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Metformin: exploring its potential as an anticancer drug

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Abstract. Metformin is a commonly used hypoglycemic agent that has received much attention in recent years for its potential in cancer therapy. This paper reviews and concludes the anti-cancer mechanisms of metformin and its clinical applications in different cancer types. It was found that metformin indirectly inhibits cancer cell growth by activating AMPK and inhibiting the mTOR pathway and decreasing insulin and IGF-1 levels. In addition, metformin directly inhibits cancer cell proliferation by inducing apoptosis and autophagy. Clinical data suggest that metformin significantly improves survival and reduces cancer recurrence in patients with gastric, renal, endometrial and esophageal cancers. However, despite the preliminary evidence provided by existing studies, discrepancies remain between the results of different studies, and further large-scale randomized controlled trials are needed to validate its anticancer effects and optimize application strategies. Future studies should focus on clarifying the specific mechanism of action of metformin and its potential application prospect in individualized therapy.

Keywords: Metformin, Anticancer mechanism, Clinical application, Survival, AMPK, mTOR.

1. Introduction

Metformin is a common antidiabetic drug, and in recent years, the repurposing of metformin for oncology treatment has attracted significant interest. Metformin is known for its favorable safety profile and low price, and its potential anticancer properties have been demonstrated through various mechanisms, including inhibition of hepatic gluconeogenesis and activation of the adenosine monophosphate-activated protein kinase (AMPK) pathway [1]. Its role in reducing cancer incidence and improving survival outcomes has been observed in different cancer types, including ovarian, prostate, and hepatocellular carcinomas.

Several observational studies and clinical trials have explored the efficacy of metformin as an adjuvant cancer therapy. For example, a study analyzing the effects of metformin on hepatocellular carcinoma (HCC) found that the use of metformin significantly reduced all-cause mortality and cancer-specific mortality [1]. Similarly, a study of diabetic patients with ovarian cancer showed a higher survival rate in patients using metformin compared to those not using metformin [2]. The study also found that the use of metformin was associated with a higher survival rate in diabetics. Metformin is a potential cancer preventive drug, but the mechanism of action of metformin in cancer remains incompletely understood due to different molecular mechanisms of action and pathways of action. The aim of this paper is to analyze the available evidence on metformin in cancer therapy, highlighting its

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mode of action, clinical outcomes, and potential as an adjuvant therapy. However, this paper will also present the shortcomings and barriers in the current research, as well as possible future directions.

2. Mechanism of Action of Metformin

The anti-tumor properties of metformin are multifaceted and include interactions between the molecule and the environment. The limiting steps of metformin activity include activation of AMPK (adenosine monophosphate-activated protein kinase), which affects the function of the mTOR pathway - a signaling cascade necessary for cell growth and proliferation [3]. In addition, metformin causes a decrease in insulin and IGF levels, which also play a crucial role in the development and spread of cancer. Together, these effects combine to produce an inhibitory effect on cell reproduction, increase cell death rates, and ultimately inhibit cancer growth.

Metformin also impacts metabolic processes by playing an essential role. Through the glucose and insulin synthesis inhibition, metformin leads to the lowering of systemic levels of both, which leads to hyperinsulinemia and hyperglycemia, two major factors for cancer progression commonly seen [4]. The interaction of metformin with the metabolism of cancer cells has been found to be a powerful promoter of cancer development.

The direct effects of metformin on cancer cells primarily involve inhibition of the mTOR pathway and activation of AMPK. inhibition of mTOR leads to a decrease in protein synthesis and cell proliferation, which directly affects cancer cell growth. This mechanism has been observed in a variety of cancers including esophageal cancer and prostate cancer [5-6]. Metformin also induces apoptosis in cancer cells, resulting in anti-tumor effects.

Another important mechanism is the role of metformin in regulating metabolic processes. By inhibiting mitochondrial complex I, metformin reduces ATP production and increases the AMP/ATP ratio, thereby activating AMPK. This activation reduces protein synthesis and cell proliferation [7]. In addition, metformin lowers systemic blood glucose and insulin levels, thereby alleviating hyperinsulinemia and hyperglycemia, which are often associated with cancer progression. Lowering insulin and IGF levels is especially important in cancers affected by these hormones, such as prostate cancer [6].

3. Clinical Evidence

Clinical studies have demonstrated the potential benefits of metformin in cancer treatment. For example, a study of high-risk prostate cancer patients showed that metformin use was associated with improved survival [8]. Similarly, a study of esophageal cancer showed that metformin use was associated with a reduction in all-cause mortality in patients with diabetes [5]. Another study showed that metformin reduced the risk of complications in patients with abdominal aortic aneurysms. These findings support the hypothesis that the metabolic and direct cellular effects of metformin contribute to its anticancer properties.

