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ABSTRACT*: Metformin is one of the oldest, most widely used, and most cost-effective drugs for the treatment of type 2 diabetes mellitus as monotherapy or combination therapy. However, the exact biologic mechanisms of action for this semisynthetic biguanide are still not clear. Numerous in vitro and in vivo studies demonstrate that metformin may exert direct or indirect antitumor effects by targeting insulin or the insulin-like growth factor axis, signal transduction pathways essential for tumor transformation, tumor proliferation, and tumor angiogenesis. Recently, epidemiologic, preclinical, and clinical evidence indicates that metformin has antitumor benefits beyond glycemic control. In this review, the potential antitumor biologic mechanisms and the evidence supporting the role of metformin in various cancer therapies will be discussed.*

Metformin is a semisynthetic biguanide derived from the substance galegine of the herbaceous plant goat's rue (*Galega officinalis*). Metformin is FDA-indicated for type 2 diabetes mellitus (T2DM), with potential off-label use for diabetes mellitus prophylaxis, hyperinsulinar obesity, hypersecretion of ovarian androgens, polycystic ovary syndrome, and antipsychotic therapy-induced weight gain.[1] Metformin is the initial antihyperglycemic drug of choice for the management of T2DM by improving insulin sensitivity and decreasing blood glucose levels by decreasing hepatic gluconeogenesis through

LKB1/AMPK (serine-threonine liver kinase B1/5' adenosine monophosphate–activated protein kinase) mediated mechanism and intestinal glucose absorption.[2]

Metformin has been widely used in conjunction with lifestyle modifications, and can be used in combination with other antidiabetic medication such as a glucagon-like peptide 1 (GLP-1) receptor agonist or insulin.[3] Beyond glycemic control, metformin has been used in the management of various conditions such as lipid disorders, HIV lipo-dystrophy syndrome, nonalcoholic fatty liver disease, heart failure, aging, and inflammation.[4]

Numerous studies indicate that increased cancer risks, such as of breast, pancreatic, and colorectal cancers, are associated with T2DM.[5,6] It has been reported that there is an increase risk of death in breast, endometrial, colon, and rectal cancer patients who have diabetes compared to nondiabetic cancer patients. In addition, the use of antihyperglycemic agents such as insulin or other antidiabetic drugs can further increase the risk of pancreatic cancer in diabetic patients.[5,6] Recently, pioglitazone has been withdrawn from the market in many countries due to significantly increased risk of bladder cancer associated with its use.[7] In contrast, intriguing in vitro and in vivo evidence demonstrates that metformin may exert direct or indirect antitumor effect by targeting tumor initiation, tumor progression, and tumor angiogenesis, and may improve antitumor immunity.

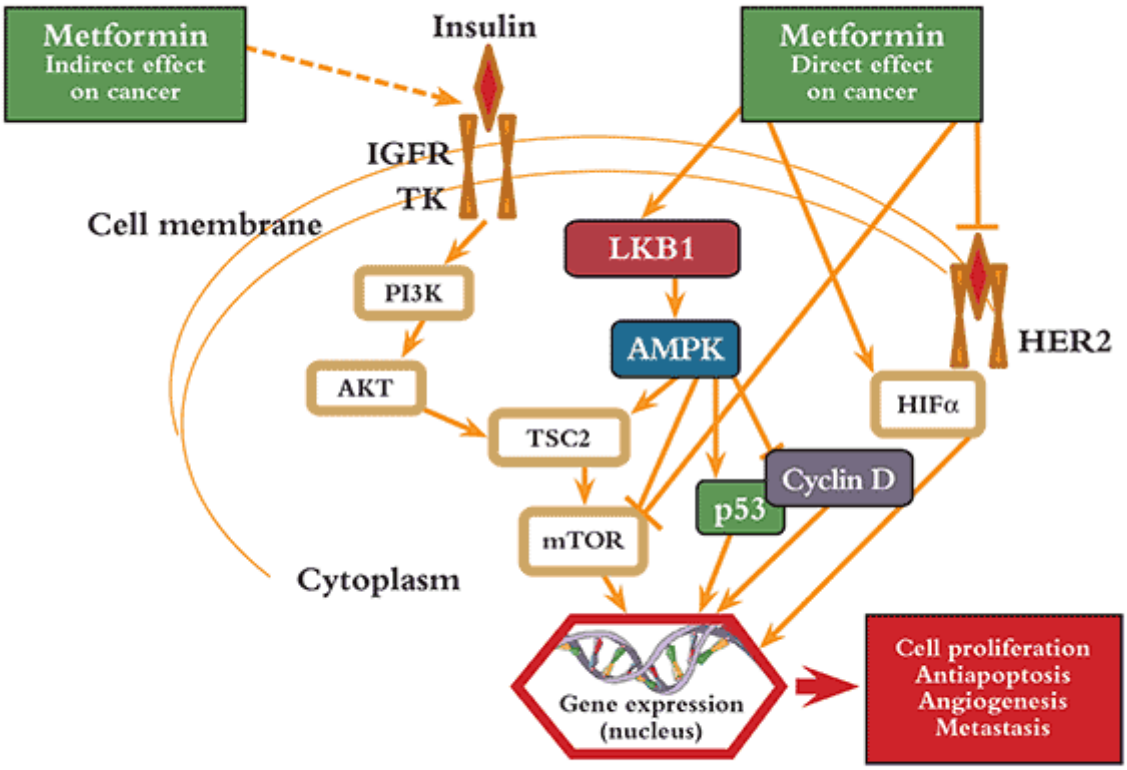
More and more epidemiologic, preclinical, and clinical evidence indicates that metformin has antitumor benefits beyond glycemic control.[8] Thus, metformin monotherapy or combination therapy has potential to decrease the cancer risk factors associated with T2DM and its treatment. Although metformin is generally well tolerated, it can rarely increase risk of lactic acidosis, especially in diabetic patients with severe renal impairment.[3]

