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Review

Repurposing Metformin for Cancer Treatment: A Great Challenge of a Promising Drug

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Abstract. *The safety windows and toxicity of clinically available known drugs allow drug repurposing to be a popular treatment strategy for several diseases, including cancers. Several common drugs, e.g., metformin, statin, and aspirin are on clinical trials for repurposing in oncology treatment. Most of repurposed drugs, however, cannot be used as single agents and some do not exert any clinically significant effects. The limitations and possible biases from observational studies and preclinical models to repurpose these drugs are debatable. In this article, the limitations and probability of using metformin, one of the most repurposed drugs for cancer treatment and in oncological practice, are discussed.*

During the past decade, drug repurposing has become a popular treatment strategy in several diseases, including cancer (1). An implication of a known drug targeting a new disease helps shortcut the time and budget in drug investigation. The safety window and toxicity of clinically available medications allows drug investigators to bypass a phase I clinical trial in most cases (1). In oncology research, many common drugs are proposed for their repurposed effects, *e.g.*, metformin, statin, and aspirin (2). Observational studies reported satisfactory outcomes of patients with various cancers who used these drugs for their concurrent diseases compared to those not using these drugs. The promising results from observational studies prompt researchers to investigate and confirm the efficiency of the drugs in preclinical studies which may later translate to a clinical trial for the repurposing aims.

Theoretically, drug repurposing is an efficient method to shortcut drug development; an estimation of only 3.4% of investigated drugs can be considered successful for repurposing in oncology (3). In addition, most repurposed drugs cannot be used as single agents and, in the worst case, they do not exert any clinically significant effects. Therefore, the limitations and possible biases from observational studies and preclinical models convincing researchers to repurpose the drugs are debatable (4). In this article, the limitations and probability of using metformin, one of the most repurposed drugs for cancer treatment, in oncological practice is discussed.

Metformin: An Old Drug With a New Potential

Metformin (*N, N*-dimethylbiguanide) belongs to the biguanide antidiabetic medication. It has been suggested as a first-line medication for type 2 diabetes mellitus (DM) by the American Diabetes Association and is suggested by the clinical practice guidelines worldwide (5). The primary actions of metformin are activation of 5'-AMP-activated protein kinase (AMPK), by increasing the ratio of AMP/ATP resulting from the inhibition of the mitochondrial complex I (6). The activated AMPK, in turn, inhibits gluconeogenesis of hepatocytes providing euglycemic status. AMPK is a multifunctional protein kinase capable of interacting with multiple signaling pathways. The AMPK-modulated pathways are phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt), mammalian target of