A study investigating the effects of metformin on gastric cancer suggests that metformin use is associated with improved survival outcomes. This retrospective study found that gastric cancer patients treated with metformin had a lower risk of death compared to those who did not use metformin [9]. This suggests that metformin has a potentially beneficial role in the treatment of gastric cancer. Besides, a study on the effects of metformin in patients with kidney cancer provides valuable information to understand the potential benefits of metformin. The study highlighted several important findings.

First, the use of metformin in kidney cancer patients significantly reduced progression. This effect was particularly pronounced in patients who had been taking metformin for a long time. The mechanism is thought to be inhibition of mTOR signaling, which is critical for cancer cell growth and proliferation [10].

Second, overall survival was improved in those who used metformin compared to those who did not. Studies have reported that metformin's ability to lower blood glucose levels and improve insulin sensitivity may be a factor in reducing cancer-related mortality. This metabolic effect coupled with direct antitumor activity highlights the dual efficacy of metformin [10].

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Last, the study also explored the effects of combining metformin with other therapies such as tyrosine kinase inhibitors (TKIs). It found that patients treated with both metformin and TKIs had better outcomes than those treated with TKIs alone. This suggests that metformin may enhance the efficacy of existing kidney cancer therapies, providing a synergistic effect [10].

A retrospective study focusing on endometrial cancer showed that metformin improves overall survival in overweight diabetic patients. The study found several important outcomes. Metformin use was associated with prolonged overall survival in patients with endometrial cancer. This benefit was particularly evident in overweight diabetic patients, highlighting the drug's potential to improve cancer prognosis by modulating metabolism [11]. Besides, studies have found that metformin users have lower rates of endometrial cancer recurrence. This suggests that metformin not only helps to control diabetes but may also be protective against cancer recurrence through its effects on insulin and IGF levels [11].

Similar to renal cancer, the benefits of metformin were more pronounced in specific patient subgroups, particularly those with higher body mass index (BMI) and insulin resistance. This highlights the importance of stratifying patients to maximize the efficacy of metformin in cancer treatment.

These studies suggest that taking metformin is associated with a reduction in cancer-related mortality. In another meta-analysis covering a variety of cancer types, metformin was shown to significantly reduce the risk of death in cancer patients. These combined analyses support the hypothesis that metformin has a broad-spectrum anticancer effect [12].

4. Discussion

4.1. Overview of metformin's anticancer effects

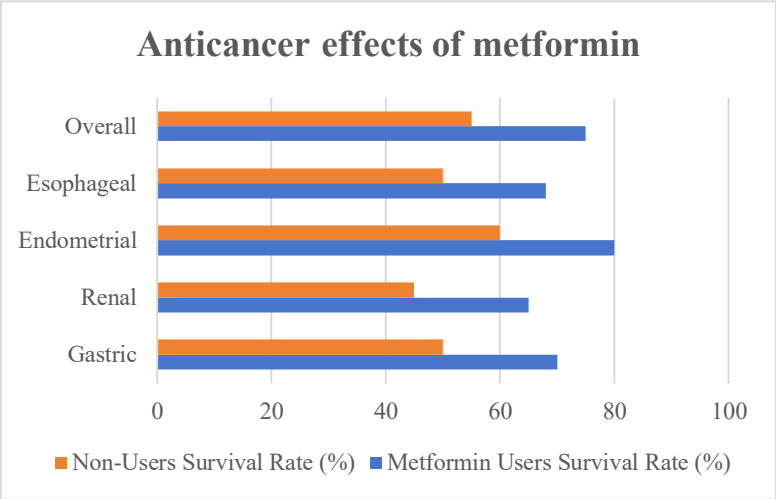

Figure 1. Effect of metformin on mortality from different cancers

This bar graph illustrates the survival rates of cancer patients using metformin compared to those not using metformin. The chart includes data for different types of cancer: stomach, kidney, endometrial, and esophageal, as well as overall survival rates for the different cancers.

The data shows that metformin users generally have higher survival rates than non-users across all cancer types. Specifically, patients with gastric cancer who used metformin had a 70% survival rate, compared to 50% for those who did not use metformin. Among kidney cancer patients, the survival rate for metformin users was 65%, significantly higher than the 45% for non-users. Endometrial cancer patients using metformin had a survival rate of 80% compared to 60% for non-users. For esophageal cancer, the survival rate was 68% for metformin users compared to 50% for non-users. The overall survival rate for cancer patients using metformin was 75%, compared to 55% for those not using metformin.