Potential Biologic Mechanisms of Metformin in Cancer Control

Although the exact biologic mechanisms of action for this semisynthetic biguanide are still not clear, it has been clearly demonstrated that mechanistically metformin activates LKB1 and its downstream target AMPK. LKB1 is a well-recognized tumor suppressor. The glycemic control facilitated by metformin is mainly mediated through the activation of AMPK, although metformin can also reduce hepatic gluconeogenesis through AMPK-

independent electron transport in hepatocyte mitochondria.[2] The antitumor benefits of metformin have been suggested to constitute an indirect insulin-dependent pathway and a direct insulin-independent pathway (FIGURE 1). In the indirect pathway, metformin activates AMPK, which down-regulates the insulin/insulin-like growth factor axis. This results in reduced signaling through the phosphoinositide-3-kinase (PI3K) pathway, thus inhibiting the growth or proliferation of cancer cells.[2,6]

Figure 1. Major Potential Antitumor Mechanisms of Metformin



AKT: v-akt murine viral oncogene; AMPK: 5' adenosine monophosphate-activated protein kinase; HER2: human epidermal growth factor receptor 2; HIFα: hypoxia-induced factor alpha; IGFR: insulin-like growth factor receptor; LKB1: serine-threonine liver kinase B1; mTOR: mammalian target of rapamycin; p53: tumor suppressor protein; PI3K: phosphoinositide 3-kinase; TK: tyrosine kinase; TSC2: tuberous sclerosis complex 2.

The direct pathway has an insulin-independent mechanism. In this pathway, activation of AMPK causes inhibition of the mammalian target of rapamycin (mTOR) signaling pathway. Inhibition of mTOR downregulates the tumor cell growth and proliferation and induces apoptosis of cancer cells. Metformin can also decrease oncogene human epidermal growth factor receptor 2 (HER2) and the cell cycle protein cyclin D1 synthesis in tumor cells. It has been reported that metformin activates AMPK on prosurvival pathways associated with therapeutic resistance to treatment with HER2 antagonists, such as

trastuzumab and lapatinib.[2,6] Since mTOR is also essential for tumor angiogenesis, metformin might play an important role in regulating tumor angiogenesis.

In addition, AMPK activation enhances apoptosis through the increase of p53 expression and stimulates cell cycle arrest by decreasing cyclin D1 expression.[2,6] Likewise, the AMPK-independent antitumor properties of metformin have also been extensively described, such as the Rag GTPase–dependent inhibition of mTOR, and the growth inhibition of AMPK-silenced ovarian cancer cells. It is important to mention that metformin can increase memory CD8 T cells, which may contribute to the antitumor effect of metformin. Lastly, metformin can also regulate hypoxia-induced factor (HIF), which is essential for tumor proliferation and tumor angio-genesis.[8-11]

Epidemiologic Evidence

Epidemiologic studies indicate that there is a decreased trend of cancer incidence and mortality from cancer in diabetic patients with metformin treatment. In a prospective study that enrolled 1,353 T2DM patients with a median follow-up time of 9.6 years, Landman and colleagues reported decreased cancer-related mortality in diabetic patients treated with metformin compared to diabetic patients without metformin treatment (adjusted hazard ratio [HR] 0.43; 95% CI, 0.23-0.80). Furthermore, for every one-gram increase in metformin dose, the hazard for cancer mortality decreased by 42% in this prospective study.[12]

