

## Review

**Metformin in Cancer Therapy: A New Perspective for an Old Antidiabetic Drug?**Issam Ben Sahra<sup>1,2</sup>, Yannick Le Marchand-Brustel<sup>1,2,3</sup>, Jean-François Tanti<sup>1,2</sup>, and Frédéric Bost<sup>1,2</sup>**Abstract**

Metformin is the most widely used antidiabetic drug in the world, and there is increasing evidence of a potential efficacy of this agent as an anticancer drug. First, epidemiological studies show a decrease in cancer incidence in metformin-treated patients. Second, metformin decreases insulin resistance and indirectly reduces insulin level, a beneficial effect because insulin promotes cancer cell growth. Third, several reports outline a direct inhibitory effect of metformin on cancer cell growth and an antitumoral action. Finally, metformin activates the AMP activated protein kinase (AMPK) pathway, a major sensor of the energetic status of the cell, which has been proposed as a promising therapeutic target in cancer. *Mol Cancer Ther*; 9(5); 1092–9. ©2010 AACR.

**Introduction**

Metformin (N',N'-dimethylbiguanide) belongs to the biguanide class of oral hypoglycemic agents and is a widely used antidiabetic drug now prescribed to almost 120 million people in the world for the treatment of type II diabetes. In addition to its efficacy in lowering glucose levels, metformin has the clinical advantage of not inducing any risk of hypoglycemia. Metformin is very safe and well tolerated and is only associated with very low incidence of lactic acidosis (<1/10,000), predominantly in patients with poor renal function (1). Of note, Chen and colleagues recently showed that metformin increased the accumulation of  $\beta$ -amyloid peptides, which are pivotal in Alzheimer disease, *in vitro* and *in vivo* through the AMP activated protein kinase (AMPK) pathway, an effect that could be deleterious. Nevertheless, they also showed that the combination of metformin and insulin enhances insulin's ability to reduce the  $\beta$ -amyloid peptide accumulation (2). In diabetic patients, metformin confers cardiovascular protection, an effect not only related to its anti-hyperglycemic effect but also to its favorable action on lipid metabolism (3).

The mechanism of metformin action is well studied in liver, adipose tissue, skeletal, and heart muscles. Its glucose lowering effect is mainly a consequence of reduced hepatic glucose production, increased insulin sensitivity,

and glucose use by muscles and adipocytes resulting in decreased insulinemia. The exact mechanism through which metformin reduces hepatic production requires LKB1/serine threonine kinase 11 (STK11), which controls the AMPK/mammalian target of rapamycin (AMPK/mTOR) pathway and neoglucogenic genes (4). Metformin facilitates trafficking of glucose transporters 1 and 4 in several tissues (5), including skeletal muscle and adipocytes, thereby improving glucose uptake. Finally, the lipid favoring effects are due to increased fatty acid oxidation via phosphorylation of acetyl CoA carboxylase (ACC) by AMPK.

Metformin regulates the AMPK/mTOR pathway, implicated in the control of protein synthesis and cell proliferation. Indeed, mTOR is activated by mitogenic-responsive pathways (Ras/ERK, PI3K/Akt) and pathways that signal the availability of intracellular energy and nutrients such as amino acids. However, mTOR is negatively regulated by AMPK, which is activated on ATP decrease, inducing inhibition of cell growth. These observations drew the attention of many laboratories and led them to evaluate the role of mTOR on cell proliferation and cancer incidence in patients treated with this drug. Thus, several recent concordant series of epidemiological, animal, and cellular studies support an antineoplastic effect of metformin. Indeed, if one of the indirect beneficial effects of metformin in diabetic patients is a decrease in insulin, a growth-promoting hormone, cellular and animal studies show that metformin can also directly affect cancer cell proliferation. Further investigations, including clinical trials using a combination of metformin and conventional anticancerous agents in nondiabetic patients, are ongoing to clarify its potential use in cancer therapy. In this review, we will summarize the current knowledge of metformin action on cancer cells and discuss why metformin could be proposed as an anticancer agent in nondiabetic patients.

