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Review

Metformin: An anti-diabetic drug to fight cancer

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ABSTRACT

Since epidemiologic data have highlighted the positive effects of metformin to reduce cancer incidence and mortality, many *in vitro* and *in vivo* studies as well as a large number of clinical trials have been conducted in order to study its potential.

The many anticancer actions of metformin lead to a cytostatic effect. Two distinct but not exclusive mechanisms can be implicated in these actions. First, by decreasing insulinemia and glycaemia, metformin can block the PI3K/MAPK signalling pathway implicated in cell growth. Second, metformin can directly act on cancer cells by targeting various pathways including tumour metabolism, inflammation, angiogenesis or cancer stem cells, mainly through the activation of the AMPK pathway.

Nonetheless, although metformin alone displays chemopreventive properties, it does not seem to be sufficient to treat cancer, raising the need to be combined with other drugs (*e.g.* chemotherapy or glycolysis inhibitors) in order to synergistically reveal its cytotoxic action.

However, in particular conditions such as specific mutations (*e.g.* LKB, p53 or OCT1) or low glucose availability, metformin alone does have cytotoxic effects. Thus, it is essential to consider the associated biomarkers in order to determine the potential of metformin in different types of cancers.

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1. Introduction

Metformin, or 1,1-dimethylbiguanide, is derived from the alkaloid galegine or isoamylene guanidine, the active substance of *Galega officinalis,* also known as Goat's Rue, the French lilac or Italian Fitch [1].

It has been widely used in the treatment of Type 2 Diabetes Mellitus (T2DM) since its approval in 1958 in the United Kingdom and in 1995 in the United States [2], and is currently recommended as first-line therapy for all newly diagnosed T2DM patients (American Diabetes Association, 2014).

The extensive use of this drug with nearly 120 million prescriptions worldwide each year is due to its favourable benefit-risk profile [3]. Indeed, among the three biguanides developed for diabetes therapy (namely metformin, phenformin and buformin), only metformin has remained on the market after the withdrawal of the other two in the 1970s, due to their toxicity related to lactic acidosis [4,5]. The glucose-lowering effect induced by metformin is clinically associated with a superior safety profile related to less cardiac mortality and rare cases of lactic acidosis at therapeutic doses (less than three cases per 100.000 patients per year). Moreover, compared to other antidiabetic agents, metformin does not induce hypoglycaemia or weight gain [5].

As a result of its worldwide spread for over 50 years, some epidemiological, clinical and preclinical data concerning other potential indications of metformin have emerged, and it is also used today as a cardiovascular protective agent [6,7], an anti-inflammatory [8], a neuroprotective agent [9] or an anticancer agent [10].

According to recent data, these pleiotropic effects of metformin are linked to its action on mitochondria.

In fact, metformin accumulates in mitochondria *via* the interaction between the mitochondrial membrane potential and the positive charge of metformin [11]. After its entry, metformin inhibits the complex I of the mitochondrial electron transport chain, resulting in a decrease in cellular ATP concentration and an increase in both ADP/ATP and AMP/ATP ratios, which reflects a low energy level. This energy depletion is responsible for the activation of the 5′ adenosine monophosphate-activated protein kinase (AMPK), a major energy sensor involved in several processes within the cell in order to restore energy homeostasis [12].

AMPK is a heterotrimeric complex formed by three subunits: α, β and γ. The α-subunit is responsible for the catalytic activity whereas the β and γ subunits are linked to the regulation of the kinase activity [5,12]. In order to promote its kinase activity, AMPK must be phosphorylated on the residue Thr172 of the α-subunit by LKB1 (liver kinase b1), and to a lesser degree by CaMKK (Calcium/calmodulin-dependent protein kinase). However, this phosphorylation is finely modulated by allosteric modifications. When the cellular energy level is low, AMP/ADP levels increase and then bind to the AMPK γ-subunit, promoting the AMPK phosphorylation on Thr172 and leading to an increase of the kinase activity [13].

AMPK activation leads to an increase of catabolic reactions that produce energy such as β-oxidation, glycolysis or autophagy, and on the contrary to an inhibition of anabolic reactions that require energy (*e.g.* fatty acid, triglyceride, cholesterol and protein synthesis), thereby ensuring cellular energy balance and avoiding bioenergetic crisis and cell death [14,15].

Thus, due to the central role of AMPK as a regulator of multiple processes within the cell, its deregulation is associated with several pathological conditions, including diabetes and other metabolic diseases [16], cancers [17], neurodegeneration [18] and cardiac hypertrophy [19].

Epidemiological studies have demonstrated a correlation between T2DM and a higher incidence of malignancies, especially cancers of the liver, the pancreas, and endometrium with approximately a twofold increased risk as well as cancer of the colon, kidneys, bladder and breast with smaller associations (about 1.2–1.5 fold) [20–22].

Considering the worldwide population taking metformin daily at usual doses to treat T2DM (from 1500 mg to 2250 mg/day in adults), retrospective epidemiological studies have been launched in order to determine the effect of metformin on cancers [2].

Overall, in the T2DM population, metformin treatment is associated with decreased cancer risk in terms of incidence and mortality, compared to other antidiabetic agents [10].

According to Evans et al., cancer incidence decreases by around 50% (adjusted odds ratio of 0.56; 95% CI of 0.43–0.74) if the patients have been treated with metformin for more than four years [23].

Another meta-analysis has confirmed that cancer incidence in T2DM patients receiving metformin reduces by 30–50%, most significantly in pancreatic cancer, hepatocellular carcinoma, and colon cancer [24].

In addition to the decrease of cancer incidence, metformin intake was also associated with a lower mortality due to cancer.

A prospective observational trial that followed 1300 T2DM patients receiving metformin (289 patients) or another antidiabetic medication (1064 patients) for 9.6 years shows that metformin intake is associated with a decrease of cancer mortality in a dose-dependent manner, with an adjusted hazard ratio of 0.43 (95% CI 0.23–0.80) [25].

However, even if these studies are promising and support the concept that metformin possesses anticancer effects, there is still a lack of clinical evidence for metformin antitumour activity in non-diabetic patients.

This is why some clinical studies are currently being conducted to determine the anticancer actions of metformin in diabetic and non-diabetic patients, and define its anticancer properties beyond its action on hyperinsulinemia/hyperglycaemia.

As a result of epidemiological evidence, a large number of studies concerning the possible mechanisms of action of metformin that could be relevant in oncology have been carried out. In this review, we examine the current advances in metformin research in order to determine its potential use as an anticancer agent.

2. Metformin as an anticancer agent

Accumulating evidence from *in vitro* and *in vivo* studies supports the fact that anticancer effects of metformin can be divided into two non-exclusive categories: an indirect effect by reducing the blood glucose and insulin levels, and a direct effect on cancer cells, partially through the activation of AMPK [5,26] (see Fig. 1).

2.1. Indirect effects of metformin

The most famous and described role of metformin is its antidiabetic effect. Indeed, it has been shown for decades that metformin