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Metformin use and gynecological cancers: A novel treatment option emerging from drug repositioning

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ABSTRACT

Metformin exerts antitumor effects mainly through AMP-activated protein kinase [AMPK] activation and phosphatidylinositol 3-kinase [PI3K]-Akt-mammalian target of rapamycin [mTOR] inhibition. This drug leads to activation of the cellular energy-sensing liver kinase B1 [LKB1]/AMPK pathway. LKB1 is implicated as a tumor suppressor gene in molecular pathogenesis of different malignancies. AMPK is a serine/threonine protein kinase that acts as an ultra-sensitive cellular energy sensor maintaining the energy balance within the cell. AMPK activation inhibits mRNA translation and proliferation in cancer cells *via* down-regulation of PI3K/Akt/mTOR pathway. Moreover, metformin decreases the production of insulin, insulin-like growth factor, inflammatory cytokines and vascular endothelial growth factor, and therefore it exerts anti-mitotic, anti-inflammatory and anti-angiogenetic effects. Recent *in vitro* and experimental data suggest that metformin electively targets cancer stem cells, and acts together with chemotherapy to block tumor growth in different cancers. Several epidemiological studies and meta-analysis have shown that metformin use is associated with decreased cancer risk and/or reduced cancer mortality for different malignancies. The present review analyzes the recent biological and clinical data suggesting a possible growth-static effect of metformin also in gynecological cancers. The large majority of available clinical data on the anti-cancer potential of metformin are based on observational studies. Therefore long-term phase II–III clinical trials are strongly warranted to further investigate metformin activity in gynecological cancers.

1. Introduction

According to the World Health Organization, 171 million people worldwide have type II diabetes and this number is expected to double by 2030 (Wild et al., 2004). Metformin is an oral biguanide which inhibits gluconeogenesis, reduces insulin resistance, and

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lowers insulin levels (Viollet et al., 2012). Several epidemiological studies and meta-analysis have shown that metformin use is associated with decreased cancer risk and/or reduced cancer mortality (Zhang et al., 2011a; Wang et al., 2014; Zhang et al., 2013a; Deng et al., 2015; Hwang et al., 2015; Decensi et al., 2010; Noto et al., 2012; Franciosi et al., 2013; Bowker et al., 2006; Evans et al., 2005; Bodmer et al., 2011; Romero et al., 2012). For instance, Decensi et al. (2010), who analyzed eleven observational studies or clinical trials reporting 4042 cancer events, found a 31% reduction in overall cancer relative risk [RR] (0.69; 95% confidence interval [CI] = 0.61–0.79) in patients taking metformin compared with those receiving other anti-diabetic drugs. The inverse association was significant for pancreatic and hepatocellular cancer, with a trend to a dose-response relationship. Noto et al. (2012) analyzed 11.117 (5.3%) cases of incident cancer at any site among 210.892 diabetic patients included in 10 studies. The pooled RRs among metformin users compared with non-metformin users were 0.67 (95%CI = 0.53–0.85) for all-cancer incidence, 0.68 (95%CI = 0.53–0.88) for colorectal cancer, 0.20 (95%CI = 0.07–0.59) for hepatocellular cancer, and 0.67 (95%CI = 0.45–0.99) for lung cancer. Franciosi et al. (2013), who reassessed forty-one observational studies including 1,029,389 patients, found a significant association between exposure to metformin and reduced risk of all malignancies (Odds ratio [OR] = 0.73, 95%CI = 0.61–0.88), hepatocellular cancer (OR = 0.34; 95%CI = 0.19–0.60), colorectal cancer (OR = 0.83, 95%CI = 0.74–0.92), pancreatic cancer (OR = 0.56, 95%CI = 0.36–0.86), gastric cancer (OR = 0.83, 95%CI = 0.76–0.91), and esophageal cancer (OR = 0.90, 95%CI = 0.83–0.98).

In a Canadian cohort of 10,309 people newly treated for type 2 diabetes and followed for about 5 years, a significant reduction in cancer mortality was noted among patients treated with metformin when compared with those treated with sulfonylureas or insulin (3.5% *versus* 4.9% *versus* 5.8%) (Bowker et al., 2006). At multivariate analysis, the sulfonylurea cohort had greater cancer-related mortality compared with the metformin cohort (hazard ratio [HR] = 1.3, 95%CI = 1.1–1.6; p = 0.012) and insulin use was associated with HR of 1.9 of cancer-related mortality (95%CI = 1.5–2.4; p < 0.0001).

Metformin has been also found to reduce the incidence and mortality of ovarian cancer (Bodmer et al., 2011; Romero et al., 2012; Kumar et al., 2013; Dilokthornsakul et al., 2013; Zhang and Li, 2014), endometrial cancer (Zhang and Li, 2014; Shafiee et al., 2014; Sivalingam et al., 2014; Ko et al., 2015; Tseng, 2015), and breast cancer (Zhang and Li, 2014; Bosco et al., 2011).

The aims of drug repositioning are to discover new pharmacological effects of a drug and to expand its therapeutic use to other diseases (Banno et al., 2015). Metformin, which reduces insulin and insulin-like growth factor-1 [IGF-1] levels and inhibits different intracellular signaling pathways, may represent an interesting agent for some gynecological cancers.

