Repurposing biguanides to target energy metabolism for cancer treatment

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Metformin is a drug commonly used for treating type 2 diabetes—yet there are more than 100 ongoing trials of metformin at conventional antidiabetic doses for cancer treatment. This situation has arisen in large part because, in contrast to newly synthesized and patented drug candidates where drug supply is controlled and clinical trials are coordinated in a central office, there is a low 'barrier to entry' to initiate a clinical trial of an inexpensive generic drug for a potential new indication. When there is an intriguing rationale and a low risk of toxicity, as is the case for treatment of cancer with metformin, many investigators launch clinical trials, but the coordination associated with conventional drug development programs is absent.

Metformin is a biguanide compound known to partially inhibit oxidative phosphorylation[1],

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which results in energetic stress and a variety of cell-lineage–specific secondary effects. In the context of type 2 diabetes, the liver is a key target organ, as energetic stress in hepatocytes leads to inhibition of gluconeogenesis[2,3], which lowers hyperglycemia and causes a secondary decline in hyperinsulinemia (**Fig. 1**). Many retrospective pharmacoepidemiologic studies[4], some of which are controversial[5], have suggested that patients with diabetes treated with metformin have reduced cancer risk and/or improved cancer prognosis relative to individuals with diabetes who were prescribed other therapies. These provocative reports raised the possibility that metformin has antineoplastic activity and motivated both laboratory research and the initiation of clinical trials of metformin for cancer treatment.

The initially proposed mechanism for antineoplastic activity of metformin is as follows, and it remains plausible. High insulin levels are associated with adverse outcomes of many cancers[6], and many cancers express insulin receptors. In turn, insulin activates the phosphoinositide 3-kinase–mammalian target of rapamycin (PI3K-mTOR) signaling pathway, which favors mRNA translation, cell survival and proliferation. Metformin is known to lower the elevated insulin levels common in type 2 diabetes and hence may reduce activation of the PI3K-mTOR pathway in cancers.

Meanwhile, as the initial clinical trials of metformin in cancer treatment proceed, laboratory studies are revealing new information relevant to potential applications of biguanides in oncology[7]. Biguanides can act directly act on neoplastic cells, causing energetic stress (**Fig. 1**). Although most cancers display increased aerobic glycolysis (known as the Warburg effect), oxidative phosphorylation is not dispensable; on the contrary, mitochondria continue to provide substantial ATP and a host of essential metabolic functions[8]. In response to biguanide-induced energetic stress, some transformed cells adaptively reduce energy-consuming processes such as mRNA translation and proliferation, and this results in at least a cytostatic effect[9,10]. Others continue high rates of energy consumption despite diminished supply, leading to an energetic crisis and cytotoxic effects[11,12].

A recent report in *Nature* by Birsoy *et al.*[13] reveals exciting new evidence that sensitivity to biguanides is increased in the substantial proportion of cancers with mutations in genes encoding proteins of respiratory complex I of the mitochondrial electron transport chain. Prior evidence suggested that complex I is an important target of biguanides. Therefore, pharmacologic inhibition of mitochondrial energy metabolism already diminished by

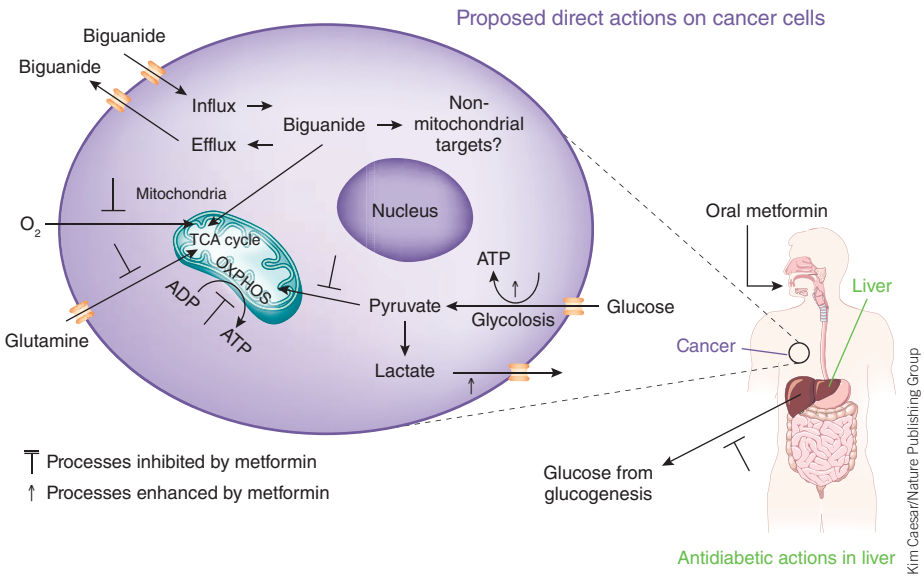

Figure 1 Repurposing metformin. The repurposing of metformin as an anticancer drug may involve several targets. The current major clinical application of the drug is in diabetes treatment, where it acts in the liver to inhibit gluconeogenesis and cause secondary metabolic and endocrine changes, such as reduction of hyperinsulinemia and hyperglycemia. Some of metformin's anticancer effect may be attributable to these systemic actions, but there is also evidence that metformin and other biguanides may act directly on cancers, particularly those with mutations in respiratory complex I, by causing energetic stress. However, this may require optimization of pharmacokinetics to achieve adequate drug concentration in neoplastic tissue. OXPHOS, oxidative phosphorylation; TCA, tricarboxylic acid cycle.