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## Epidemiological Evidence for a Beneficial Role of Metformin as an Anticancer Agent

Metformin action on the AMPK/mTOR pathway prompted epidemiologists to compare cancer incidence in metformin users with nonusers. Indeed, several retrospective studies reported a decrease in cancer risk in diabetic patients treated with metformin. Evans and colleagues were the first to show that metformin treatment is associated with a reduced risk of all cancers (6). Bowker and colleagues, in a study including 10,309 diabetic patients, compared the incidence of cancer during treatment, i.e., insulin, metformin, or sulfonylureas (which increase insulin secretion), for a period of 5 years. They found that patients treated with metformin had a significantly lower rate of cancer-related mortality compared with patients exposed to sulfonylureas or insulin (7). Indeed, the cancer mortality rate in percent (per 1,000 person-years of follow-up) was 6.3% and 9.7% for metformin and sulfonylurea cohorts, respectively, and insulin users had higher incidence of cancer-related mortality than patients not receiving insulin. Similarly, Currie and colleagues showed that patients on insulin or insulin secretagogues were more likely to develop solid cancers than those on metformin. In the same study, metformin use was associated with decreased incidence of colon or pancreas cancer, but did not affect breast or prostate cancer. Recently, Libby and colleagues observed in a large observational cohort study of 8,000 patients with type 2 diabetes, that cancer was diagnosed among 7.3% of metformin users compared with 11.6% of nonusers, with median times to cancer of 3.5 and 2.6 years, respectively ( $P < 0.001$ ; ref. 8). Furthermore, in later years of follow-up, high doses of metformin were associated with the greatest reduction in the risk of cancer. In addition to these studies on all cancers, specific investigations have been done. For example, a Finnish study showed that the overall risk of developing prostate cancer was decreased by 34% for men with 7 years of antidiabetic treatment compared with men without any antidiabetic medication (9). Finally, Jiralerspong and colleagues (10) reported that the rate of pathologic complete response, defined as absence of tumor in the removed tissue at time of surgery, in response to neoadjuvant chemotherapy in breast cancer, was 24% among diabetic patients receiving metformin as opposed to only 8% for those in the non-metformin group ( $P < 0.001$ ). Despite the large number of patients analyzed in these epidemiological studies, which are all retrospective, most of them lack important information such as the dose of metformin, body mass index, or glycemic control. Indeed, type II diabetic patients are often overweight or obese, two conditions that favor the incidence of cancers (11). Hyperinsulinemia and type II diabetes are associated with an increased risk of many cancers (12, 13). Because insulin is a growth-promoting hormone with mitogenic effects (14), it has been suggested that hyperinsulinemia combined with insulin resistance might promote carcinogenesis (15). Metformin

