Metformin: A promising drug for human cancers (Review)

HONGNIAN WU[1*], DAN HUANG[2*], HONG ZHOU[1], XUEQIN SIMA[3], ZHE WU[3], YANLING SUN[3], LONG WANG[4], YING RUAN[5], QIAN WU[6], FENG WU[7], TONGHUI SHE[8], YING CHU[2], QIZHI HUANG[9], ZHIFENG NING[1] and HAO ZHANG[10]

[1]Department of Human Anatomy, Basic Medicine School, Hubei University of Science and Technology, Xianning, Hubei 437100; [2]Department of Burn and Plastic Surgery, Enshi State Central Hospital, Enshi, Hubei 445099; Departments of [3]Histology and Embryology and [4]Microbiology, Basic Medicine School; [5]Department of Dermatology, Clinical Medicine School; [6]Nursing School; [7]Stomatology and Optometry School; [8]Department of Pathology, Basic Medicine School; [9]Department of Clinical Lab, Second Affiliated Hospital, Hubei University of Science and Technology, Xianning, Hubei 437100; [10]Institute of Precision Cancer Medicine and Pathology, Department of Pathology, Jinan University Medical College, Guangzhou, Guangdong 510630, P.R. China

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Abstract. Small-molecule chemical drugs are of great significance for tumor-targeted and individualized therapies. However, the development of new small-molecule drugs, from basic experimental research and clinical trials to final application in clinical practice, is a long process that has a high cost. It takes at least 5 years for most drugs to be developed in the laboratory to prove their effectiveness and safety. Compared with the development of new drugs, repurposing traditional non-tumor drugs can be a shortcut. Metformin is a good model for a new use of an old drug. In recent years, the antitumor efficacy of metformin has attracted much attention. Epidemiological data and *in vivo*, and *in vitro* experiments have shown that metformin can reduce the incidence of cancer in patients with diabetes and has a strong antagonistic effect on metabolism-related tumors. Recent studies have shown that metformin can induce autophagy in esophageal cancer cells, mainly by inhibiting inflammatory signaling pathways. In recent years, studies have shown that the antitumor functions and mechanisms of metformin are multifaceted. The present study aims to review the application of metformin in tumor prevention and treatment.

Correspondence to: Mr. Qizhi Huang, Department of Clinical Lab, Second Affiliated Hospital, Hubei University of Science and Technology, 58 Chahua Road, Xianning, Hubei 437100, P.R. China
E-mail: huangqzhome@126.com

Dr Ying Chu, Department of Burn and Plastic Surgery, Enshi State Central Hospital, 158 Wuyang Avenue, Enshi, Hubei 445099, P.R. China
E-mail: 12977698 @qq.com

*Contributed equally

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Contents

1. Introduction

In the field of antitumor therapy, small-molecule drug therapy is a targeted form of treatment with high specificity and few adverse reactions. Small-molecule drugs are called 'biological missiles' and are gradually becoming a hot spot in research, development and clinical application. Repurposing old small-molecule drugs is an active focus of research. Metformin is a typical 'old medicine with new uses'. Metformin is a 1,1-dimethylbiguanide hydrochloride isolated from the legume *Galega officinalis*. It was first reported in 1957 as a hypoglycemic drug (1). Studies have found that metformin has weight loss, anti-aging, and anti-cardiovascular effects (2). In recent years, studies have reported an antitumoral effect of the drug, which has been confirmed in various malignant tumor cells such as liver (3), ovarian (4) and lung cancer cells. The present study summarizes knowledge on the anti-tumoral effects of metformin and its mechanism in order to provide evidence for the repurposing of this drug for tumor treatment.

