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The PI3K-AKT Signaling Axis Modulates Gastric Cancer Cell Proliferation and Multidrug Resistance

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Abstract:

Worldwide, GC ranks among the top five most commonly diagnosed cancers, with its incidence and mortality rates remaining at a high level for a long time. Patients with advanced GC often lose the opportunity for surgical resection due to disease spread, and their treatment relies heavily on systemic chemotherapy and local radiotherapy. However, patients still tend to experience a decline in therapeutic efficacy during the treatment cycle and eventually fall into the dilemma of treatment failure, with MDR being the core cause of this outcome. A large number of studies have shown that the PI3K/AKT pathway plays a crucial role in tumor drug resistance, through mechanisms including inhibiting apoptotic pathways, promoting tumor growth, and regulating tumor metabolism. This review focuses on the specific pathways by which the aberrant activation of the PI3K/AKT axis regulates MDR in GC—including the modulation of autophagy, enhancement of drug efflux, promotion of anti-apoptotic responses, and suppression of ferroptosis in cancer cells. It also summarizes key MDR-related targets within this pathway (encompassing proteins such as NF-κB, mTOR, and NRF2) and further explores how the dysregulated PI3K/AKT pathway influences tumor resistance from both chemotherapy and radiotherapy perspectives. The ultimate aim of this article is to provide a novel and comprehensive theoretical framework for the application of PI3K/AKT axis inhibitors in GC combination therapy strategies.

Keywords: Gastric cancer; PI3K/AKT pathway; Multidrug resistance; PI3K/AKT inhibitors; Combination therapy.

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1. Introduction

Gastric cancer (GC) holds the fourth position among common tumors across the globe and remains a frequent cause of mortality attributed to cancer [1]. In the treatment of advanced GC, systemic chemotherapy and local radiotherapy are the main tools, but the emergence of multi-drug resistance (MDR) often makes the therapeutic efficacy much less effective, which may eventually render the treatment ineffective. MDR in cancer cells is influenced by various factors. Among these, an over-activated Phosphatidylinositol 3-kinase/Protein Kinase B (PI3K/AKT) pathway is considerable. PI3K is activated by multiple cell surface receptors, triggering downstream activation of AKT and other effector molecules. These molecules collectively regulate cell proliferation, survival and metabolic homeostasis—functions that are dysregulated in cancer cells to drive MDR [2]. Therefore, deeper investigations into this pathway will provide valuable insights to facilitate the further advancement of therapeutic strategies for GC. However, there is a lack of up-to-date systematic review about the effect of PI3K and its downstream effector AKT on MDR in GC.

Therefore, this article is intended to explore the mechanisms of GC resistance and the development of PI3K/AKT-targeted drugs, with the aim of providing new ideas and strategies for the treatment of clinically advanced GC.

2. PI3K/Akt Pathway

This pathway is primarily activated by Receptor Tyrosine Kinases (RTKs) or G Protein-Coupled Receptors (GPCRs) (Figure1). Based on their lipid substrate specificity, PI3Ks include three classes (I, II, and III). Class I has great contribution to regulating the functions of both tumor and immune cells.A further division of Class I PI3Ks yields two subfamilies, namely IA and IB, with the IA subfamily consisting of three kinases, p110α, p110β, p110δ and three junction proteins, p85α, p85β, p55γ. The IB subfamily consists of one kinase, p110γ and two junction proteins, p101, p84 and the gene coding for the p110α subunit is frequently mutated in GC cancer tissues and cell lines [3,4].

As an upstream regulator of AKT, PI3K can phosphorylate its substrate to generate Phosphatidylinositol-3,4,5-trisphosphate (PIP3). This PIP3 then acts as a docking molecule to recruit AKT to the cell membrane, where it further promotes AKT activation. Akt regulates cell survival and development through interactions with a variety of substrates [4].