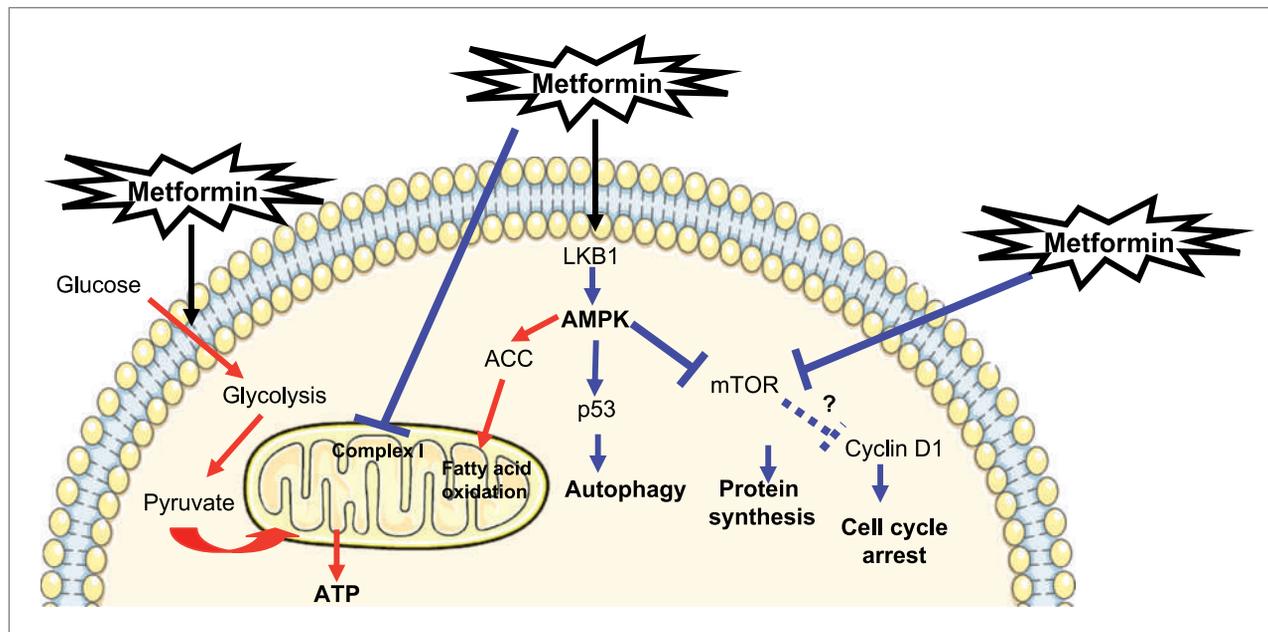
decreases insulinemia and could, therefore, indirectly inhibit insulin-promoting effects. By contrast, metformin does not seem to affect the serum concentrations of insulin-like growth factor (IGF-1), a growth promoting tumor, and prevents the proliferative effect of IGF-1 through AMPK in bovine granulosa cells (16). In addition, hyperinsulinemia decreases the amount of IGF binding protein available (IGFBP), resulting in the increase of active (free) IGF1. Therefore, one could hypothesize that metformin decreases insulinemia and free IGF-1.

One of the issues is to determine whether the effect of metformin is indirect, i.e., due to its lowering action on insulin concentration and/or direct on tumor cell proliferation.

## Metformin Targets the AMPK/mTOR Axis to Inhibit Cancer Cell Growth

In the majority of the studies using metformin in cancer cells, the energy sensor pathway of the cell, the AMPK/mTOR axis, plays a central role suggesting that metformin interferes with the energetic metabolism of the cell and protein synthesis (Fig. 1). The AMPK/mTOR pathway is under the control of LKB1. LKB1 is a serine-threonine kinase acting as a tumor suppressor (17). Mutations in LKB1 are associated with the Peutz-Jeghers syndrome a rare autosomal syndrome characterized by benign gastrointestinal polyps (hamartomas) and an increased risk of tumors (18). Once activated, LKB1 phosphorylates the energy-sensing kinase AMPK, which is inactive unless it has been phosphorylated by upstream kinases in response to cellular stresses that deplete cellular energy level and increases the AMP to ATP ratio (19). Metformin activates the AMPK pathway in normal and cancer cells (3), possibly because of the inhibition of the complex I. A direct consequence of AMPK activation is the inhibition of the mTOR pathway via tuberous sclerosis 2 protein (TSC-2). mTOR upregulates many energy consuming cellular processes and has a central role in regulating cell growth by controlling mRNA translation and ribosome biogenesis. Because activation of AMPK inhibits energy consuming pathways and protein synthesis (20), metformin has been proposed to inhibit cell proliferation through AMPK.

In agreement with this hypothesis, using siRNA directed against the catalytic  $\alpha$  subunit of AMPK or using mouse embryonic fibroblasts deficient for LKB1, it has been shown that the effect of metformin on proliferation and protein translation is mediated by the LKB1/AMPK pathway in breast cancer cells (21, 22). Similarly, compound C, a specific inhibitor of AMPK, partially reverts the antiproliferative effect of metformin in ovarian cancer cells (23). The implication of the LKB1/AMPK axis was confirmed in HeLa cells, which are deficient for LKB1 and insensitive to metformin (22). Furthermore, Dowling and colleagues showed that metformin-mediated AMPK activation leads to a reduction of translation initiation in