Antitumoral advantages of small molecule drugs. Biomacromolecular drugs are considered one of the most promising fields in drug development in this century. Common biomacromolecular antitumor drugs include monoclonal antibodies, recombinant protein drugs and vaccines (5). These biomacromolecular drugs have some shortcomings in clinical

use: i) Lack of selectivity for targeted lesion tissues in contrast to normal tissues, which may cause serious adverse reactions; ii) most drugs cannot enter cells to exert an antitumoral effect and iii) their mechanism of action on tissues, organs, cells and molecules within the body is frequently uncertain, therefore it is difficult to evaluate their efficacy (6). These factors lead to unsatisfactory clinical therapeutic effects of biomacromolecular drugs. By contrast, small-molecule drugs are more popular in the clinics because they may have better therapeutic efficacy and fewer adverse reactions. More importantly, they are relatively inexpensive (7). However, with the widespread application of these drugs, their shortcomings have also became prominent: Ease in development of drug resistance and multiple adverse reactions, resulting in reduced clinical efficacy. For example, gefitinib and erlotinib used in the treatment of non-small cell lung cancer (NSCLC) (8), imatinib in the treatment of chronic myeloid leukemia (8) and gastrointestinal stromal tumors (9) are reported to have several side effects and develop tumor resistance.

Among the numerous strategies available to improve tumor treatment (10), the development of new drugs is worth considering. However, this development requires a large amount of funding, a long testing period and large-scale and multi-center clinical trials. The economic and time costs of new drug research and development are huge, and it is difficult to improve the current status of tumor treatment in the short term. Therefore, exploring the functions and indications of existing non-antitumoral small-molecule drugs to evaluate their potential antitumoral efficacy, and therefore repurposing 'old drugs' is an important way to improve the clinical efficacy of antitumoral treatment.

Metformin, the chemical structure of which is shown in Fig. 1, is the first-line drug used clinically for type 2 diabetes. In recent years, it was discovered that the drug has antitumoral effects, which is a typical form of repurposing (11). In addition to metformin, there are a number of small-molecule drugs that have regained a 'new life' in the anti-cancer field, such as aspirin (12), thalidomide (13), statins (14), vitamin D (15) and green tea extract (16).

Metformin bioavailability. The cellular uptake and secretion rate of metformin largely depends on the expression of organic cation transporters and of multidrug and toxin extrusion proteins (17). The organic cation transporter, toxin extrusion protein and plasma membrane monoamine transporter distribute metformin to several tissues, such as the liver, kidneys and small intestine, and also mediate metformin metabolism and secretion. Oral metformin is mainly absorbed through the upper small intestine. Knockout mice for the toxin extrusion protein transporter show a significant reduction in the clearance and distribution of metformin, usually without an effect on tissue distribution or pharmacological effects (10). The bioavailability of oral metformin is 40-60% (18). Metformin uptake is dose-dependent, but saturable (19). In clinical trials, the plasma elimination half-life is ~5-6 h in patients with normal renal function under repeated metformin administration (20). Approximately 90% of oral metformin is secreted through the kidneys within 24 h. However, for patients with advanced cancer and gastrointestinal tumors with poor prognosis, the possibility of reaching high blood concentrations is low (21). In a cell line model, the half-inhibitory concentration (IC_{50}) of metformin is between 5 and 20 mM. In breast cancer cell lines, the IC_{50} of metformin is increased and apoptosis and cell cycle arrest induced by metformin are decreased at high glucose levels compared with low glucose levels (22). The *in vitro* activation of cellular AMP-activated protein kinase (AMPK) requires at least 1 mM metformin in numerous cancer cell lines (23). This is equivalent to an intracellular concentration of 131 μM, which is close to the plasma concentration of metformin in mice receiving an intraperitoneal injection of 145 μM. Compared with oral metformin, the intraperitoneal injection can increase the bioavailability of metformin in mice. In particular, the metformin concentration in the blood, liver and kidneys increases, significantly (18). In mouse tumor models, the biodistribution of ^{11}C-metformin administered intravenously shows relatively high tracer uptake in the kidneys and liver, and relatively low tracer uptake in the blood and tumors (24). ^{11}C-metformin-positron emission tomography can be combined with mutation screening of metformin sensitivity-related genes and can be used clinically to identify metformin-sensitive tumors. In a rat model of lipopolysaccharide-induced systemic inflammation, the concentration of metformin varies between different brain regions, with the highest concentration of metformin in the pituitary gland and cerebrospinal fluid (~30 μM).