2. Antineoplastic activity of metformin

Metformin exerts antitumor effects mainly through AMP-activated protein kinase [AMPK] activation and phosphatidylinositol 3-kinase [PI3K]-Akt- mammalian target of rapamycin [mTOR] inhibition (Brown et al., 2013; Del Barco et al., 2011; Engelman and Cantley, 2010; Gallagher and LeRoith, 2011) (Fig. 1). This drug, which inhibits mitochondrial oxidative phosphorylation and ATP production, leads to activation of the cellular energy-sensing liver kinase B1 [LKB1]/AMPK pathway (Del Barco et al., 2011; Engelman and Cantley, 2010; Gallagher and LeRoith, 2011). LKB1 is implicated as a tumor suppressor gene in the molecular pathogenesis of different malignancies (Liu et al., 2012a; Richer et al., 2015; Dunlop, 2002). AMPK is a heterotrimeric serine/threonine protein kinase,composed of a catalytic subunit (α_1 and α_2) and regulatory

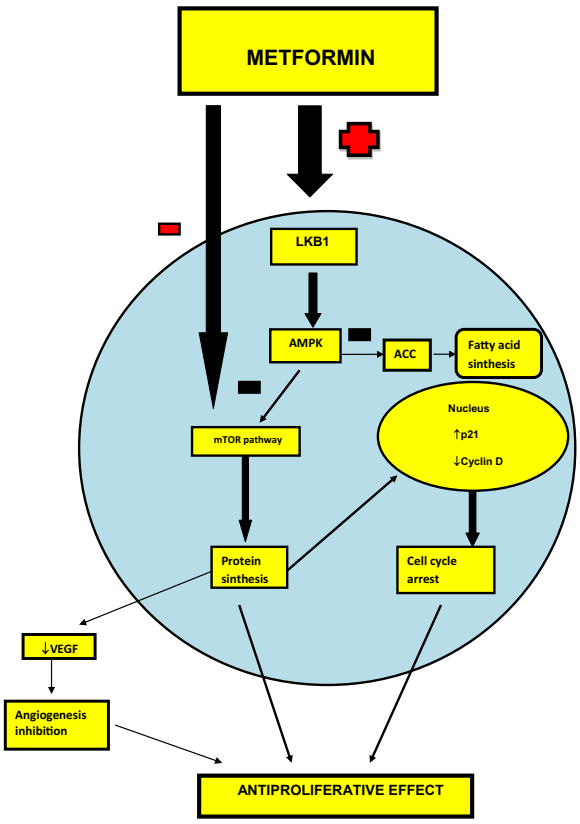

Fig. 1. Antitumoral effect of metformin. Metformin exerts antitumor effects mainly through AMP-activated protein kinase [AMPK] activation and phosphatidylinositol 3-kinase [PI3K]-Akt-mammalian target of rapamycin [mTOR] inhibition. Metformin exerts antitumor effects mainly through AMP-activated protein kinase [AMPK] activation and phosphatidylinositol 3-kinase [PI3K]-Akt-mammalian target of rapamycin [mTOR] inhibition (ACC,acetylcocarboxylase).

subunits (β_1, β_2, γ_1, γ_2 and γ_3), that acts as an ultra-sensitive cellular energy sensor maintaining the energy balance within the cell (Hardie, 2007, 2008). AMPK is activated in response to changes of AMP/ATP ratio under stress conditions and it is modulated by hormones, such as leptin and adiponectin (Hardie, 2008). mTOR controls protein synthesis by phosphorylation of the eukaryotic initiation factor 4E [eIF-4E]-binding protein-1 [4E-BP1] and of the S6 ribosomal protein kinase [p70S6K]. 4E-BP1 binds to eIF-4E, blocking the formation of the mRNA translation initiation complex and the synthesis of key proteins, such as c-myc, cyclin D1 and vascular endothelial growth factor [VEGF] (Wullschleger et al., 2006). When 4E-BP1 is phosphorylated, eIF-4E is released and the translation initiation complex is formed (Wullschleger et al., 2006). AMPK activation inhibits mRNA translation and proliferation in cancer cells *via* down-regulation of PI3K/Akt/mTOR pathway (Wullschleger et al., 2006; El-Mir et al., 2000). Another mechanism by which AMPK can exert anti-growth activity is the block of lipid biosynthesis *via* inhibition of the acetyl co-carboxylase [ACC], a rate limiting enzyme of the fatty acid synthesis (Hardie, 2008).

Rattan et al. (2011a) found that metformin inhibits proliferation of several chemo-responsive and -resistant ovarian cancer cell lines, leading to G1 phase growth arrest with concomitant inhibition of cyclin D1 and induction of p21 expression. These authors down-regulated AMPKα_1 expression in ovarian cancer cells using specific small interfering RNA [siRNA], and found that metformin was still able to block cell growth, although this inhibition was significantly less (~20%) compared with AMPK expressing parental cells. The anti-proliferative effects of metformin persisted in AMPK-silenced ovarian cancer cells, but not in LKB1-inactivated cells, thus