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Review article

A review for clinicians: Prostate cancer and the antineoplastic properties of metformin

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Abstract

Objectives: Metformin has numerous antineoplastic effects including an AMP-activated protein kinase–dependent mechanism, AMP-activated protein kinase–independent mechanisms, alteration of insulin and insulin-like growth factor signaling pathways, and suppression of androgen signaling pathways that trigger prostate cancer growth and proliferation. In contrast to other malignancies that are associated with increased incidence among patients with obesity and type II diabetes mellitus (T2DM), epidemiological studies suggest that obesity and T2DM may impart a protective effect on prostate cancer incidence by creating a set of metabolic conditions that lower androgen levels.

Methods and materials: The PubMed and Web of Science databases were searched using the terms "prostate cancer," "metformin," "antineoplastic," "antitumorigenic," and "diabetes" up to the first week of August 2016. Articles regarding metformin's antineoplastic properties on prostate cancer were reviewed.

Results: Treating T2DM with metformin may reverse the metabolic conditions that suppress androgen levels, thereby enabling higher levels of androgens to stimulate prostate growth, proliferation, and tumorigenesis. Thus, the antineoplastic properties of metformin may not be appreciable in the early stages of prostate cancer development because metformin corrects for the metabolic conditions of T2DM that impart a protective effect on prostate cancer. These findings, although inconclusive, do not support the use of metformin as a preventive agent for prostate cancer. However, the future appears bright for metformin as either a monotherapy or an adjunct to androgen deprivation therapy, external-beam radiation therapy, prostatectomy, or chemotherapy. Support for this includes meta-analyses that suggest a mortality benefit to patients with prostate cancer on metformin, a clinical trial that demonstrates metformin leads to significant improvement in metabolic syndrome parameters for patients with prostate cancer on androgen deprivation therapy, and a clinical trial that shows metformin has modest activity in the treatment of some patients with asymptomatic or minimally symptomatic metastatic castration–resistant prostate cancer.

Conclusions: This review summarizes the literature regarding the antineoplastic mechanisms, clinical implications, and future trajectory of clinical research for metformin in prostate cancer.

Keywords: Prostate cancer; Metformin; Antineoplastic; Diabetes mellitus

1. Introduction

Metformin reduces hepatic glucose production, increases insulin sensitivity, and increases glucose use by peripheral tissues. The decrease in blood glucose levels by metformin is only observed in patients with type II diabetes mellitus (T2DM) and has no effect on euglycemic individuals unless subjected to prolong fasting [1]. Moreover, metformin has well-known therapeutic benefits for nondiabetic indications. Metformin is used in polycystic ovarian syndrome to manage metabolic disturbances related to insulin resistance, thereby providing beneficial effects on subfertility, hyperlipidemia, and hypertension [2]. Metformin is also used to treat weight gain induced by antipsychotic medications [3], management of the metabolic syndrome [4], and prevention of T2DM in high-risk population groups [5]. Emerging evidence suggests that metformin may be useful in the

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prevention and treatment of cancer. Metformin is being tested in conjunction with anticancer agents in nondiabetic patients and is coadministered virtually with all anticancer agents in patients with diabetic cancer [6].

2. Metformin's antineoplastic mechanisms

2.1. Metformin's AMP-activated protein kinase–dependent mechanism

Metformin inhibits transcription of gluconeogenesis genes in the liver and stimulates peripheral uptake of glucose, resulting in insulin sensitization, and reduction of hyperglycemia and hyperinsulinemia. This occurs because metformin is an activator of AMP-activated protein kinase (AMPK), a serine/threonine protein kinase that regulates cellular energy metabolism. AMPK may play a role in the relationship between metabolism and cancer, as suppression has been linked to proaging and tumor growth pathways. Activation of AMPK stimulates ATP-generating pathways such as glycolysis and fatty acid oxidation and inhibits ATP-consuming pathways such as fatty acid and protein synthesis [7]. Metformin activates AMPK by inhibiting complex I of the mitochondrial electron transport chains, which mimics cellular stress [8]. Cellular stress leads to an increase in the ratio of AMP/ATP causing liver kinase B1 (LKB1)–mediated AMPK activation. The activation of AMPK by tumor suppressor gene LKB1 results in decreased mammalian target of rapamycin (mTOR) activation, resulting in growth inhibition via cell cycle arrest and cell growth inhibition [9]. mTOR is a serine/threonine kinase and downstream effector of the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway—a signaling pathway associated with cancer cell growth and cancer pathogenesis with roles in the regulation of cellular growth and proliferation [10]. In summary, the AMPK-dependent mechanism lowers blood glucose and insulin concentrations, inhibits gluconeogenesis, inhibits energy-consuming processes, and stimulates processes that generate ATP.