These results are consistent with data from a pilot case-control study with 314,127 patients in record linkage databases developed in Tayside, Scotland: a diabetes clinical information system (DARTS) and a database of dispensed prescriptions (MEMO). It suggested that the greater the metformin exposure, the stronger the risk reduction for cancer. Compared to control, the group with the total amount of metformin dispensed >964,000 mg had significant lower cases of cancers (adjusted HR 0.57; 95% CI, 0.43-0.75).[13]

In a retrospective cohort study with 62,809 patients, Currie et al demonstrated that patients receiving metformin had the lowest risk of cancer incidence compared to sulfonylurea monotherapy (HR 1.36; 95% CI, 1.19-1.54), metformin plus sulfonylurea combination therapy (HR 1.08; 95% CI, 0.96-1.21), or insulin treatment (HR 1.42; 95% CI, 1.27-1.60). For those patients

with insulin treatment, there is significant lower risk of cancer in those patients with metformin treatment (HR 0.54; 95% CI, 0.43-0.66).[14] Similar results were also reported by Bowker and colleagues in a population-based cohort study, which indicates that the sulfonylurea cohort (adjusted HR 1.3; 95% CI, 1.1-1.6) and the insulin cohort (adjusted HR 1.9; 95% CI, 1.5-2.4) have significantly higher risk of cancer compared to the metformin cohort.[15]However, using a national health insurance database for Taiwan, Wang et al reported that there was no significant cancer risk reduction associated with metformin treatment in Taiwanese diabetic patients (odds ratio [OR] 1.06; 95% CI, 0.89-1.26).[16]

In a meta-analysis, Zhang and colleagues assessed 37 clinical studies analyzing the association of metformin use with cancer incidence and mortality.[17] Results demonstrated that summary relative risk (SRR) for overall cancer incidence (SRR 0.73; 95% CI, 0.64-0.83) and mortality (SRR 0.82; 95% CI, 0.76-0.89) is significantly lower in the metformin treatment groups compared to the nonmetformin groups. They also compared the risk reduction for common cancers associated with diabetic patients and demonstrated that the risk reduction associated with metformin use for liver, pancreatic, colorectal, and breast cancer incidence is 78%, 46%, 23%, and 6%, respectively.[17]

In another meta-analysis, Soranna et al demonstrated that metformin use was associated with significantly decreased SRR of all cancers (SRR 0.61; 95% CI, 0.54-0.70), colorectal cancer (SRR 0.64; 95% CI, 0.54-0.76), and pancreatic cancer (SRR 0.38; 95% CI, 0.14-0.91). However, the association and SRR reduction for breast cancer (SRR 0.87; 95% CI, 0.69-1.10) and prostate cancer (SRR 0.92; 95% CI, 0.73-1.17) were not statistically significant.[18]

Metformin and Breast Cancer

HER2 is typically overexpressed and is the major driver of tumor proliferation in HER2-positive breast cancers.[19] Metformin reduces HER2 protein expression through the inhibition of the mTOR effector p70S6K1 in human breast carcinoma cells.[20] Studies have shown that metformin can block HER2 activity at a lower concentration.[20,21] In addition, metformin can prevent drug resistance to cancer treatments targeting HER2 (trastuzumab, lapatinib) by inhibiting certain triggers that upregulate survival. The above mechanisms

may support the combined use of metformin with HER2 therapy by providing possible synergistic effects.[22,23] Using a chart review of 253 diabetic patients with breast cancer, Besic et al reported a significant reduction of T3 and T4 tumors in patients with metformin treatment compared to those without metformin treatment (16% vs. 26%; *P* = .035).[23]

Chlebowski et al studied postmenopausal breast cancer patients participating in Women's Health Initiative clinical trials and demonstrated that diabetic patients receiving metformin treatment had a lower incidence of breast cancer compared to those without metformin treatment (HR 0.75; 95% CI, 0.57-0.99).[24] Chlebowski's group also demonstrated that there is significant lower incidence of invasive breast cancer in diabetic women taking metformin compared to those taking other diabetic drugs.[24] However, using a population-based study with 2,361 breast cancer patients, Lega et al reported no significant association between improved survival and increased cumulative metformin duration in older breast cancer patients with recent-onset diabetes.[25]

Metformin and Prostate Cancer

In vitro and in vivo experimental evidence indicates that metformin inhibits the proliferation of the prostate cancer cell line and decreases the expression of the c-Myc oncogene through activation of the AMPK pathway.[26] The c-Myc oncogene plays an important role in preneoplastic and malignant stages of prostate cancer growth. In addition, hyperinsulinemia and insulin resistance cause a decrease in sex hormone binding–globulins, thus leading to an increase in available free unbound androgen that is important to prostate cancer growth. Hyperinsulinemia has been shown to increase prostate cancer mortality.[27]

