# Untuning the tumor metabolic machine

**Several decades of scientific observations followed by years of basic and now clinical research support the notion that the metabolic power of tumor cells can provide the long-desired Achilles' heel of cancer. Yet many questions remain as to what defines the true metabolic makeup of a tumor and whether well-known factors and pathways involved in metabolic signaling act as tumor suppressors or oncogenes. In 'Bedside to Bench', Kıvanç Birsoy, David M. Sabatini and Richard Possemato discuss how retrospective studies of diabetic individuals with pancreatic cancer treated with the antidiabetic drug metformin point to a possible anticancer effect for this drug. Further research will need to discern whether this drug acts at the organismal level or by directly targeting the power plant of tumor cells. In 'Bench to Bedside', Regina M. Young and M. Celeste Simon peruse the complex function of a key metabolic factor that mediates the cell's response to low oxygen levels, often found in tumors. This hypoxia-inducible factor (HIF) comes in two flavors, which can be either tumor promoting or tumor suppressive, depending on the type of cancer. Because of this, the therapeutic use of HIF inhibitors must proceed with caution. Further defining the relationship between metabolic regulation of HIF and tumor progression may open up new diagnostic tools and treatments.**

■ BEDSIDE TO BENCH

## Targeting cancer metabolism: a bedside lesson

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The decades-old observation that most tumors have an elevated glucose consumption rate compared to normal tissues has received renewed attention in the laboratory as scientists have come to appreciate that altered cancer metabolism is a hallmark of the transformed state[1]. Metabolic enzymes act as tumor suppressors, such as the Krebs cycle enzymes fumarate hydratase and succinate dehydrogenase, which are mutated in hereditary leiomyomatiosis and renal cell cancer and in hereditary paraganglioma and pheochromocytoma, respectively[2]. But mutations can also confer oncogenic capacity to metabolic enzymes, such as isocitrate dehydrogenase 1 (IDH1) or IDH2, driving subtypes of brain cancer and acute myeloid leukemia[3].

Unexpectedly, essential metabolic pathways, such as the serine biosynthetic pathway, are activated by gene amplification or epigenetic changes in estrogen receptor–negative breast cancer, and, surprisingly, essential metabolites such as glycine are highly consumed in rapidly proliferating cancer cells[4,5]. Finally, well-established cancer-relevant pathways, such as the RAS/AKT and mTOR (mammalian target of rapamycin) cascades, and transcription factors, including c-myc and HIF, can exert substantial influence over glucose uptake, glycolysis, glutaminolysis, fatty acid oxidation and respiration[6].

The increased glucose consumption of tumors has long been exploited by clinicians through monitoring tumor uptake of a fluorine radioisotope of glucose by positron emission tomography (FDG-PET). This technique has been used to stage cancer, identify metastatic sites and monitor treatment effectiveness. Furthermore, the initial degree of FDG-PET positivity has been correlated to overall patient outcome across cancer types, and can vary by cancer subtype[7]. However, a full characterization of the metabolic phenotype of cancer is still in its initial stages, and recent basic research findings have not yet been translated in the clinic. Yet, traditional chemotherapeutics such as fluorouracil, methotrexate and gemcitabine indeed inhibit metabolic enzymes, indicating that targeting cancer metabolism has clinical potential.

Therapies targeting cancer metabolism typically target either the metabolic state of the organism—such as through caloric restriction[8], ketogenic diets[9] and modulation of circulating nutrient levels through enzymes such as asparaginase[10]—or target the altered metabolism of the tumor itself—such as with 2-deoxyglucose, a glucose mimetic and hexokinase-competitive inhibitor, and 3-bromopyruvic acid, a putative glycolytic inhibitor, in addition to those mentioned above[11]. With the exception of asparaginase, a drug approved for childhood acute lymphoblastic leukemia for decades, the other approaches have shown promise in limiting tumor growth in animal models but have considerable hurdles to overcome before becoming approved therapies.

Surprisingly, several recent retrospective studies have shown in a wide variety of cancer types the substantial antitumor effects of the US Food and Drug Administration–approved antidiabetic drug metformin[12,13]. For example, a retrospective study of diabetic individuals with pancreatic cancer, of whom 117 had received metformin and 185 had not, analyzed the correlation of metformin use with survival and showed an increase in 2-year survival from 15.4% in the control group to 30.1% in the group taking metformin[12]. These studies demonstrate that targeting energy sensing and use may be a viable anticancer strategy and provide basic researchers with some clues for improving upon such strategies, including a potential role of metformin in directly targeting the mitochondria of cancer cells[14].

Centuries before biguanides, such as metformin, became routinely prescribed for diabetes, the French lilac *Galega officinalis* was known to contain an agent that reduced the frequent urination associated with this disease (**Fig. 1**)[15]. It was only in the 1920s that the active ingredient in the French lilac, guanidine, was isolated, nucleating the biguanide class of drugs. Much of the basic research on biguanides since then has focused on their ability to suppress liver gluconeogenesis, which is believed to occur through activation