2. Metformin as an antitumor candidate drug

Multiple functions of metformin. Metformin was originally chemically synthesized in 1929 (25). It was first approved as a clinical drug in 1957 and has since been used to treat diabetes (26). In 1998, metformin was discovered to have a protective effect on the cardiovascular system (27). Since then, other functions of the drug have been discovered (Fig. 2). For example, metformin can be used in the adjuvant treatment of tuberculosis (28), and it is also used in the routine treatment of polycystic ovary syndrome (29). In addition, metformin can delay aging and improve the symptoms of non-alcoholic fatty liver (30), prevent and treat uveitis (31), reduce the prevalence of Parkinson's disease (32) and improve the intestinal flora imbalance in diabetic patients (33). Basic research has shown that metformin inhibits the expression of mammalian target of rapamycin (mTOR) by activating AMPK to improve rheumatoid arthritis (34). Metformin combined with risperidone can significantly improve fasting blood glucose, triglyceride levels, high-density lipoprotein levels, and body mass index in patients with schizophrenia complicated with metabolic syndrome, and effectively reduce the incidence of metabolic syndrome (35).

Antitumoral effects of metformin

The basis of the antitumoral effect of metformin. In 1910, Maynard suggested that diabetes is associated with tumors (36). Since then, an increasing number of studies have shown that diabetes can increase the risk of various malignant tumors (37-39). Diabetes and tumors have common risk factors, including age, sex, diet and smoking and their onset is related to the insulin/insulin-like growth factor (IGF) pathway (40). Patients with diabetes are prone to develop tumors. At present, most studies suggest that hyperglycemia, hyperinsulinemia,

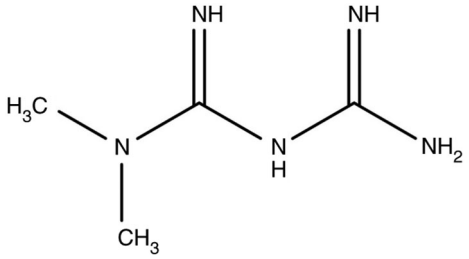

Figure 1. Chemical structure of metformin.

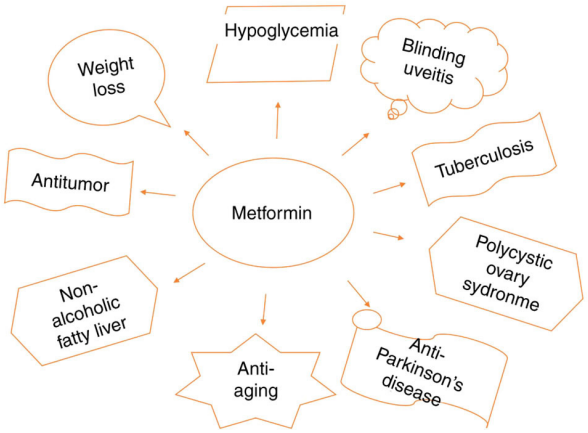

Figure 2. Multiple functions of metformin. In addition to hypoglycemia, metformin displays antitumor, anti-aging, anti-Parkinson's disease and weight loss effects.

IGF-1, DNA damage, inflammatory factors and obesity may be involved in the pathological process of diabetes-related tumors (41-43). Adequate blood sugar control is beneficial in reducing the risk of malignant tumors. Obese patients with type 2 diabetes have a higher risk of developing cancer such as liver (44), biliary tract (45), pancreatic (46), colorectal (47), kidney (48), bladder (49), breast (50) and endometrial cancer (51). Insulin resistance leads to unsatisfactory treatment effects in diabetes, and is a chronic, non-specific inflammatory process. Insulin resistance not only leads to an increase in insulin and IGFs, but also promotes mitosis (52), activates the PI3K/AKT cell proliferation signaling pathway, promotes tumor cell growth (53) and aggravates the tumor inflammatory response to promote tumor invasion and metastasis.

Studies have reported that metformin has an effect on tumors of non-obese patients. Metformin can inhibit growth and promote differentiation of ovarian (54), endometrial (55), and breast cancer (56), thereby reducing the risk and mortality of these tumors. Jayalath *et al* (44) found that metformin reduced the level of serum prostate-specific antigen and delayed the progression of prostate cancer. In addition, metformin increases the sensitivity of patients with colorectal cancer (especially those with diabetes) to radiotherapy and improved the progression-free survival of patients with NSCLC (57). Additionally, metformin inhibits metastasis of malignant gliomas (58).