Using a population-based retrospective cohort administrative database, Margel et al demonstrated that cumulative duration of metformin treatment for diabetic patients aged □66 years with prostate cancer was associated with significant lower risk of prostate cancer–related mortality (adjusted HR 0.76; 95% CI, 0.64-0.89) for each additional 6 months of metformin treatment.[28] In a retrospective chart review of 233 consecutive cases, He et al demonstrated that metformin usage is a significant predictor of improved overall survival for diabetic patients with prostate cancer (HR 0.55; 95% CI, 0.315-0.960).[29] Although there are many retrospective studies that demonstrate an

association of prostate cancer with metformin use, Margel and colleagues did not find significant association between metformin use and prostate cancer incidence in elderly patients with diabetes.[30]

Metformin and Pancreatic Cancer

Experimental evidence indicates that metformin can significantly decrease the cancer stem cell (CSC) marker expression and induce reexpression of microRNA in pancreatic cancer cells, which suggests that metformin could play a role in mitigating pancreatic cancer therapeutic resistance. Nakamura et al reported that metformin decreases the expression of Sonic hedgehog (Shh), which is essential for the oncogenesis of pancreatic cancer.[31] In a retrospective clinical study, Cheon et al demonstrated that the survival rate in pancreatic cancer patients with elevated hemoglobin A1C was significantly worse (P = .038) compared to a control group without elevated A1C.[32] For patients with A1C >7%, the median overall survival time is extended in patients with metformin treatment compared to those with nonmetformin oral antidiabetic treatment (273 days vs. 145 days), although this result was not statistically significant (P = .058).[32]

In another retrospective cohort study, Hwang and colleagues failed to demonstrate the association of metformin treatment with improved survival in pancreatic cancer patients (HR 1.11; 95% CI, 0.89-1.38).[33] Using the FDA Adverse Event Reporting System (FAERS) database, Feng et al demonstrated that the pancreatic cancer risks associated with metformin and sitagliptin combination therapy are significantly lower compared to sitagliptin monotherapy (OR 0.277; 95% CI, 0.210-0.365).[34] More well-controlled clinical trials need to confirm the antitumor benefit of metformin in diabetic patients with pancreatic cancer.

Metformin and Colorectal Cancer

Emerging in vitro and in vivo experimental evidence indicates that metformin inhibits colorectal cancer (CRC) cell growth, inhibits colon carcinoma growth stimulated by a high-energy diet (i.e., providing 4.3 kcal/g), and delays tumor onset in animal subjects for p53 mutant colon cancer. A meta-analysis of five studies including 108,161 diabetic patients suggested that metformin significantly reduced the risk of CRC associated with diabetes (RR 0.63; 95% CI, 0.50-0.70).[35] Another study examined the association between metformin and CRC-specific mortality among stage I-III CRC patients receiving

treatment for diabetes.[36] There was a 39% reduction of CRC risk in metformin-treated patients, although it was not statistically significant (*P* = .06). This is consistent with another study indicating significantly lower overall mortality (HR 0.66; 95% CI, 0.476-0.923) and CRC-specific mortality (HR 0.66; 95% CI, 0.450-0.975) in CRC patients receiving metformin treatment compared to those not receiving metformin. This study also evaluated insulin and thiazolidinedione use, but both did not affect overall or CRC-specific mortality.[37]

Mei and colleagues assessed the survival benefits of metformin for diabetic patients with CRC in a meta-analysis and concluded that metformin use is associated with significant benefit in overall survival (HR 0.56; 95% CI, 0.41-0.77), and CRC-specific survival (HR 0.66; 95% CI, 0.50-0.87).[38] Kanadiya et al reviewed 7,382 colonoscopy reports and demonstrated that there is an increased risk of colorectal adenoma associated with T2DM (OR 1.35; 95% CI, 1.08-1.70). This meta-analysis showed that there was a significantly lower risk of CRC in patients taking metformin (OR 0.55; 95% CI, 0.34-0.87).[39]

Conclusion

Although intriguing experimental, medical, epidemiologic, preclinical, and clinical evidence indicates that metformin has novel antitumor benefits beyond glycemic control, well-designed controlled clinical trials are needed to confirm the antitumor benefits for a variety of cancers commonly associated with diabetes. According to ClinicalTrials.gov, there are currently over 20 clinical trials being conducted to assess the chemoprotective effect of metformin for breast, prostate, lung, colorectal, liver, endometrial, and ovarian cancers. It is essential for clinicians to understand the potential antitumor benefits of metformin for diabetic patients and to recommend metformin as first-line monotherapy or combination therapy for all T2DM patients who can tolerate metformin.

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