

PX-866 is a potent pan-PI3K inhibitor that inhibits cell growth *in vitro* and *in vivo* and reduces the activation of PI3K downstream targets (Ihle et al. 2004). Clinical trials on the application of PX-866 in prostate cancer, head and neck squamous cell carcinoma, glioblastoma, non-small-cell lung cancer (NSCLC) and advanced solid tumors have been completed (Hotte et al. 2019; Jimeno et al. 2015; Levy et al. 2014; Pitz et al. 2015). In a phase II clinical trial, PX-886 was combined with cetuximab in patients with metastatic colorectal cancer. Cetuximab was used in the control group without PX-886. The primary endpoint is progression-free survival (PFS), and secondary endpoints include objective response rate and overall survival (OS). However, the results show that adding PX-866 to cetuximab does not improve PFS, objective response rate, or OS in patients with metastatic CRC. In addition, the combined use produced greater toxicity, which may be harmful in this study (Bowles et al. 2016). The latest phase Ib study investigated the safety and effectiveness of Binimetinib (MEK inhibitor) and Buparlisib (PI3K inhibitor) in the treatment of patients with advanced solid tumors with RAS/RAF changes (44 CRC, 49.4%) (Bardia et al. 2020). Although the treatment brought some positive signs, the toxicity characteristics of the combination regimen resulted in lower-than-expected dose intensity.

2.2.1.2. BKM120 (buparlisib)

BKM120 (buparlisib) is a pan-PI3K/mTOR inhibitor, which plays an anti-tumor effect mainly by inducing tumor cell apoptosis and inhibiting the tumor cell growth (Burger et al. 2011; Chen et al. 2017; Pereira et al. 2015; Yu et al. 2016). The BURAN study (ClinicalTrials.gov Identifier: NCT04338399) is a randomized, open-label phase III study that aims to evaluate the impact on overall survival of the combination of Buparlisib and Paclitaxel compared to Paclitaxel alone in patients who have failed Cisplatin based treatment or Cisplatin based treatment and anti-PD1 based treatment. The completion of the study is tentatively scheduled for December 2023. A number of phase

Table 1: Preclinical studies of synthetic PI3K inhibitors in colorectal cancer cells

Inhibitor	Classification	Cell lines	References
GDC-0941	Pan-PI3K inhibitor	HCT116, HT29 (*in vivo* or *in vitro*)	(Beale et al. 2016;Haagensen et al. 2013)
DHNQ	Pan-PI3K inhibitor	Colo-205, HCT-116	(Hussain et al. 2016)
BKM120	Pan-PI3K inhibitor	HT29 (*in vivo* or *in vitro*)	(Tosi et al. 2018)
NVPBEZ235	Dual mTOR/PI3K inhibitor	HT29, HCT116, SW480, SW620, CSC480	(Alqurashi et al. 2018)
BEZ235	Dual mTOR/PI3K inhibitor	HCT-116, HT-29 (*in vitro* or *in vitro*)	(Hu et al. 2021;Zou et al. 2016)
HS-173	Selective-PI3K inhibitor	CT26 (*in vivo* or *in vitro*)	(Landry et al. 2020)

Table 2: Representative clinical studies of PI3K inhibitors in colorectal cancer

Inhibitor	Classification	Phase	Combination therapy	Reference or NCT number
PX-866	Pan-PI3K inhibitor	II	With or without Cetuximab	(Jimeno et al. 2015)
BKM120 (Buparlisib)	Pan-PI3K inhibitor	I/Ib	\	(Bendell et al. 2012)
		I/Ib	\	(Rodon et al. 2014)
		I/Ib	mFOLFOX6 (5-FU/LV + Oxaliplatin)	(McRee et al. 2015)
		I/Ib	Trametinib	(Bedard et al. 2015)
		I/Ib	Binimetinib	(Bardia et al. 2020)
GDC-0941 (Pictilisib)	Pan-PI3K inhibitor	I	\	(Sarker et al. 2015)
Apitolisib (GDC-0980)	Dual mTOR/PI3K inhibitor	I	\	(Dolly et al. 2016)
PF-05212384/PKI-587 (Gedatolisib)	Dual mTOR/PI3K inhibitor	I	\	(Shapiro et al. 2015)
PF-04691502 and Gedatolisib (PF-05212384)	Dual mTOR/PI3K inhibitor	I	Irinotecan or the MEK Inhibitor PD-0325901	(Wainberg et al. 2017)
PF-04691502	Dual mTOR/PI3K inhibitor	I	\	(Britten et al. 2014)
DS-7423	Dual mTOR/PI3K inhibitor	I	\	NCT01364844
BEZ235	Dual mTOR/PI3K inhibitor	I/Ib	\	(Burris et al. 2010; Toyoda et al. 2019)
GSK2636771	Selective-PI3K inhibitors	I	\	(Mateo et al. 2017)
MEN1611	Selective-PI3K inhibitors	I/Ib	\	NCT04495621
BYL719	Selective-PI3K inhibitors	II	LGX818 and cetuximab	NCT01719380