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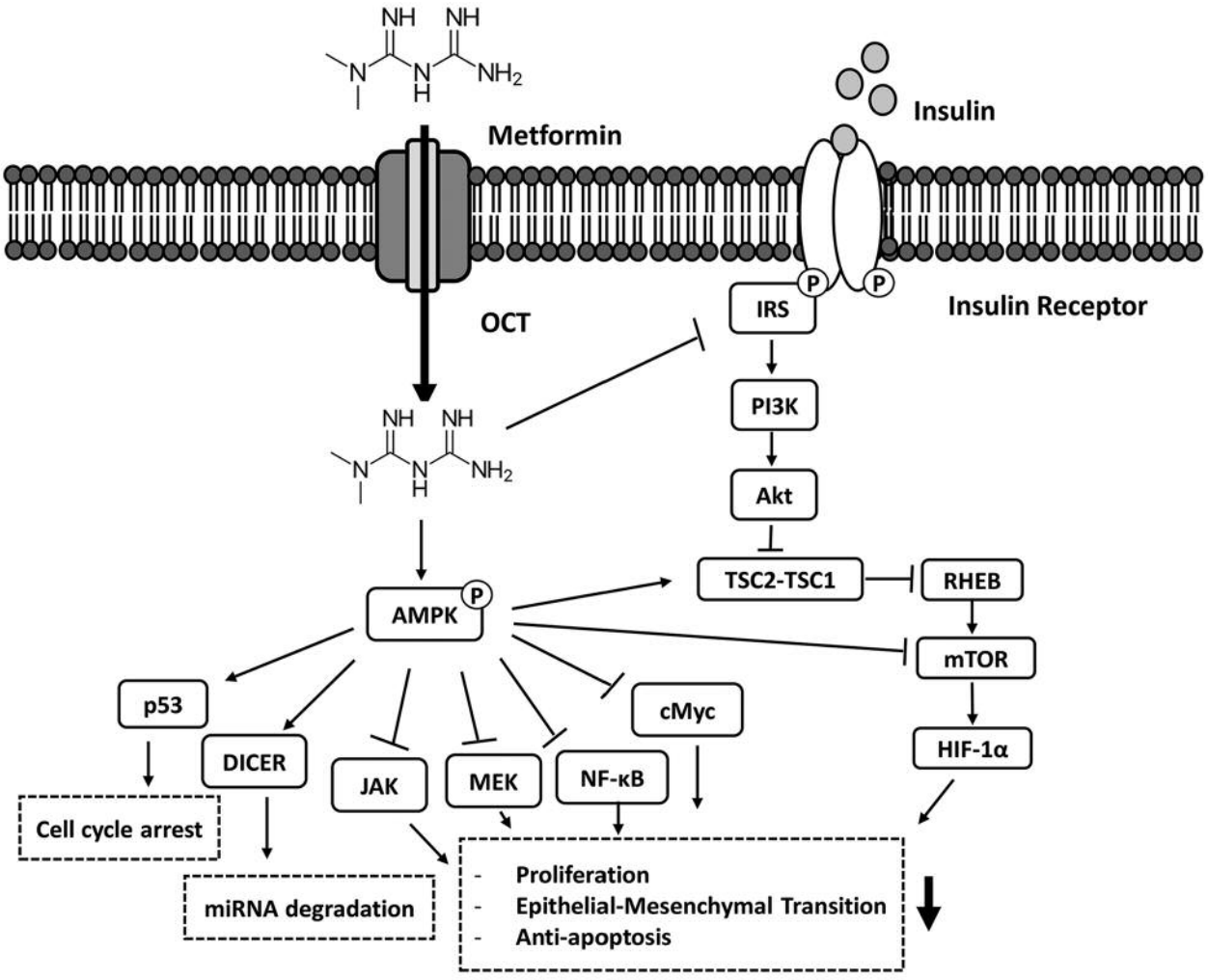

Figure 1. *Mechanisms of action of metformin at the cellular level. Metformin requires a transporter protein: e.g., organic cation transporter (OCT), for intracellular uptake. Metformin increases AMP/ATP ratio in cells which in turn activates AMP-activated protein kinase (AMPK). AMPK, thus, interacts with other signaling pathways and molecules; namely insulin receptor substrate (IRS)/phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt), mammalian target of rapamycin (mTOR), Janus kinase/signal transducer and activator of transcription (JAK/STAT), nuclear factor-κB (NF-κB), MAPK/ERK kinase (MEK), cMyc, and p53. The interactions with these pathways result in inhibition of the progressive phenotypes of cancer cells in many cancer types. TSC: Tuberouse sclerosis protein complex, HIF-1α: hypoxia-inducible factor-1alpha.*

rapamycin (mTOR), mitogen-activated protein kinase (MAPK), Janus kinase/signal transducer and activator of transcription (JAK/STAT), and nuclear factor-κB (NF-κB) (7), (Figure 1). Some of these pathways participate in insulin resistance; an etiology of type 2 DM, thus metformin is also recognized as an insulin sensitizer. As mentioned, pathways and insulin receptors share a common function in cancer progression, thus, the inhibitory effect of metformin *via* activated AMPK suggests the repurposing of metformin as a potential therapeutic agent in cancer. By controlling the pro-carcinogenic pathways, metformin becomes a popular candidate in cancer research including carcinoma, sarcoma, and hematologic malignancy (8).