Epidemiological research on the antitumoral effect of metformin. In recent years, epidemiological data have shown that diabetes increased the risk of a number of tumors. The cancer mortality rate in patients with diabetes is 1.41 times that of patients without diabetes (59). Studies have shown that metformin reduced the incidence of cancer by 30-50%, especially pancreatic cancer (60), hepatocellular carcinoma (61) and colon cancer (62). Febbraro *et al* (63) conducted a retrospective cohort study on 341 patients with ovarian cancer and found that, the 5-year progression-free survival rate of diabetic patients taking metformin was higher than diabetic patients who did not take metformin and non-diabetic patients., but the 5-year overall survival rates were not significantly different. Xu *et al* (64) reported that the pathological complete response rate of patients with diabetes and breast cancer taking metformin was 24%, which was higher than that of patients not taking metformin (8%) and also higher than that of patients without diabetes taking metformin (16%), suggesting that metformin may improve the prognosis of breast cancer in patients with diabetes. Wang *et al* (65) proved through randomized controlled trials that for patients with breast cancer but without diabetes, metformin could improve the prognosis of breast cancer by reducing blood insulin and testosterone levels. Tseng (66) showed that metformin significantly reduced the incidence of prostate cancer in men with type 2 diabetes mellitus. In a follow-up study of patients with newly developed diabetes between 1998 and 2002, as of the end of 2009, the incidence of prostate cancer in patients with diabetes taking metformin was 239.42/100,000 per year, while the incidence of non-users was 737.10/100,000 person-years, and the adjusted risk odds ratio was 0.467 (95% CI, 0.446-0.488). A comparison of the survival of 750 patients with stage 4 NSCLC aged 65-80 years old found that 61% of the patients were already taking metformin when they were diagnosed with lung cancer (67). The median survival time of the metformin group was 5 months, while that of the non-users was 3 months with a statistically significant difference (67). Studies on the risk of thyroid cancer in patients with type 2 diabetes taking metformin have also shown that metformin could reduce the incidence of thyroid cancer (68). The incidence rate of patients taking metformin was 24.09/100,000 person-years, while the incidence rate of those not taking metformin was 87.33/100,000 person-years, with an adjusted risk ratio of 0.683 (95% CI, 0.598-0.780) (68). Other studies have also shown that metformin decreases the risk of esophageal adenocarcinoma (69) and endometrial cancer (70). Bowker *et al* (71) conducted a five-year follow-up of 10,309 newly-diagnosed patients with type 2 diabetes, and found that the tumor-related mortality of patients taking metformin was significantly lower than that of patients using sulfonylurea-type hypoglycemic drugs or insulin. Another meta-analysis on 13,008 patients with type 2 diabetes and tumors showed that the survival rate of tumor patients using metformin was significantly higher than that of non-users, and cancer-related mortality was significantly lower than that of non-users (72). Metformin is likely to inhibit tumor progression in patients with type 2 diabetes and can reduce the progression risk of patients with tumors and tumor-related mortality, thereby improving patient survival.

Experimental research on metformin antitumoral activity. Emerging evidence has shown that metformin can inhibit the growth of several types of cancer cells *in vitro* (73-75). At the

same time, its antitumoral effect in a mouse tumor model has also been confirmed (76). Huang *et al* (76) reported that PTEN knockout mice fed with 300 mg/kg/day metformin had delayed tumorigenesis, and that metformin effectively inhibits growth of colon polyps. In addition to inhibiting spontaneous and carcinogen-induced tumors, metformin could inhibit allograft tumors. Phoenix *et al* (77) implanted tumor cells cultured in a high-sugar and high-insulin environment into mice, and found that the administration of metformin at a dose 40 times higher than the clinical dose effectively reduces the growth rate of tumors. Anisimov *et al* (78) found that metformin significantly inhibited tumor growth in HER2/neu transgenic mice and increased their average life span. Memmott *et al* (79) used the tobacco carcinogen NNK to generate an A/J mouse lung cancer model and found that metformin could delay tumorigenesis and reduced tumor burden in mice. It was hypothesized that the antitumoral effect of metformin was related to the downregulation of insulin and IGF-1 receptor. The AKT receptor pathway was also involved. Metformin could indirectly reduce the expression of mTOR (the 'master factor' of protein synthesis in cells) in the mouse lung tissue through the AKT pathway, leading to the inhibition of tumor cell growth.