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These data suggest that metformin may help improve survival in cancer patients, supporting its potential role as an adjuvant therapy in oncology.

4.2. Mechanism analysis

It has been pointed out before that the regulatory pathways of metformin are mainly divided into two kinds:

Regulation of insulin and IGF-1 levels: metformin indirectly inhibits the growth and division of cancer cells by reducing the levels of insulin and IGF-1. This mechanism is particularly effective in patients with diabetes combined with cancer.

AMPK activation and mTOR inhibition: Metformin activates AMPK, which in turn inhibits the mTOR pathway and blocks protein synthesis and cell growth in cancer cells. AMPK, as a sensor of intracellular energy status, is activated by metformin by sensing changes in the intracellular AMP/ATP ratio. Activated AMPK inhibits mTOR, a key cell growth and proliferation signaling pathway, which in turn inhibits cancer cell growth and proliferation.

Metformin induces apoptosis in cancer cells and reduces the survival of cancer cells. This effect has been observed in several cancer types. Metformin promotes the process of apoptosis by activating AMPK, inhibiting the mTOR signaling pathway, and affecting the expression of Bcl-2 family proteins. This effect not only limits the growth of cancer cells, but also makes them more sensitive to other treatments [13].

Metformin is also able to promote the autophagic process in cancer cells, removing damaged organelles and proteins and inhibiting tumor growth. Autophagy is a mechanism by which cells maintain cell survival by breaking down and recycling intracellular components under stressful conditions such as a lack of nutrition. Metformin regulates the expression of autophagy-related genes and enhances the autophagy process by activating AMPK, thus limiting the growth and survival of cancer cells [14].

Overall, most studies have consistently found that metformin significantly improves survival and reduces recurrence rates in patients with a wide range of cancers. Several studies and meta-analyses have shown that metformin users have significantly higher survival rates than non-users in several cancer types, such as gastric, renal, endometrial, and esophageal cancers.

The inconsistent performance of metformin's effects in certain studies may be related to factors such as the patient's specific medical condition, dosage of the drug, and duration of treatment. For example, some studies have found metformin to be less effective in prostate and lung cancers, possibly due to differences in the specific biology of these cancer types and the metabolic status of the patients.

5. Prospects and Challenges for Clinical Applications

Metformin, as a drug commonly used in diabetes treatment, has been widely validated for its safety and tolerability. The long-term effects of its use in cancer patients still need to be further investigated, but preliminary data show that metformin has a good safety and tolerability profile in cancer treatment with fewer side effects [6].

In exploring the potential of metformin for different cancer types and different treatment stages, current studies have focused on gastric, renal, endometrial, and esophageal cancer types, but the potential application of metformin to other cancers deserves further exploration.

For future research directions, large-scale randomized controlled trials appear to be necessary to verify the anticancer effects and mechanisms of metformin. Although some of the existing studies provide some preliminary evidence, large-scale randomized controlled trials can more accurately assess the clinical benefits of metformin and provide more reliable dosing guidance.

And the study of metformin biomarkers in different cancer types is also an important direction, for the screening of different biomarkers can optimize the individualized treatment regimen for patients. For example, studying the relationship between specific genetic mutations or metabolic profiles and metformin efficacy could help identify patient groups most likely to benefit.

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The challenge will also be to stratify the management of patients, who should be individualized and screened for metformin treatment strategies based on their metabolic status, genetic background, and disease characteristics. Metformin can only show better therapeutic effects when selected for patients with metabolic syndrome or those with specific genetic mutations. Optimizing the use of metformin through a precision medicine approach maximizes therapeutic efficacy and safety.

6. Conclusions

In summary, metformin not only excels in diabetes management, but also shows broad anti-cancer potential. Multiple studies have consistently shown that metformin is able to modulate metabolism and cell proliferation, thereby improving survival in patients with a wide range of cancers. In patients with gastric, renal, endometrial and esophageal cancers, metformin users had significantly higher survival rates than non-users. In addition, the combination of metformin with other anticancer drugs has shown synergistic effects. However, despite the preliminary evidence provided by existing studies, the specific mechanism of metformin in cancer treatment has not been fully clarified, and the results of different studies are somewhat variable. More large-scale randomized controlled trials are needed to further validate its clinical benefits and explore the best application strategies. Studying the biomarkers of metformin in different cancer types will also help to individualize the treatment regimen to maximize treatment efficacy and safety.

Overall, metformin has great potential in cancer treatment, but its wide application still requires more in-depth studies and clinical validation. Future studies should focus on optimizing the treatment regimen, clarifying the mechanism of action and identifying the most suitable patient groups to fully utilize the anticancer effects of metformin.

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