I clinical trials on the use of Buparlisib alone or in combination in patients with colorectal cancer have been completed or are ongoing. In a phase I clinical trial involving 83 patients with advanced solid tumors (including 31 patients with colorectal cancer), the safety and preliminary efficacy of buparlisib were evaluated. The results showed that Buparlisib was well tolerated, with doses up to 100 mg/day, and showed initial activity in patients with advanced cancer (Rodon et al. 2014). Other clinical trials of Buparlisib are summarized in Table 2.

2.2.1.3. GDC-0941 (pictilisib)

Pictilisib is a pan-PI3K inhibitor with rapid absorption after oral administration, and its pharmacokinetic (PK) curve is dose-proportional (Sarker et al. 2015). In a phase I clinical trial involving 60 patients with solid tumors (including 16 patients with colorectal cancer), the safety, tolerability, and preliminary clinical activity of pictilisib (GDC-0941) were evaluated in a human dose escalation trial for the first time (Sarker et al. 2015). The results show that Pictilisib is well tolerated. There are no other ongoing trials of pictilisib in the treatment of colorectal cancer.

2.1.2. Dual mTOR/PI3K inhibitors

2.2.2.1. PF-05212384, PKI-587 (gedatolisib)

Gedatolisib is an ATP-competitive, highly selective and effective dual inhibitor of PI3K and mTOR (Mallon et al. 2011). An open-label phase I study of gedatolisib was conducted in eight centers and finally reported the safety, tolerability and preliminary activity of gedatolisib in patients with advanced solid tumors (including 19 patients with colorectal cancer) (Shapiro et al. 2015). The results show that in patients with advanced solid tumors, the maximum tolerated dose MTD of single-agent gedatolisib is estimated to be 154 mg per week.

2.2.2.2. PF-04691502

PF-04691502 is a potent dual inhibitor of dual PI3K and mTOR. A phase I clinical trial on its treatment in patients with advanced solid tumors showed that its maximum tolerated dose (MTD) was determined to be 8 mg per day (Britten et al. 2014; Yuan et al. 2011).

A multi-arm phase I study of PF-04691502 and gedatolisib (PF-05212384) plus irinotecan or the MEK inhibitor PD-0325901 in advanced cancer has been completed (Wainberg et al. 2017). The primary endpoint is the dose-limiting toxicity of each combination. Secondary endpoints include safety, pharmacokinetics and preliminary anti-tumor activity. The purpose of this trial is to determine the MTD and/or recommended phase II doses of PF-04691502 and gedatolisib in combination with irinotecan or MEK inhibitors. Moreover, evaluate its safety, pharmacokinetics (PK) and preliminary anti-tumor activity in patients with advanced solid tumors, and determine the best tolerable combination. The combination of gedatolisib and irinotecan produced a response rate of approximately 5% and clinical benefit (PFS, progression-free survival, 2.8 months) in 16% of patients with advanced colorectal cancer.

2.2.2.3. NVP-BEZ235 (dactolisib)

As a dual protein kinase inhibitor, NVP-BEZ235 can simultaneously target PI3K and mTOR pathways. Preclinical studies have shown that NVP-BEZ235 exerts anti-tumor effects by inhibiting the proliferation and migration of HT-29 human colorectal adenocarcinoma cells, inducing apoptosis and autophagy (Yu et al. 2016). At the same time, BEZ235 attenuates radiation-induced AKT/mTOR signal activation and inhibits the DNA-DSB repair mechanism to enhance the radiosensitivity of colorectal cancer (CRC) *in vitro* and *in vivo* (Chen et al. 2015).

In the first human (FIH) study of BEZ235, several formulations of BEZ235 were studied, such as hard gelatin capsule formulations and special delivery system (SDS) formulations provided as capsules or sachet particles (including 10 CRC, 17%). But at doses of 400 mg and higher, SDS capsules still show high inter-patient variability, but the PK curve of SDS sachet preparations seems to be more consistent (Burris et al. 2010). In a phase I clinical trial conducted in Japan, BEZ235 SDS sachets were used to treat patients with advanced solid tumors (including 16 CRC, 26%), and the maximum clinically tolerable dose was determined to be 1200 mg. There is a high inter-individual variability of the plasma concentration of BEZ235 in Japanese patients, but the plasma

concentrations were consistent with the range reported in previous studies on western cancer patients and the results are comparable to the conclusions of the global phase I study of BEZ235 (Toyoda et al. 2019).