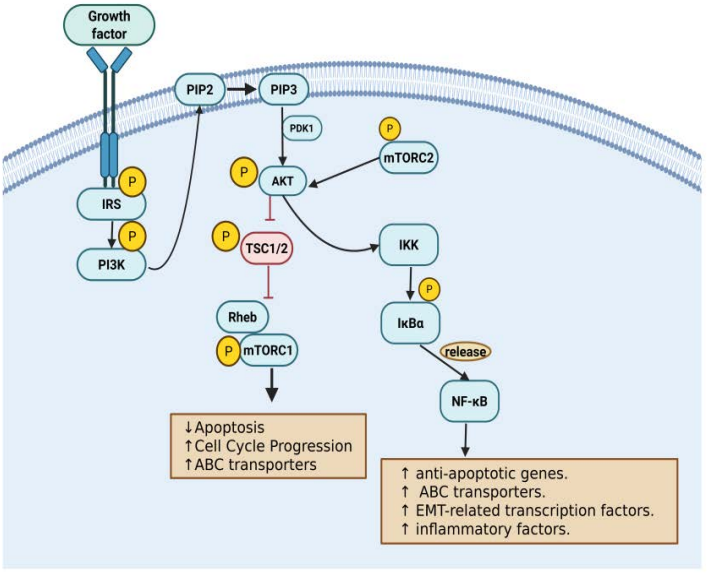

Fig. 1 Growth factor binding receptor activates insulin receptor substrate, catalyzes PIP2 via PI3K to generate PIP3, and recruits activation of PDK1, AKT, and others.mTORC2 further activates AKT and then inhibits Sclerosis Complex 1/2 (TSC1/2) indirectly activating mTORC1 to regulate anti-apoptosis, cycle progression, and ABC transporter proteins, At the same time, AKT activates IKK to phosphorylate IκBα to release NF-κB, which regulates the anti-apoptosis-associated genes expression, ABC transporter proteins, epithelial-mesenchymal transition-related transcription factors, and inflammatory factors.

3. PI3K/AKT Pathway Leading to GC MDR

3.1 PI3K/AKT/NF-κB

The activated IKK complex subsequently phosphorylates inhibitor of nuclear factor kappa-B (IκB), leading to its degradation. This releases the cytoplasmic NF-κB heterodimer—most commonly composed of the p65 (RelA) and p50 subunits—which then translocates to the nucleus. Once in the nucleus, NF-κB binds to specific sites within the enhancer regions of target genes, thereby activating the transcription of genes associated with cell survival, inflammation, and immune responses (anti-apoptotic genes and cytokine genes). These transcriptional events promote tumor growth, stimulate drug resistance genes (P-glycoprotein), inhibit tumor cell death, collectively contributing to the MDR in tumors [5].

Guo Q and colleagues first established cisplatin (CDDP)-resistant variants from human GC cell lines. Subsequently, they treated these drug-resistant GC cells with Ubenimex, an inhibitor of Aminopeptidase N. To assess changes in signaling pathway activity, the research team adopted protein immunoblotting for detection. Results showed notable decreases in the phosphorylation levels of PI3K, AKT, and NF-κB p65, which means that the PI3K/AKT/NF-κ B pathway's activity was decreased. Further analysis revealed that the activation of this pathway contributes to enhanced drug insensitivity in GC cells, it achieves this by promoting two cellular processes, namely the induction of autophagy and the epithelial-mesenchymal transition (EMT).

Cellular experiments showed that Ubenimex caused a marked decline in the Half-Maximal Inhibitory Concentration value and significantly increased the responsiveness of CDDP-resistant gastric cancer cells to CDDP. For example, the IC50 of MKN-45/DDP cells decreased from 6.37±0.03 μg/m to 1.91±0.04 μg/ml, and the RI decreased from 16.02±0.14 to 4.55±0.17. These data illustrated the correlation between Aminopeptidase N expression levels and CDDP-resistant phenotype, and Ubenimex had a reversal effect [6].

3.2 PI3K/AKT/mTOR

mTOR consists of two protein complexes, mTORC1 and mTORC2. Among these, mTORC1 plays a primary role in regulating cellular growth and metabolic processes. mTORC2 often exhibits excessive activity in malignant tumors, this complex can maintains the PI3K/AKT pathway in a persistently activated state by phosphorylating the AKT protein and boosting AKT's functional activity. Notably, abnormal activation of mTOR contributes to several biological effects that favor tumor progression, including the inhibition of apoptotic cell death and the increased expression of drug resistance-related proteins [7,8].

