Khansari N, Int J Case Rep Ther Stud 2021, 3: 016
DOI: 10.24966/CRTS-310X/100016

HSOA International Journal of Case Reports and Therapeutic Studies

Mini Review

Metformin and Cancer

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Abstract

Metformin is a widely used to treat type 2 diabetes (T2DM) as well as polycystic ovary syndrome. It is a derivative of biguanide (1,1-dimethy biguanide hydrochloride) that has been used for over a century. Metformin is the first choice to treat T2DM due to its ability to decrease plasma glucose level. However, over time, different uses of metformin have been discovered. Today, various benefits of metformin for cancers, obesity, liver diseases, cardiovascular diseases, renal diseases, and even aging have been verified. This low cost, low side effect drug, may exerts its beneficial effects through deferent signaling pathways and/or mechanisms for divers' diseases. Since, the underlying mechanisms of the action of metformin in different diseases are still unclear, this mini review is committed to provide a brief summary of benefits, and mechanistic action of metformin in cancer suppression and prevention.

Keywords: Metformin; Cancer; mTOR; AMPK; Treg; T8+, CD25; CD4

Introduction

Metformin is one of the most commonly used drugs to treat type 2 diabetes [1]. In recent years, many additional unexpected but effective role of metformin were found. Studies showed that that metformin exerts a strong effect on numerous cancers [2], cardiovascular disease [3], liver diseases [4], renal diseases [5], neurogenerative diseases [6], and obesity [7]. Mechanism of action of metformin is trough inhibition mitochondrial complex I [8], which leads to AMPK activation. Mitochondrial complex I is vital to electron transport [9]. As a result, the production of Adenosine Triphosphate (ATP) decreases and the intracellular concentration of Adenosine Diphosphate (ADP) increases which leads to increase of cellular levels of Adenosine Monophosphate (AMP) and consequent activation of AMPK [10].

A large number of epidemiological studies have suggested that metformin may prevent or even suppress cancer development. In vitro and in vivo studies have confirmed that metformin may inhibit the proliferation of a variety of tumor cells but the mechanism underlying this has not yet been fully elucidated [11]. However, at the present, two pathways are postulated as the major ways in which metformin may exerts its anti-tumor effect. The first pathway, the I/IGF (insulin and insulin-like growth factor) pathway, may reduce the level of I/IGF-1 in the blood circulation, there by inactivating its downstream mTOR signaling pathway to inhibit tumor cells proliferation. The second pathway, the AMPK signaling pathway may facilitate metformin to directly act on tumor cells, upregulate AMPK and inhibit downstream mTOR [12].

It should be noted that I/IGF promote cell mitosis, stimulate cell growth and inhibit cell apoptosis, all of which are important functions in tumor genesis and development [13]. It has been shown that glycogenesis in the liver is reduced indicating that metformin may effectively reduce blood insulin level by increasing the sensitivity of surrounding tissue to insulin and inhibiting the intestinal cells from absorbing glucose [14]. This suggests that metformin may reduce blood insulin levels and cause inactivation of I/IGF signaling pathway to exert its anti-tumor effect [15]. In addition, other studies demonstrated that, in breast cancer patients without overt diabetes, the use of metformin may significantly decrease insulin levels and improve insulin resistance [16]. Another study showed that when mice were exposed to the tobacco carcinogen [(4-metylnitrosamino0-1-(3-pridyl)-1-butanon], the use of metformin reduced lung tumor burden by up to 53% [17]. This mechanistic study revealed that metformin may directly inhibit mTOR by activating AMPK in liver tissue and may indirectly inhibit mTOR by decreasing activation of insulin receptor/IGF-1 in lung tissue. Karrnevi et.al. [18] demonstrated that metformin may inhibit IGF-I receptor and activate AMPK in pancreatic cancer cells. Other studies observed that the proliferation cells in leukemia, lymphoma, prostate, ovarian, colon, endometrial and liver cancer was inhibited by metformin through the AMPK/mTOR pathway [19,20].