mutations may result in severe oxidative phosphorylation deficits for which adequate compensation (for example, by increased glycolysis) is difficult. This implies the possibility of a favorable therapeutic index: cancers with oxidative phosphorylation deficits may be more sensitive to biguanides than normal tissues.

Separate evidence suggests that rational combinations of biguanides with other agents may also be clinically useful. For example, experimental models (reviewed in ref. 14) show that if an oncogenic kinase drives increased glycolysis, acute inhibition of glycolysis following exposure to a kinase inhibitor can lead to a requirement for increased oxidative phosphorylation to avoid an energetic crisis in the targeted cancer. In this situation, co-administration of biguanides would be expected to attenuate this compensatory increase in oxidative phosphorylation, thereby enhancing the antineoplastic consequences of kinase inhibition.

However, there are important gaps in knowledge that must be addressed before the design of clinical trials to evaluate biguanide 'repurposing' can be optimized. A key issue for many repurposing studies is pharmacokinetics. Most laboratory models that demonstrate antineoplastic activity of metformin involve concentrations of the drug that are substantially higher than those in the serum of individuals treated for diabetes. Therefore, it is not clear whether conventional oral metformin dosing will achieve adequate drug concentration in neoplastic tissue. Not all metformin is absorbed from the gastrointestinal tract. Evidence for high unabsorbed drug concentration in the colon is provided by data demonstrating increased colon glucose uptake by patients receiving metformin[15]; this is consistent with reduced oxidative phosphorylation by colon epithelial cells on exposure to high luminal metformin concentrations, with a compensatory increase in glucose uptake and glycolysis. Metabolism of hepatocytes is clearly influenced by metformin, in keeping with the facts that these cells not only are exposed to high drug concentrations via the portal circulation following oral dosing but also express high levels of cell surface transport proteins such as OCT1 that are needed for accumulation of the drug[7]. One would anticipate that exposure of transformed cells to metformin could lead to clonal selection for low expression of these transporters. However, such pharmacokinetic challenges can be addressed in several ways: for example, biguanides such as phenformin are less dependent than metformin on active transport for transit into cells. Although these more lipophilic biguanides are too toxic for routine diabetes treatment, their risks would be lower than those of most currently used cancer drugs and justifiable if they provided substantial benefit.

Given the results seen by Birsoy *et al.*[13], careful patient selection will probably be a feature of well-designed clinical trials. If the direct mechanism is important, patients who have cancers with complex I mutations may have the most to gain[13]. For clinical exploitation of the proposed 'indirect' mechanism of action of metformin on cancer, it must be recalled that although some cancers are sensitive to insulin, others are not, and for these, reduction of insulin levels would be irrelevant. Furthermore, the retrospective pharmacoepidemiologic evidence for an antineoplastic activity of metformin was based on hyperinsulinemic patients with diabetes, where the magnitude of metformin-induced declines in insulin is higher than that in metabolically normal subjects. On the other hand, it is now recognized that certain cancer therapies cause hyperinsulinemia that may attenuate their efficacy. These include androgen-targeting treatments for prostate cancer and most PI3K inhibitors used for solid tumors. This provides a specific rationale for studies of these agents in combination with biguanides.

Current research continues to advance understanding of the mechanisms of action relevant to the established indications of many drugs considered to be candidates for repurposing. This is particularly true for biguanides. It will be important to determine, for example, whether inhibition of mitochondrial glycerophosphate dehydrogenase, recently reported to be involved in suppression of hepatic gluconeogenesis by metformin[16], also occurs in cancer cells exposed to achievable drug concentrations.

Exploration of the possibility that metformin might have a new role in cancer treatment shows how drug-repurposing research may be more challenging than it first appears. The simplest kind of 'home run' in repurposing research would be a clinical trial demonstrating that a drug useful for one indication is effective for treating another illness at the same dose and route of administration. However, definition of the precise context in which repurposing of an agent would be most useful in the clinic may require initial laboratory investigations to guide optimum clinical trial design. Although more than 100 trials of metformin in oncology are ongoing, most of these will test only the home-run hypothesis. Negative results of first-generation trials would not rule out the possibility of clinical utility of rational drug combinations or of metformin derivatives with pharmacokinetics optimized for oncologic indications, nor the possibility of benefits confined to subsets of patients defined by specific host or tumor characteristics. It is to be anticipated that in some cases, a repurposing hypothesis may be valid but only demonstrated in the clinic if attention is given to these issues.

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