**Figure 1.** Potential mechanism of metformin action on cellular metabolism and cell proliferation. Metformin increases glucose uptake and glycolysis. It activates AMPK leading to the phosphorylation of ACC and ultimately increases fatty acid oxidation. Metformin also inhibits the mitochondrial complex 1. Finally, metformin affects cell growth: it induces p53-dependent autophagy, inhibits mTOR and protein synthesis, and induces cell cycle arrest through a decrease in cyclin D1 protein level.

breast cancer cells (21). Indeed, metformin did not affect translation in MDA-MB-231 cells (LKB1<sup>-/-</sup>) and TSC2<sup>-/-</sup> mouse embryonic fibroblasts. More recently, Huang and colleagues showed that administration of biguanides (metformin; phenformin) at 300 mg/kg or a pharmacological activator of AMPK (A-769662) significantly reduces the occurrence of tumors in mice with wild-type LKB1 compared with hypomorphic mice displaying a reduction in LKB1 expression (24). In contrast, we have shown that metformin can mediate its effects independently of AMPK in prostate cancer cells, and inhibition of the two catalytic units of AMPK with siRNAs did not prevent the antiproliferative effect of metformin in human prostate cancer cells (25). Other groups have shown that metformin mediates its effects independently of AMPK. For example, Hue's group has recently shown that the effects of metformin and AICAR (5 amino-imidazol-4-carboxamide-1- $\beta$ -4-ribofuranoside) on the function of glucokinase in hepatocytes are still observed in mice lacking  $\alpha$ 1 and  $\alpha$ 2 catalytic units (26). These discrepancies highlight the importance of deciphering the involvement of AMPK in the effects of metformin using appropriate molecular tools targeting both catalytic units. Although metformin's effects are AMPK dependent in some cell lines, it is obvious that it could also be AMPK independent in other cancer cells.

AMPK regulates p53 expression and phosphorylation (27–29), and p53 has been shown to be implicated in cell metabolism (30). The implication of p53 in metformin action is the subject of debate. Indeed, Buzzai and col-

leagues showed that only HCT116 cells deficient for p53 and not HCT116 with p53 wild-type are sensitive to metformin (31), but others have shown that cancer cell lines such as LNCaP and MCF-7 with functional p53 displayed similar sensitivity to metformin compared with p53 null cells (22, 25, 32). Metabolic adaptations are critical to maintain survival in response to stress conditions, and the hypothesis that p53 is necessary to overcome the deleterious effects of metformin is satisfactory. On the other hand, p53 may also be necessary to trigger cell cycle arrest upon metformin treatment, which is observed in LNCaP and MCF-7 cells. Finally, a third option may be that the metformin antiproliferative effect is independent of p53. Data from the literature favor the last hypothesis, as a vast majority of studies show that metformin acts independently of the p53 status on cell proliferation.

Overall, metformin treatment leads to the downregulation of mTOR in all cell lines eventually. How it bypasses AMPK to target mTOR in some cell lines remains an open question, which could lead to the discovery of new pathways implicated in the regulation of mTOR and protein synthesis.

### Cellular Mechanisms Implicated in the Inhibition of Cancer Cell Proliferation by Metformin

Evidence for the direct action of metformin on cancer cell growth has been clearly established in a series of *in vitro* studies. Indeed, metformin exhibits a strong

and consistent antiproliferative action on several cancer cell lines including breast, colon, ovary, pancreas, lung, and prostate cancer cells at concentrations ranging from 5 to 30 mM (see Table 1) with differences in their sensitivity (i.e., LNCaP prostate cancer cells were more sensitive than MCF-7 breast cancer cells). In addition, we have shown that normal epithelial prostate cells are barely affected by metformin sensitivity (25), sug-

gesting that the sensitivity to metformin depends on cancer cell origin and is specific to cancer cells. Of note, the *in vitro* experiments used high concentrations of metformin (typically 5 to 30 mM), which are 100 to 300 times higher than the recommended therapeutic doses. Interestingly, a landmark study showed that low doses of metformin (0.1 to 0.3 mM) inhibited transformation and selectively killed cancer stem cells