Chemopreventive and Synergistic Effects of Metformin With Standard Chemotherapy Has Been Observed in Epidemiological Studies

The benefit of metformin for a reduced risk of carcinogenesis is observed in several cancer types, although a null effect is also reported. In addition, the benefit of using metformin on chemoprevention over other antidiabetic medications has been suggested (9). Apart from an association with a reduced risk, patients with cancer who have had metformin for their DM treatment also have a better prognosis. Examples can be found in patients with malignancy of the breast (10) and pancreas (11). In fact, an observational study has several limitations

Table I. *Randomized controlled trial of metformin effect on survival of cancer patients.*

Cancer type and subtype	Region of study	Number of participants	Primary end point	Hazard ratio metformin *vs.* control (95% Confidence interval)	Ref
Non-small cell lung carcinoma (advanced stage, non-squamous cell subtype)	USA	- 17 for carboplatin+paclitaxel+ Bevacizumab - 18 for carboplatin+paclitaxel+ Bevacizumab+metformin	- PFS at 1 year	-NA (early terminated due to the change of standard regimen for non-small cell lung cancer)	Marrone *et al*., 2018 (15)
Lung cancer (stage IIIB-IV lung adenocarcinoma with EGFR mutation)	Mexico	- 70 for EFGR-tyrosine kinase inhibitor -69 for EGFR-tyrosine kinase inhibitor+metformin	- PFS	0.60 (0.40-0.94, p=0.03)	Arietta *et al*., 2019 (17)
Breast cancer (advanced or metastatic, post-menopausal women)	China	- 30 for aromatase inhibitor+Placebo - 30 for aromatase inhibitor+metformin	- PFS	1.20 (0.7-2.1, p=0.48)	Zhao *et al*., 2017 (21)
Pancreatic cancer (advanced stage)	Netherlands	- 61 for gemcitabine+ erlotinib+Placebo - 60 for gemcitabine+ erlotinib+Metformin	- OS at 6 months	1.1 (0.7-1.6, p=0.78)	Kordes *et al*., 2015 (22)
Pancreatic cancer (metastatic)	Italy	- 31 for cisplatin+epirubicin+ capecitabine+gemcitabine (PEXG) - 29 for PEXG+metformin	- PFS at 6 months	0.73 (0.4-1.2, p=0.23)	Reni *et al*., 2016 (23)
Ovarian cancer (epithelial subtype)	China	- 24 for paclitaxel+ carboplatin - 20 for paclitaxel+ carboplatin+metformin	-PFS -OS	- ND	Zheng *et al*., 2019 (25)

EGFR: Epidermal growth factor receptor; PFS: progression-free survival; OS: overall survival; ND: not determined; NA: not applicable.

regarding the nature of the study design. Moreover, avoiding confounding factors, an immortal time bias, and a selection bias, are often limited. Cautionary interpretation of a causative effect of metformin on the improved prognoses and survival of patients with cancer remains. DM is an established risk for many types of cancer. Diabetogenic conditions; hyperglycemia and hyperinsulinemia, are involved in cancer progression (12). The benefit of metformin, hence, might be a result of both systemic effect on modification of diabetogenic factors as well as a direct effect on cancer cells (7). The application of metformin in cancer patients without DM is still controversial and requires further investigation.

Are *In Vitro* and *In Vivo* Effects of Metformin Clinically Translatable?

Many preclinical studies, both *in vitro* and *in vivo*, have been carried out to prove a direct effect of metformin on cancer cells. Metformin affects a broad spectrum of phenotypes of cancer cells. The inhibitory effects of metformin on cancer cell proliferation, metastasis, and induction of cell-cycle arrest, apoptosis and anoikis have been reported (7). Metformin also sensitizes cancer cells to other therapeutic modalities, such as chemotherapeutic drugs, immunotherapy, and radiotherapy. Metformin affects target cells depending on several factors, *e.g.*, a metformin transporter. As hepatocytes predominantly express organic cation transporter 1 (OCT1), a key transporter protein for metformin (6), therefore, metformin exerts a potent effect on hepatocellular carcinoma cells both *in vitro* and *in vivo*. An effective dose of metformin for cancer treatment in experimental models is, however, substantially higher (at a scale of mM) than the therapeutic dose for DM treatment in clinical practice. The inhibitory effects of metformin on cancer cells *in vitro* require approximately 10-fold of the practical dosage used for diabetic patients who have intact renal function (13).

Thereby, the effectiveness of metformin in clinical oncology practice remains questionable. The organs with a high promise for the clinical efficiency are those with highly expressed metformin transporters, *e.g.*, intestine and liver (14). The concentration of metformin in liver is substantially higher than in a portal vein of the experimental animals which is clinically

relevant in human. Whether the preclinical model is translatable to clinical use needs to be elucidated whereas ongoing clinical trials are the keys to address this critical question.