2.2.2.4. DS-7423

In a phase I clinical trial of DS-7423 for the treatment of patients with advanced solid malignant tumors, the first step is to determine the maximum tolerated dose (MTD), and the second step is to conduct preliminary efficacy evaluation in patients with advanced colorectal cancer or endometrial cancer (ClinicalTrials.gov Identifier: NCT01364844). The recruitment status of this study has been completed, and the planned completion time is November 2013, but the results have not yet been announced.

2.2.2.5. GDC-0980 (apitolisib)

By modifying the chemical structure of GDC-0941 (pictilisib), the mTOR inhibitory function was added to GDC-0941 to obtain the dual mTOR/PI3K inhibitor (GDC-0980) (Sutherlin et al. 2011). In a phase I study of apitolisib (GDC-0980) in patients with advanced solid tumors (24 CRC, 10%), the dose of apitolisib at 30 mg (orally, once a day) was reasonably tolerated and showed moderate but long-lasting anti-tumor activity (Dolly et al. 2016).

2.2.3. Selective-PI3K inhibitors

2.2.3.1. GSK2636771

GSK2636771 is a potent and oral selective inhibitor of PI3Kβ with anti-tumor activity in PTEN-deficient cancers (Mateo et al. 2017). 65 cancer patients participated in the study. The most common tumor types were colorectal cancer (n=23, 35%) and prostate cancer (n=12, 18%). It is finally determined that 400mg once a day is the recommended phase II dose (RP2D) of GSK2636771. A Phase II study (MATCH Treatment Subprotocol N) on GSK2636771 for the treatment of patients with PTEN mutation or deletion tumors is ongoing (ClinicalTrials.gov Identifier: NCT04439149). The primary endpoint of the trial is the objective response rate (ORR), and the secondary endpoints are the objective response rate (ORR) and progression-free survival (PFS).

2.2.3.2. MEN1611

MEN1611 is a potent and selective class I PI3K inhibitor. The maximum tolerated dose (MTD) of MEN1611 administered as a single agent was evaluated in a phase I trial in patients with colorectal cancer patients with PIK3CA mutations (ClinicalTrials.gov Identifier: NCT04495621). The trial first will determine the RP2D of MEN1611 used in combination with cetuximab. The second step of the study will continue to expand the cohort to explore the anti-tumor activity, safety and tolerability of the selected dose of MEN1611 in combination with cetuximab. The expected completion date of the trial is July 2023.

3. Concluding remarks: obstacles and opportunity

3.1. Drug-related toxicity

Drug-related toxicity is a major obstacle to the development of PI3K inhibitors including cutaneous reactions, hypertension, diarrhea and neuropsychiatric symptoms (Esposito et al. 2019). In a randomized phase II trial of cetuximab with or without PX-866 in the treatment of patients with metastatic colorectal cancer, the combined treatment group had higher overall toxicity (including treatment-related toxicity) than the cetuximab group. Especially in all grades of nausea (66% vs. 37%), vomiting (50% vs. 29%), diarrhea (64% vs. 18%) and rash (66% vs. 37%) (Jimeno et al. 2015). The occurrence of drug-related toxicity leads to frequent dose delays or dose reductions, which may prevent sustained therapeutic drug concentration.

3.2. Hyperglycemia and increased insulin production

The PI3Kα subunit plays a key role in insulin signaling and glucose homeostasis, and hyperglycemia usually occurs within the first month of treatment. In the phase I study of pictilisib in patients with advanced solid tumors, 7 of 32 evaluable patients had significant increases in plasma insulin and glucose levels (Sarker et al. 2015). Similar results have appeared in many other clinical trials (Goodwin et al. 2020; Juric et al. 2018). The pancreas attempts to normalize serum glucose levels, thereby increasing insulin secretion. Since insulin is a powerful stimulator of PI3K signaling in tumors, it can have a profound effect on cancer progression. Hopkins et al. (2018) confirmed that preventing insulin feedback through diet or medication methods improved the efficacy/toxicity ratio of PI3K inhibitors.

3.3. Patient stratification strategy

The successful development of PI3K inhibitors in breast cancer patients and the results of clinical trials in CRC patients have shown that pharmacological inhibition of human PI3K is feasible. PIK3CA mutations are found in 10-20% of colorectal cancer tumors and are associated with the prognosis of colorectal cancer (Hamada et al. 2017; Liao et al. 2012). Although clinical activity was observed independently of PIK3CA mutation status, clinical benefit was observed in a higher proportion of patients with PIK3CA mutation tumors (Mayer et al. 2017). In another phase I study, the clinical benefit rate (CBR) of alpelisib in tumors with PIK3CA hotspot mutations was 44% and in PIK3CA-wild-type tumors was 20% (Juric et al. 2018). The patient stratification strategy may bring new opportunities for the development of PI3K in colorectal cancer.

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