**Table 1.** Summary of epidemiological *in vivo* and *in vitro* studies done with metformin in different cancers

Type of cancer	Conclusions	Epidemiological studies	Preclinical studies	<i>In vitro</i> studies	
Prostate	Metformin is associated with a reduction of prostate cancer incidence	(66)			
	Metformin inhibits human prostate cancer cell (LNCaP, PC3, and DU145) proliferation and tumor growth via inhibition of cyclinD1		(25)	(25)	
	Metformin inhibits PC3 proliferation			(22)	
Breast	Higher response to chemotherapy in patients treated with a combination of metformin and chemotherapy	(67)			
	Metformin inhibits the development of mammary tumors in HER-2/neu mice		(40)		
	Metformin growth inhibition is mediated by AMPK			(22)	
	Metformin inhibits translation initiation in a LKB1/AMPK-dependent way			(21)	
	Metformin blocks cell cycle progression at S phase and induces apoptosis in triple-negative breast cancer cells			(35)	(35)
	Human genome array of metformin-responsive genes in MCF-7, SKBR3, and MCF-7/HER2				(64)
	Metformin induces cell cycle arrest in MCF-7, BT-474, and SKBR-3				(34)
	Metformin restores lapatinib sensitivity in MCF-7/HER2 LapR				(65)
	Metformin suppresses erbB-2 expression via inhibition of mTOR in SKBR3 and MCF-7/HER2				(37)
	Metformin induces cell cycle arrest and cyclin D1 inhibition in MDA-MB-231 cells				(32)
	Metformin inhibits MDA-MB-435 cancer cell growth but promotes angiogenesis and tumor growth <i>in vivo</i>			(43)	(43)
	Metformin selectively kills cancer stem cells at low doses (0.1-0.3 mmol/L). Synergistic effect of doxorubicin and metformin			(33)	(33)
	Pancreas	Metformin use is associated with reduced risk of pancreatic cancer	(68, 69)		
Metformin prevents carcinogen-induced pancreatic cancer induction in hamsters			(39)		
Metformin disrupts the crosstalk between G protein-coupled receptors and insulin receptor signaling and inhibits cancer cell and tumor growth			(38)	(38)	
Metformin induces apoptosis in ASPC-1, BxPc-3, PANC-1, and SW1990				(36)	
Colon	Metformin use is associated with reduced risk of colon cancer	(69)			
	Metformin inhibits tumor growth in HCT116 P53 <sup>-/-</sup> cells and induces autophagy in a p53-dependent way		(31)	(31)	
Lung	Metformin attenuates the effect of a high-fat diet on mouse lewis lung carcinoma (LLCC1) xenograft		(42)	(42)	
Ovary	Metformin inhibits the proliferation of epithelial ovarian cancer cells OVCAR-3 and OVCAR-4			(23)	
	Metformin acts through AMPK to inhibit ovarian cancer cell growth			(70)	

resistant to chemotherapeutic agents (33). However, these low doses failed to affect the viability of non-cancer stem cells.

At the cellular level, metformin interferes with cell cycle leading to G0/G1 or S phase arrest. We have shown that metformin provoked a cell cycle arrest at the G0/G1 stage with a reduction in cyclin D1 protein levels in human prostate cancer cells *in vitro* and in a xenograft model (25). Similar results were obtained in breast cancer cells, in which metformin-induced cell cycle arrest requires p27<sup>Kip</sup> or p21<sup>Cip</sup> in addition to cyclin D1 decrease (32, 34). S phase arrest was observed in pancreatic and triple negative breast cancer cell lines associated with the induction of apoptosis (35, 36). Of note, only these two studies show that metformin induces apoptosis.

In addition to its effects on cell cycle, metformin can interfere with some receptors, because metformin decreases the oncoprotein level of Her2 (*erbB-2*) or epidermal growth factor receptor in breast and pancreatic cancer cells, respectively (36, 37). This latter aspect is the best argument to legitimate clinical trials in breast cancer because Her-2 gene amplification and/or protein overexpression have been identified in 10 to 30% of all breast cancers. More recently, Kisfalvi and colleagues showed that metformin abolished insulin-induced proliferation of pancreatic cancer cells, because of a disruption of the crosstalk between insulin receptor and G-protein coupled receptor (GPCR; ref. 38). Specifically, metformin prevented insulin-induced augmentation of Ca<sup>2+</sup> signaling, DNA synthesis, and anchorage-independent proliferation in response to stimulation with GPCR agonists.