Metformin's antineoplastic activity occurs through the AMPK pathway, which inhibits mTOR signaling and results in inhibition of protein synthesis, fatty acid synthesis, and cell proliferation [11]. Cells derived from prostate, breast, and colon cancers constitutively overexpress fatty acid synthase, which is necessary for de novo fatty acid biosynthesis and malignant phenotype. Reduction in fatty acid synthase and acetyl-CoA carboxylase expression by AMPK activation diminishes the viability and growth of prostate cancer cells [12]. Prostate cancer is characterized by increased de novo fatty acid synthesis and cholesterol synthesis, which provide the building blocks for malignant transformation. Zadra et al. showed that direct activation of AMPK inhibits prostate cancer cell growth in androgen-sensitive and castration-resistant prostate cancer (CRPC) models by inducing mitotic arrest and apoptosis. In addition to mTOR blockade, Zadra et al. [13] also found that suppression of de novo lipogenesis is responsible for AMPK-mediated prostate cancer growth inhibition. Loubière et al. demonstrated that metformin inhibits lipogenesis in several prostate cancer cell lines primarily by a cellular energy deficit, that is, metformin decreases ATP in a dose-dependent manner, which correlated with the inhibition of lipogenesis [14]. These findings provide novel therapeutic targets for prostate cancer (Fig.).

2.2. Metformin's AMPK-independent mechanisms

Metformin-induced activation of AMPK was the first mechanism to explain how metformin inhibits hepatic gluconeogenesis and provides anticancer protection. Recent studies suggest that metformin may use AMPK-independent mechanisms to treat diabetes mellitus (DM) and activate

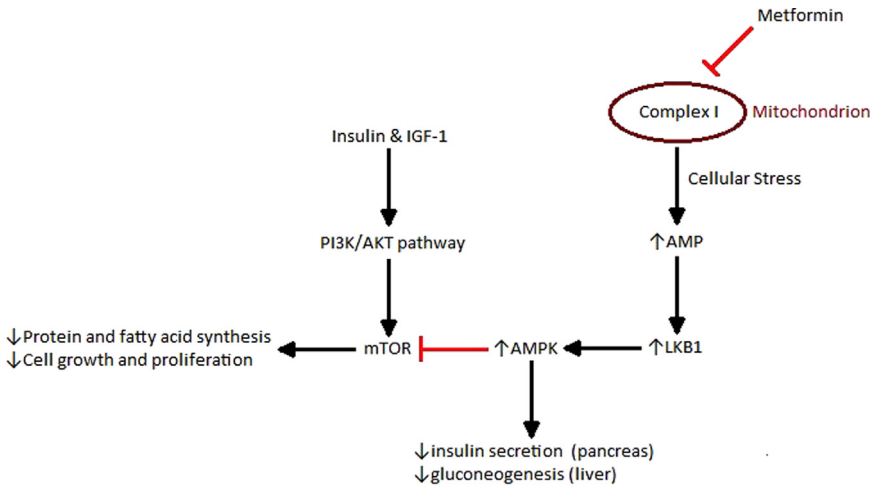

Fig. Diagram showing the proposed mechanism of metformin's AMPK-dependent pathway. Insulin and IGF-1 activate mTOR leading to increased protein and fatty acid synthesis and increased cell growth and proliferation, which could promote prostate cancer tumorigenesis. (Color version of figure is available online.)