Zeng L and his research team detected key molecules of the PI3K/AKT/mTOR pathway in the GC-resistant cell line SGC-7901/5-fluorouracil (5-FU). It found that the activation of mTOR and the expression of downstream effector molecules were significantly reduced in drug-resistant cells after knockdown of XLOC_006753, which means that mTOR pathway activity was inhibited. Meanwhile, the levels of protein linked to drug resistance—Multidrug Resistance 1 (MDR1), Low-Density Lipoprotein Receptor-Related Protein 1 (LRP1), and Breast Cancer Resistance Protein (BCRP) decreased. The levels of apoptotic molecule cysteine-aspartic acid protease 9 (caspase9) increased, suggesting that activation of the mTOR pathway can up-regulate drug-resistant proteins, impede apoptosis, and aggravate drug resistance. Moreover, resistant cells with decreased mTOR pathway activity showed G1-phase block (cell cycle inhibition) and significantly increased apoptosis rate (e.g., the apoptosis rate of SGC-7901/DDP increased from 8.83% to 18.8%), suggesting that mTOR causes drug resistance by regulating cell cycle progression and inhibiting apoptosis [8].

In addition, relevant studies have shown that mTOR can regulate ATP-Binding Cassette (ABC) family of transport proteins through two pathways. Firstly, the Hypoxia-Inducible Factor-1α(HIF-1α), which can drive the expression of P-glycoprotein (P-gp) and Multidrug Resistance-associated Protein 1 (MRP1) expression. In rapamycin-treated SGC7901/MDR cells, mTOR expression was suppressed, meanwhile, the expression levels of HIF-1α and P-gp also decreased. At a rapamycin concentration of 80 μg/mL, mTOR expression became nearly undetectable, while the HIF-1α and P-gp declined approximately 80% and 70% in their expression, respectively, compared with the control group.

Secondly, Proton Pump Inhibitors are capable of upregulating the expression of TSC1/2 while downregulating the expression of Ras Homolog Enriched in Brain (Rheb) in SGC7901/MDR cells. Since TSC1/2 functions as a negative regulator of mammalian target of rapamycin (mTOR)—more precisely, it has the ability to block Rheb-mediated activation of mTOR—such molecular alterations result in further suppression of mTOR activity. In the end, this chain of events brings about a reduction in the mRNA levels of P-gp and MRP1, which in turn reverses the multidrug-resistant phenotype of tumor cells [9].

According to relevant experimental studies, the PI3K/AKT pathway activation in GC leads to a marked up-

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regulation in the expression of several ABC transporter proteins. These transporters include ABCC1 (also known as MRP1), ABCC3 (also known as MRP3). These ABC transporters enable active efflux of platinum-based chemotherapeutic agents, such as CDDP and oxaliplatin from GC cells. As a consequence of this efflux, the intracellular accumulation of these platinum drugs becomes insufficient, and their ability to induce DNA damage in cancer cells is ultimately weakened [10,11].

3.3 Ferroptosis Inhibition: Resistance to Lipid Peroxidation-mediated Death

Iron dependency defines a unique form of cell death referred to as ferroptosis, and its central mechanism lies in the unstable nature of polyunsaturated fatty acid-rich lipids on cell membranes, which are susceptible to oxidative reactions that can cause damage to cell membranes. When intracellular antioxidant enzymes such as Glutathione Peroxidase 4 (GPX4) are deficient, the accumulation of iron and reactive oxygen species-induced lipid peroxidation causes the cell membrane to rupture, and the cell ultimately dies [12].

Aberrant activation of the PI3K/AKT pathway enhances antioxidant levels and reduces ferroptosis susceptibility in cancer cells by regulating the downstream Nuclear Factor Erythroid 2-Related Factor 2 (NRF2) as well as both mTORC1 targets.

In the GC, AKT enhances NRF2-mediated transcription, leading to the expression of GPX4 and Solute Carrier Family 7 Member 11 (SLC7A11). SLC7A11 is a core component of the cystine/glutamate antiporter system (System Xc^-), which is responsible for cystine uptake to synthesize Glutathione (GSH). In turn, GPX4 relies on GSH to inhibit lipid peroxidation, thereby suppressing ferroptosis. Additionally, the activation of AKT can phosphorylate Glycogen Synthase Kinase 3β (GSK-3β) to inhibit its activity; this prevents GSK-3β from effectively mediating the phosphorylation of NRF2 and subsequent degradation of NRF2 via the ubiquitin-proteasome system. Consequently, NRF2maintains high stability and continuously activates the transcriptional expression of antioxidant genes such as GPX4 and SLC7A11, further inhibiting ferroptosis (Figure 2A) [13].