Metformin also can exert anti-tumor effect in an AMPK-independent mechanism. Ben Sahra et al. [21] reported that metformin may inhibit the cell proliferation and induce the cell-cycle arrest of prostate cancer cell lines by increasing regulation in development and DNA damage response I expression in a p53-dependent manner in the absence of AMPK. Kalender et.al. [22] demonstrated that metformin may inhibit mTORC1 in a rag GTPase-dependent manner in the absence of AMPK. Another study has also revealed that metformin may induce apoptosis and cell-cycle arrest of melanoma cells [23] in an AMPK-independent manner. Taken together, these studies demonstrated that metformin exert an anti-proliferation function through wide range of mechanisms.

Clinical Evidences of Metformin Effect on Cancer

Biguanides had been used in oncology four decades ago as a metabolic rehabilitation in breast, colorectal and gastric cancers patients [24]. The therapies with biguanides plus caloric restriction resulted in diminishing development and lower incident of tumor metastases [25]. Several studies assessed the effect of metformin on metabolic

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Citation: Khansari N (2021) Metformin and Cancer. Int J Case Rep Ther Stud 3: 016.

Received: December 14, 2021; **Accepted:** December 23, 2021; **Published:** December 30, 2021

status in cancer patients with and without diabetes. Ut was shown that in nondiabetic patients with early stages of breast cancers, metformin reduced fasting insulin by 22% and improved several metabolic indices [26]. Campagnoli *et.al.* in his studies, showed that routine doses of metformin used for treatment of diabetes patients, decreases testosterone and insulin levels as well as several parameters of insulin resistance situation [27]. In another study in nondiabetic with breast cancer patients, the metformin therapy resulted not only reduction of number of Ki67-positive cancer cells but also changed gene expression of molecules involved in the mTOR and AMPK pathways [28]. Hosono et al. observed that in comparison to the control group, in nondiabetic patients, small doses of metformin (250 mg/day) reduced colorectal aberrant cryptic foci (which considered as surrogate marker for colorectal cancer) by 40% [29]. Jiralerspong et al. in a study with 2,529 breast cancer patients, noticed treatment of patients with metformin in with or without diabetes, increased incidence of complete response rates [30]. However, despite of the increased incidence of complete response rates, metformin did not significantly improved survival rate of the patients. Margel et al. assessed the relation between duration of metformin therapy after prostate cancer diagnosis and mortality of patients with diabetes [31]. The data from 3,837 patients suggested that the longer duration of metformin therapy after diagnosis of prostate cancer was associated with significant decrease of not only the risk of cancer specific but also in all cause of mortality.

Metformin has been also used as adjuvant therapy in cancer patients, and in the most of the cancer clinical trials of metformin, the same typical doses that is used to treat diabetes, used for cancer patients [32].

Most of the researches up to now have been done to investigate effect of metformin in caner prevention and suppression and the molecular mechanism of anti-tumor effect of metformin. However, from decades ago we know that immune surveillance is responsible for removal of any malignant cell in the body, but this effect of metformin has not been elucidated yet. In order to address this issue, this research project has been proposed to study involvement of $CD8^+$ T cells which have effector role to destroy malignant cells and $CD4^+$, $CD25^+$ T cells which suppressor T cell (Treg). in mice bearing colorectal cancer treated with metformin as a model for human use of metformin.

Conclusion

The aim of this study is to investigate whether immunological mechanism of metformin anti-tumor function exist or not. The focus of this study would be on the increase or decrease in the number of cytotoxic and regulatory T cells in tumor bearing mice. The hypothesis is that the number of Treg cells ($CD4^+$, $CD25^+$) would be decreased while Cytotoxic T cells ($CD8^+$) would be increased. If results demonstrate a non-null hypothesis then it suggests that using metformin would be a beneficial drug to be used for treatment and/or prevention of cancer.

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