Antitumoral mechanism of metformin

The protein kinase (AMPK)/mTOR pathway. AMPK is one of the main regulators of cell energy status and key cellular processes such as lipid and glucose metabolism, cell growth, autophagy and apoptosis. This enzyme maintains mitochondrial homeostasis and is activated when the ratio of AMP or ADP to ATP increases, and compensates for energy loss by upregulating glycolysis (80). Tumors such as breast (81), pancreatic (82) and prostate cancer (83) are related to obesity, which in turn is associated with the AMPK/mTOR metabolic pathway (84). AMPK is the cell's 'energy receptor' being activated when energy is lacking and inhibited when energy is excessive. After AMPK is activated, it can regulate multiple pathways, including the mTOR pathway, thus dominating intracellular protein synthesis (84). Most studies have shown that metformin inhibits obesity-related tumors through the AMPK/mTOR pathway (85,86). In this pathway, AMPK activation by metformin requires an interaction between the regulatory factor liver kinase B-1 and inositol polyphosphate multikinase (87). In addition, the lysosomal pathway is essential for metformin to activate AMPK (88). Metformin activates AMPK through phosphorylation, which in turn downregulates the expression of key adipogenic transcription factor sterol regulatory elements combined with transcription factor 1, leading to the downregulation of lipogenic enzymes, such as Fas cell surface death receptors (89). Metformin directly and indirectly activates AMPK. AMPK can block proliferation and metastasis of tumor cells by compromising mTOR. Tumor cells cannot survive because they cannot synthesize proteins normally (90) (Fig. 3).

Metformin does not act only on AMPK to function. Compared with normal cells, cancer cells have a higher ATP demand. Metformin can reversibly inhibit NADH dehydrogenase (mitochondrial complex I) activity of the respiratory chain and exert its role as an inhibitor of oxidative phosphorylation at the molecular level, thereby inhibiting ATP production.

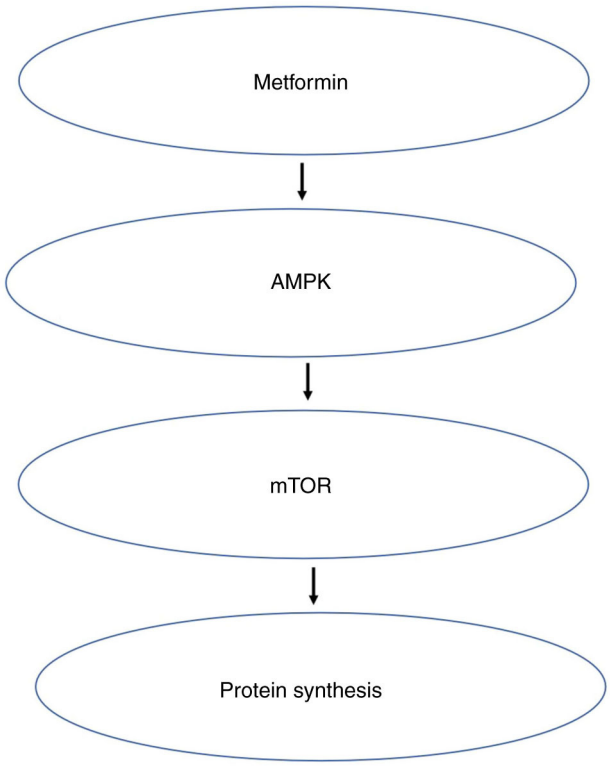

Figure 3. Anti-neoplastic activity of metformin via inhibition of AMPK/mTOR pathway. Inhibition of AMPK/mTOR pathway leading to the arrest of protein synthesis is a major anti- neoplastic activity of metformin.