In non-small cell lung cancer (NSCLC), PI3K/AKT-activating mutations also induce maturation of Sterol Regulatory Element-Binding Protein 1 (SREBP1) via its downstream mTORC1, which acts as a transcription factor to activate Stearoyl-CoA Desaturase 1 (SCD1), which protects cancer cells from ferroptosis by generating monounsaturated fatty acids to inhibit lipid peroxidation, thereby protecting cancer cells from ferroptosis (Figure 2B) [14]. Notably, similar regulatory mechanisms involving the PI3K/AKT/mTOR pathway, SREBP1, and SCD1 in mediating ferroptosis resistance have also been observed in GC, where hyperactivation of this pathway similarly enhances tumor cells' antioxidant capacity by modulating lipid metabolism. Therefore, the present review infers that PI3K inhibitors are equally effective for GC in decreasing the antioxidant properties of tumor cells and increasing the sensitivity to iron toxicity.

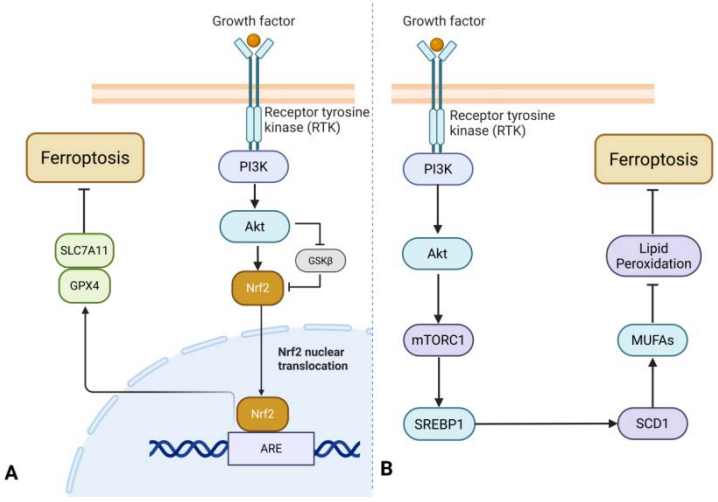

Fig. 2 A: Growth factor-binding receptor tyrosine kinase (RTK), activates PI3K, AKT and inhibits GSK3β to bring Nrf2 into the nucleus and binds to Antioxidant Response Element (ARE), which up-regulates SLC7A11 and GPX4's levels to inhibit ferroptosis. B:Growth factor activation of RTK, PI3K, and Akt via mTORC1 and SREBP1 promotes SCD1-mediated production of monounsaturated fatty acids (MUFAs), inhibits lipid peroxidation, and hinders ferroptosis. (→ stands for activation and ⊣ for inhibition)

In summary, Abnormal upregulation of PI3K leads to cancer cell resistance to chemotherapy and targeted therapies through multiple molecular mechanisms. In-depth study of the aberrant regulation of this pathway, combined with the analysis of clinical data, provides a solid theoretical basis and clinical rationale in support of developing precision treatment strategies for GC.

4. PI3K in Hibitors in Reversing MDR in GC Cells

4.1 Reversal of chemotherapy resistance

Aberrant activation of the PI3K/AKT/mTOR pathway drives chemotherapy resistance in gastric cancer via four key mechanisms: upregulating ABC transporters to boost efflux of drugs like CDDP, phosphorylating proteins to enhance DNA damage repair, increasing anti-apoptotic proteins while inhibiting caspases, and activating NRF2 to elevate glutathione and induce protective autophagy.

Three types of PI3K inhibitors address this resistance: pan-inhibitors (LY294002) block all PI3K isoforms but cause metabolic side effects. Subtype-specific ones (Alpelisib targeting PI3Kα) work precisely in Phosphatidylinositol-3-Kinase Catalytic Alpha Subunit (PIK-3CA)-mutated cases with manageable side effects. Dual PI3K/mTOR inhibitors (BEZ235) prevent compensatory activation, ideal for single-target-resistant cases. These inhibitors improve gastric cancer cells' chemo-sensitivity, aiding resistant gastric cancer combination therapy [15].