Clinical Trials of Metformin in Cancer Are Underway, But Some Have Failed

Observational, as well as experimental studies show satisfactory effects of repurposed metformin on several cancer types and may lead many drug investigators to carry out a clinical trial. Presently, 363 clinical trials have been registered (https://clinicaltrials.gov/, as of January 24, 2021). The reports from registered clinical trials are gradually launched while some of them have been terminated. A major cause of termination is that metformin did not show any additional benefit to standard treatment regimens whereas some studies were terminated due to changing of recommended regimen during recruitment (15). Noteworthy, few randomized controlled trials have been performed while the effect of metformin in both randomized controlled trials and non-randomized trials show a modest improvement of clinical outcomes. Furthermore, only subgroup of patients, namely those who had DM or metabolic syndromes (16) or those with a specific mutation of oncogenes seemed to benefit (17). A benefit of combined metformin with epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) was demonstrated in EGFR-mutated lung adenocarcinoma compared with EGFR-TKIs alone. Both progression-free survival and overall survival were significantly prolonged in patients receiving metformin as an add-on therapy. However, this official report is derived from a phase II clinical trial which lacks a double blinded analysis (17). Table I summarizes the available official reports from randomized controlled trials on the effect of add-on metformin to standard treatment in various cancers. The study of metformin as an add-on therapy in patients with non-small cell lung cancer who received carboplatin, paclitaxel, and bevacizumab as a standard treatment indicated that patients in a group receiving metformin showed a greater proportion to reach one year progression-free survival (47 *vs*. 15%). The median overall survival between groups, however, were not significantly different (15, 18). The benefit of metformin was also shown in human epidermal growth factor receptor 2 (HER2)-positive breast cancer (19). Of 8,381 patients enrolled with 5.3% diabetic, patients without metformin had shorter disease-free and overall survival than those receiving metformin. The non-metformin group in this study, nevertheless, used more exogenous insulin for DM treatment implying there might be other co-morbidities in which metformin usage is limited (19). Moreover, insulin has been shown for its mitogenic effects on breast cancer cells (20). Altogether, these factors were likely confounding the results of the study. As per the searches for the official publication of clinical trials of metformin, the results in other cancers, namely hormone receptor positive advanced breast cancer (21), advanced pancreatic cancer (22, 23), advanced non-small cell lung cancer (24), and epithelial ovarian cancer (25), did not show any benefit of add-on metformin over the standard chemotherapy. From the clinical trials that failed to show the benefit of metformin on the survival of patients, metformin, however, shows the indirect effect that may modulate the progression of cancer, *e.g*., modulating insulin-like growth factor signaling pathway in ovarian cancer (25).

Concluding Remarks: Is Metformin Still Worth Further Investigation?

Observational and preclinical studies in almost all cancers reported the promising effects of repurposing metformin for cancer treatment. Many clinical trials, however, failed to demonstrate the benefit of add-on metformin over standard chemotherapy. The possible causes of failure at clinical trial steps are: 1) metformin concentrations used in preclinical studies were substantially higher than the clinical plasma concentrations in some tissues. Thus, the effectiveness of metformin on each cancer is likely dependent on the expression of its transporters; 2) the natural limitation of an observational study with a potential bias might mislead drug investigators to study metformin in a clinical trial; and 3) from available results of clinical trials, most recruited patients were at an advanced stage and the number of patients in those trials are limited. It remains totally inconclusive at the present time whether metformin is worth further investigation since many clinical trials are underway and the results are not yet available. However, it is noticeable that cancer patients with DM are the most likely to benefit from metformin over the other antidiabetic medications.

Conclusion

In summary, epidemiological and preclinical studies suggest metformin to be a high potential repurposing drug for treatment of many cancers. Nonetheless, only a few randomized controlled trials report a benefit of add-on metformin to a standard therapy. In the next few years when more results from clinical trials are available, a right decision for the ultimate goal of repurposing metformin in cancer treatment would be made.

Conflicts of Interest

All Authors declare that they have no conflicts of interest.

Authors' Contributions

CS and SW contributed to conceptualization. Literature search, writing first draft manuscript, and illustration were done by CS.

TS and SW critically reviewed, commented, and revised manuscript. All Authors contributed to review and approved the final manuscript.

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