Metformin accumulates in the mitochondrial matrix in the presence of a polarized mitochondrial membrane potential. By inhibiting the effective coupling of redox and proton transfer domains, it reversibly inhibits the NADH dehydrogenase (mitochondrial complex I) of the respiratory chain (91), thereby inhibiting ATP production.

Inflammatory pathways and cell death induction. Metformin also has antitumoral effects on tumors of non-obese patients and can cause tumor cell death. Cell death can be divided into programmed and unprogrammed cell death, the latter of which is also known as necrosis. According to the Clarke morphological classification, programmed cell death can be divided into: i) Apoptosis); ii) autophagic cell death and iii) necrosis-like programmed cell death. Feng *et al* (92) found that metformin inhibited tumors by inducing tumor cell apoptosis and autophagy, in the treatment of esophageal cancer. Metformin-mediated apoptosis of esophageal cancer cells was subtle, and the main mechanism of cell death was autophagy. Additionally, it was found that AMPK was not the only pathway involved in metformin-mediated esophageal cancer cell apoptosis and autophagy.

Several metformin effects do not rely on AMPK mechanisms, these are known as the pleiotropic effect of metformin in tumor treatment (93-95). Biochemical studies have shown that the redox shuttle enzyme mitochondrial glycerol-3-phosphate dehydrogenase (GPDH) was another major target (96). The drug reduced the redox state of mitochondria (in the plasma and liver) and limited the conversion of lactic acid to glycerol and glucose, thereby reducing liver gluconeogenesis.

Mitochondrial GPDH was overexpressed in the tumoral thyroid compared with that of normal thyroid tissues. Thyroid cancer cells with high mitochondrial GPDH expression were more susceptible to the inhibitory effects of metformin during proliferation (97). Hexokinase II is attached to the outer mitochondrial membrane and is highly expressed in cancer cells. Cell experiments and molecular simulation studies have shown that metformin inhibited the activity of hexokinase II by occupying the binding site of glucose-6-phosphate, and directly impaired glucose metabolism (98). This induced the dissociation of hexokinase II from mitochondria, leading to the activation of apoptotic signals.

Esophageal cancer was an inflammatory tumor (99). The *Stat3* gene product is at the intersection of many cancer and inflammatory signaling pathways (100). Therefore, it was possible that the mechanism of action of metformin in esophageal cancer was related to *Stat3*. Feng *et al* (92) showed that the treatment of esophageal cancer by metformin activated the STAT3 pathway, especially the STAT3/Bcl-2/ATG network signaling pathway, promoted apoptosis and autophagy, in which autophagy had a protective effect on the metformin-mediated apoptosis, inducing an inhibition of tumor growth (Fig. 4). The results clarified the target of metformin in the treatment of esophageal cancer, revealed the possibility of combining autophagy inhibitors to enhance the clinical efficacy of metformin, and laid the foundation for the optimal design of esophageal cancer treatment options.

Other antitumoral effects of metformin. Other metformin antitumoral effects were presented in a recent study that reported that metformin had the potential to block or delay all kinds of malignant biological behaviors, such as cell cycle arrest, sensitivity to radiotherapy and chemotherapy, and inhibition of proliferation and differentiation of cancer stem cells (101).