4.2 Reversal of Radiotherapy Resistance

Radiotherapy is a commonly used treatment for advanced GC. But Radiotherapy resistance may arise due to the active state of the PI3K/AKT/mTOR pathway. However, activation of autophagy in malignant tumor cells through the use of this pathway's inhibitors can improve the sensitivity of radiotherapy [16].

In NSCLC, high expression of DNAJC19 activates the PI3K/AKT signaling pathway, promotes autophagy, and enhances radioresistance in NSCLC cell lines such as A549 and NCI-H1299, ultimately leading to shortened survival time of patients. Silencing DNAJC19 via siRNA or using the autophagy inhibitor chloroquine can inhibit the expression of PI3K and AKT, reduce autophagy, suppress cell proliferation and migration, promote apoptosis, and thereby enhance radiosensitivity [17]. In esophageal cancer, activation of the PI3K/AKT/mTOR signaling pathway strengthens the radioresistance of Eca-109 cells. Tanshinone IIA can downregulate this pathway. When combined with radiotherapy, it can inhibit cell proliferation, promote apoptosis and autophagy. The PI3K inhibitor LY294002 can further enhance this effect [18]. It is hypothesized that PI3K inhibitors may also serve as potential agents to improve the efficacy of radiotherapy in advanced GC.

5. Core Challenges for PI3K Therapeutics

In the clinical application of PI3K inhibitors for human malignant tumors, common side effects include metabolic issues such as hyperglycemia, hyperinsulinemia and dyslipidemia (hypertriglyceridemia, hypercholesterolemia). Gastrointestinal reactions include nausea, vomiting, diarrhea and oral mucositis. Hematological toxicities, including mild to moderate neutropenia, thrombocytopenia, and anemia in some patients. Systemic symptoms such as fatigue and weakness and skin adverse reactions like rash and hand-foot syndrome. A small number of patients, especially those receiving mTOR inhibitor monotherapy or combination therapy, may develop pulmonary toxicities such as interstitial lung disease and pneumonia. Among these, dual-target inhibitors (BEZ235) have a similar side effect profile to single-target inhibitors, but the incidence of toxicities like hyperglycemia is slightly higher [19].

6. Conclusion

The PI3K/AKT pathway drives MDR of GC through multiple mechanisms, including activation of AKT to up-regulate a range of proteins, among which are NF-κB and mTOR to inhibit apoptosis, up-regulation of ABC transporter proteins such as ABCC1 and ABCB1 via mTORC1 to enhance drug efflux, and activation of SREBP1/SCD1 axis to generate monounsaturated fatty acids to inhibit lipid peroxidation and block ferroptosis. Currently in GC therapy, PI3K inhibitors have the potential to reverse MDR in a multidimensional way, but there are still many urgent problems to be solved and directions worthy of in-depth exploration.In terms of basic research, our understanding of the complex inter-regulatory network between the PI3K/AKT pathway and other related pathways is not yet comprehensive and in-depth. In the future, we need to further clarify the specific regulatory mechanisms of this pathway in different gastric cancer subtypes, as well as the specific molecular mechanisms of its interaction with immune cells and mesenchymal stromal cells in the tumor microenvironment, which will provide a more solid theoretical foundation for precision therapy. In the field of drug discovery and development, since inhibitors face challenges such as off-target toxicity, it is urgent to develop new targeted drugs or drug delivery systems with high efficiency, low toxicity and good pharmacokinetic properties.For example, the use of nanotechnology to construct smarter and more precise drug delivery carriers

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to achieve specific enrichment and controlled release of drugs in tumor tissues, thus improving drug efficacy and reducing toxic side effects. In addition, combining PI3K/AKT pathway-related targeted therapies with immunotherapy, gene therapy and other emerging therapeutic tools to explore the optimal solution for combined therapy is expected to further improve the therapeutic effect of GC. At the clinical application level, relying on the mutation characteristics of PI3K/AKT pathway genes (such as PIK-3CA, PTEN and other major mutated genes), the mutation status, expression profile and epigenetic modification characteristics of the upstream and downstream genes of this pathway in GC will be analyzed through genomics technology. The establishment of a precise diagnosis and prognostic evaluation system based on genomic markers related to this pathway is of key significance for the screening of subgroups of patients who can benefit from PI3K/AKT-targeted therapies.

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