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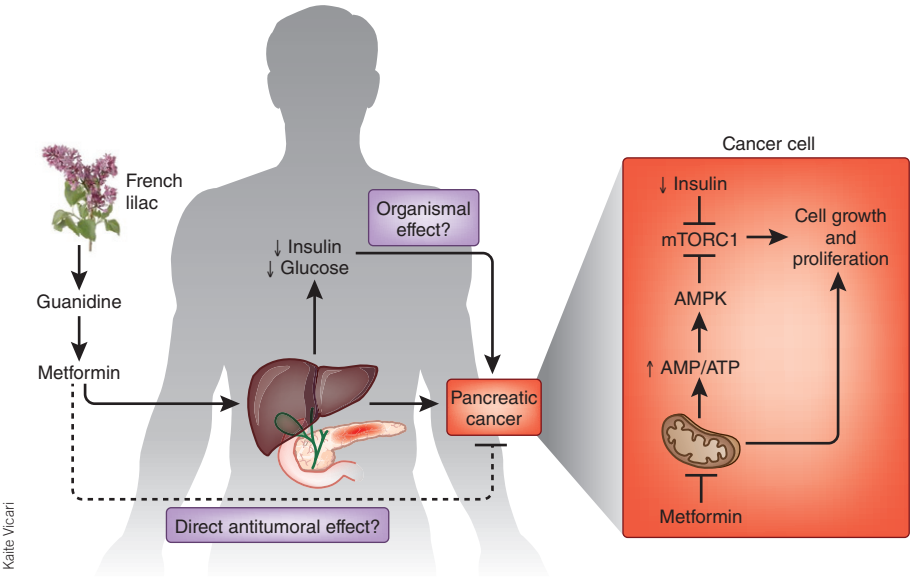


**Figure 1** Potential effects of metformin on tumor growth. Metformin is of the biguanide class of compounds, modeled after guanidine derivatives first isolated from the French lilac *G. officinalis*. This drug has a well-established role in suppressing hepatic gluconeogenesis, thereby ameliorating hyperglycemia in individuals with type 2 diabetes, but new studies are beginning to unearth a role for metformin in suppressing cancer progression. It is still unclear whether this is by direct action of the drug on the cancer cells themselves or through an indirect effect on organismal metabolism.

of hepatic AMP-activated protein kinase (AMPK) signaling[16], as biguanides achieve elevated levels in the liver compared to other tissues due to the specific expression of the OCT1 transporter in this organ.

AMPK is itself involved in a cancer-relevant signaling pathway as a downstream target of the STK11 tumor suppressor (also known as LKB1), which is inactivated in Peutz-Jaegers syndrome, a disease characterized by hamartomatous polyps of the intestine as well as an overall increased cancer risk[17]. Interestingly, most inherited syndromes characterized by hamartomatous polyps impinge upon upstream inhibitors of the mTOR complex 1 (mTORC1) pathway[18], including tuberous sclerosis (involving *TSC1* or *TSC2* mutation), the PTEN-hamartoma tumor syndromes (mutation in *PTEN*), neurofibromatosis (mutation in *NF1* or *NF2*) and perhaps also Birt-Hogg-Dubé syndrome (mutation in *FLCN*). mTORC1, a major intracellular nutrient sensor, regulates various cellular processes including protein synthesis, autophagy and ribosomal biogenesis that collectively affect cell growth, and mTORC1 activation has been suggested as a common link for diseases of this type.

Therefore, there is substantial evidence that activation of AMPK by metformin could exert an antitumor effect through modulating the AMPK/mTOR pathways. However, metformin fails to activate AMPK directly using *in vitro* kinase assays[19]. As such, the prevailing view is that this drug class indirectly acts on AMPK by causing an elevated cellular AMP/ATP ratio, which activates the AMPK pathway. Indeed, several recent studies showed metformin to inhibit mitochondrial oxidative phosphorylation[14], a major ATP source in most cells, which would explain its ability to activate AMPK.

Understanding how the organismal and cell-autonomous effects of biguanides translate into an anticancer effect will be important for using these drugs as chemotherapeutics; however, there are several potential mechanisms explaining the anticancer effects of metformin. One potential indirect mechanism is the modulation of circulating insulin levels, as many tumors are driven by insulin receptor signaling, and such tumors can be sensitive to metformin treatment[20]. But, in the retrospective study by Sadeghi *et al.*[12], metformin exerts an antitumor effect on pancreatic cancer regardless of concomitant insulin treatment. As such, the organismal effects of metformin on insulin signaling, as well as other potential organismal effects, will require further evaluation.

In support of a direct effect on mitochondrial oxidative phosphorylation in cancer cells, metformin has been shown to inhibit cancer cell proliferation *in vitro* and *in vivo* in numerous studies. However, it does so *in vitro* only at high doses that might not be achievable *in vivo* in a tumor, arguing that the observed *in vivo* effect is actually indirect. Furthermore, the glycolytic nature of tumors argues against the efficacy of a mitochondrial inhibitor, as cancer cells might derive most of their energy from glycolysis. Nevertheless, recent studies have shown that substantial mitochondrial glucose oxidation occurs in glioblastoma models *in vivo* and *in vitro*[21]. Whereas the importance of mitochondrial glucose oxidation to the tumor has yet to be fully investigated, its suppression may be linked to increased reactive oxygen species production, a loss of mitochondrial membrane potential, energy crisis due to ATP depletion, decreased citric acid cycle function or activation of the AMPK pathway directly in the tumor. Therefore, a thorough analysis of the metabolic state of tumors in animal models or in patients with cancer treated with metformin will be necessary for understanding whether metformin has a direct effect on cancer cells and whether this effect underlies the observed clinical response.

It is unclear whether the efficacy of metformin will be limited to individuals with both diabetes and cancer. Ongoing prospective studies using metformin in nondiabetics will elucidate whether the anticancer effects of metformin also occur in individuals with normal glucose homeostasis. Regardless, the current successes in the clinic are a signal to investigators that mitochondrial inhibition, be it in the liver or the tumor, may inhibit tumor growth and should provide guidance for future laboratory research.

**COMPETING FINANCIAL INTERESTS**
The authors declare no competing financial interests.

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