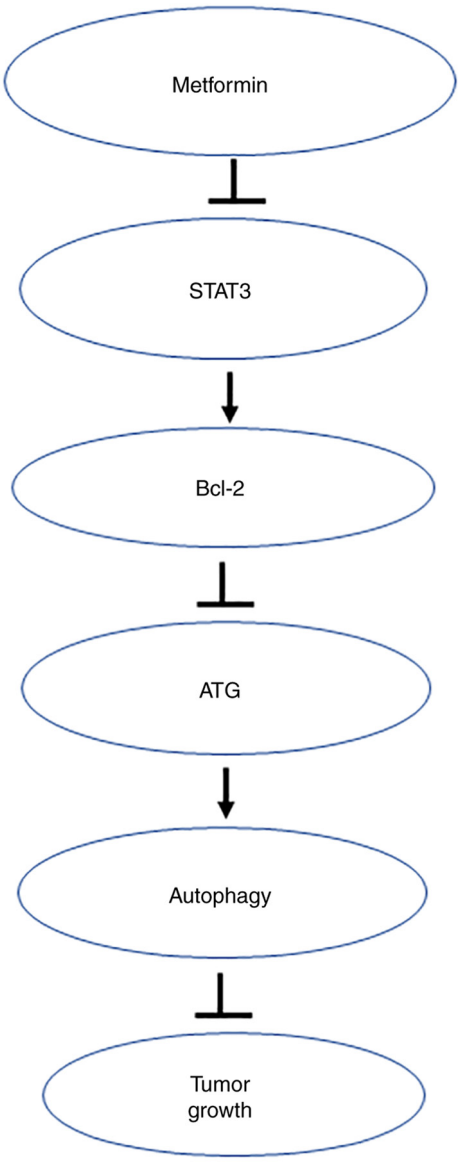

Figure 4. Metformin induces esophageal cancer cell autophagy via the STAT3/Bcl-2/ATG pathway. Metformin inhibits STAT3 expression to decrease Bcl-2 protein expression, which upregulates expression of autophagy marker ATG, thus inducing autophagy to slow tumor growth of esophageal cancer.

3. Clinical trials on metformin in the treatment of tumors

The short-term randomized clinical trial by Higurashi *et al* (102) showed that metformin could reduce abnormal colorectal polyps by 40% compared with the control group. Currently, several clinical trials (such as NCT04559308, NCT04387630 and NCT03137186) on cancer treatment with metformin have been initiated. Most ongoing clinical trials are based on the evaluation of changes in biomarkers, including insulin levels, AKT/mTOR signals and Ki67 staining. In addition, the clinical benefit of metformin, which uses response and survival rates as indicators, have also been studied, and retrospective studies have used cancer chemotherapy response and survival time as indicators, proving that metformin has potential clinical benefits (103,104).

Our research group adopted a short-term preoperative metformin neoadjuvant treatment for esophageal squamous cell carcinoma and analyzed the changes in the proliferation and apoptosis indices of cancer tissues of patients with metformin. Preliminary results confirmed that cancer proliferation is inhibited by the short-term administration of metformin before surgery, indicating that the patient can benefit from short-term sustained-release of metformin treatment before surgery (105). The main side effect of metformin in patients is gastrointestinal discomfort. These results provide a theoretical basis for further application of metformin in the treatment of esophageal cancer.

The results of a meta-analysis showed that for patients with type 2 diabetes, the effect on blood sugar control was not sufficient when using metformin alone and that metformin combined with sulfonylurea hypoglycemic agents could improve blood sugar control and reduced cardiovascular disease mortality in patients with type 2 diabetes (106). Recent research has shown that metformin combined with chemotherapy drugs can significantly decrease local recurrence in patients with diabetes and NSCLC (107). In addition, compared with VEGF-A inhibitors alone, metformin combined with VEGF-A inhibitors is more effective in inhibiting tumor growth (108), indicating that the combined application of metformin can be a promising route to increase its antitumoral efficacy.

4. Conclusions

Metformin is a small-molecule drug with multiple pharmacological functions. Although research on metformin as an antitumoral drug is still in its preliminary stage, its potential antitumoral efficacy has made people look forward to studying metformin. Based on current research, it is hypothesized that metformin combined with radiotherapy and chemotherapy can enhance the clinical efficacy against tumors, thereby benefiting patients. Further research on metformin should be carried out on the two following aspects: i) Improvement of the molecular structure and pharmaceutical form of metformin, such as modifying tablets into other pharmaceutical forms to produce targeted drugs to improve efficacy and reduce adverse reactions, or coupling certain active groups to the chemical structure of metformin to increase its specificity and effective concentration; ii) evaluation of the combination of metformin with other drugs to improve efficacy. In both cases, the ultimate goal of researchers is to fully understand and optimize the antitumoral effect of metformin in clinical practice and benefit patients.

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Availability of data and materials

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Authors' contributions

HZha, ZN, TS and YC designed the study. HW, DH, HZho, ZW, FW, LW and QW wrote the manuscript. YS, ZN, XS, YR, QH and HZha revised the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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