### Preclinical Studies and Antitumor Growth Action of Metformin

The antineoplastic action of metformin was shown for several cancers in animal models. Schneider and colleagues were the first to show that metformin prevents carcinogen-induced pancreatic cancer induction in hamsters maintained on a high-fat diet (39). Interestingly, the growth of the pancreatic cell lines' PANC1 and MIAPaCa-2 tumor xenograft was significantly reduced after daily intraperitoneal treatment with metformin (38). Similarly, chronic treatment of female HER-2/*neu* transgenic mice with metformin (100 mg/kg in drinking water) decreased the incidence and size of mammary adenocarcinoma and significantly prolonged by 8% their mean life time in comparison with control mice (40). Tumor formation was also markedly delayed in phosphatase and tensin homolog (PTEN)  $\pm$  mice that normally develop multiple tumors. Indeed, mice receiving phenformin (a metformin analog) did not develop tumors after 6 months when 60% of nontreated mice had tumors (24). Another example of metformin action on the development of *in situ* tumors was observed in the *Apc* (*Min/+*) mice models. Administration of metformin at 250 mg/kg in the diet significantly reduced the number of large polyps (41). Finally, we and

others showed that metformin efficiently inhibits tumor growth in prostate, colon, or lung cancer cell xenografts (25, 31, 42). In contrast with these numerous concordant reports, Phoenix and colleagues described opposite effects of metformin on the development of xenografts of ER $\alpha$  negative MDA-MB-435 cells (43). Although metformin represses breast cancer cell growth *in vitro*, they showed that it increased vascular endothelial growth factor expression, intratumoral microvascular density, and promoted tumor growth in nude mice. It is of note that the MDA-MB-435 cell line, which was used for a decade as a breast cancer cell line, has been recently reclassified as a melanoma cell line (44).

This finding tampers with promising preclinical data and draws attention to the natural caution with the use of this drug, especially in its dosage. Indeed, the doses used in the preclinical trials cited above varied from 750 mg/kg per day (43), which is about 45 fold more than the recommended therapeutic dose in humans to 40 mg/kg per day, which is the lowest dose used in mice (25). It is therefore difficult to extrapolate the results obtained in animal models and the potential effects of metformin in a clinical trial with standard metformin doses.

Few studies analyzed the effect of metformin on animal weight and metabolic parameters (such as insulinemia), which could help to solve the mechanism (direct or indirect) of the effect of metformin on tumors. Schneider and colleagues showed that the prevention of pancreatic cancers in hamsters treated with metformin and fed with a high-fat diet is correlated with a marked decrease in insulinemia (39). In contrast, metformin treatment did not affect insulinemia in PTEN +/-, HER-2/*neu*, and *Apc*<sup>Min/+</sup>, suggesting an insulin-independent antitumoral action of the drug (24, 40, 41).

The undisputed effect of metformin on cancer cell viability and its lowering effect on insulin concentration in diabetes rationalize the use of the drug in nondiabetic and diabetic patients. Because there is no risk of hypoglycemia reported in normoglycemic patients and rare side effects described for metformin, clinical trials using a combination of metformin and conventional anticancerous agents in nondiabetic patients should be undertaken to clarify the potential use of this drug in cancer therapy. Such work is underway in breast cancer as mentioned in recent articles (45–47), and several clinical trials are reported on the U.S. National Institutes of Health clinical trial web site (48). Indeed, the effect of a combinatorial therapy was recently experienced using breast cancer cells with a complete absence of tumor growth in nude mice treated with the combination of doxorubicin and metformin (33). This study provides an experimental basis for using the combination of metformin with chemotherapeutic drugs. Furthermore, metformin was found to induce B<sub>12</sub> deficiency (49), and some work showed that inactivation of B<sub>12</sub> by nitrous oxide induces tumor-cell kill *in vitro* and increased tissue toxicity in patients receiving adjuvant chemotherapy with methotrexate (50). This

study explains, at least partially, the previously described clinical study by Jiralerspong in which a complete pathologic response was observed in diabetic patients with breast tumors ingesting metformin who were undergoing neoadjuvant chemotherapy compared with diabetic patients not ingesting metformin (10).

### Metformin Affects Cancer Cell Metabolism

Metabolic reprogramming from oxidative phosphorylation to glycolysis is a hallmark that constitutes an undisputed advantage for cancer cells and tumor growth (51). This metabolic change known as the Warburg effect is characteristic of virtually all cancers. Unlike most normal cells, cancer cells become dependent on glycolysis for energy production, which allows them to adapt to a hypoxic environment. Although this shift to high rates of glycolysis has been considered for many years to be a by-product of the oncogenic process, recent evidence suggests that it is required for malignant progression (52).

Despite the glycolytic switch, some cancer cells preserve the capacity to produce energy through mitochondrial oxidative phosphorylation. Metformin hampers the respiratory chain complex I in hepatocytes (53). Buzzai and colleagues have shown that metformin inhibited oxygen consumption in colon cancer cells, which is consistent with the inhibition of oxidative phosphorylation. Recently, we have shown that metformin inhibits complex I and increases glycolysis in prostate cancer cells (54). Decrease in oxidative phosphorylation is equivalent to nutrient depletion in terms of ATP supply and could force the cells to engage survival processes such as autophagy and increased glycolysis leading eventually to cell death. Few studies show that metformin induces apoptosis in pancreatic cells (35, 36), although Buzzai and colleagues showed that metformin induces autophagy in HCT116 colon cancer cells (31).

Although the Warburg effect has been recognized since the 1920s, less well-appreciated are the alterations in lipid metabolism and the high rates of *de novo* fatty acid biosynthesis exhibited by many tumors (55). The expression of fatty acid synthase (FAS), a key enzyme of lipogenesis, which is extremely low in normal cells, is expressed at high levels in tumor cells. Downregulation of this enzyme may be fatal for cancer cells, making FAS a new target for cancer therapy leading to the identification of chemical inhibitors such as C-75, which displays antitumoral activity (56). Metformin interferes with fatty acid metabolism, because it inhibits FAS expression in normal cells, it activates fatty acid oxidation in HCT116 colon carcinoma cells. AICAR, an activator of AMPK, inhibits FAS expression and cell growth in prostate cancer cells (57).

All these observations show that metformin induces a stress similar to a metabolic stress leading to the inhibition of anabolic pathways and a decrease in cellular

metabolism. Consequently, the cellular response varies from apoptosis, autophagy, and cell cycle arrest depending on cell type. The implication of the AMPK pathway, a major sensor of cell energy metabolism in this response establishes a relationship between the perturbation of cell metabolism induced by metformin and its effect on cell viability.

### Conclusion

The remarkable efficiency of metformin to inhibit cancer cell growth *in vitro* and tumor proliferation in animals, and its low toxicity, favor the potential use of this agent in the treatment of cancer. However, depending on cell lines, the mechanism of action of metformin and its sensitivity toward this agent are different. Therefore, it is important to determine the cellular and molecular action of metformin in order to optimize its use in cancer therapy. As discussed in this review, alterations of cancer cell metabolism are one of the principal hallmarks of cancer. Affecting the metabolic reprogramming of cancer cells represents a promising therapeutic perspective. Metformin, by its action on cell metabolism and the AMPK/mTOR pathway may be a very good candidate (58). The use of metformin in cancer therapy especially in the treatment of breast cancer has recently been extensively debated (10, 46, 59–65). Despite some concerns on the dosage of the drug and after the intriguing preclinical study of Phoenix and colleagues showing a pro-angiogenic action of metformin (43), all the editorial comments cited above consider that metformin may have beneficial effects on breast cancer therapy. Overall, the positive action of metformin is based upon its dual action on insulinemia and its molecular action on AMPK and HER-2. As a result, we believe that trials of metformin as an adjuvant treatment in breast cancer and more generally in other cancers should move forward in nondiabetic patients.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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