Metformin and Pancreatic Cancer: A Clue Requiring Investigation

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Laboratory models show antineoplastic activity of metformin under certain conditions, and pharmacoepidemiologic studies have reported reduced cancer burden among diabetics taking metformin. Therefore, the hypothesis that metformin has antineoplastic activity is receiving increasing attention. However, gaps in knowledge must be addressed before metformin can be "repurposed" for oncologic indications. *Clin*

In this issue of *Clinical Cancer Research*, Sadeghi and colleagues (1) report on a retrospective study involving diabetic patients with pancreatic cancer and observe improved survival with use of metformin as diabetes treatment. Do the observations demonstrate that metformin has antineoplastic activity? No. Do the observations justify further research regarding this hypothesis? Clearly, yes. As the authors point out, this kind of retrospective study cannot establish a causal relationship between exposure to metformin and improved survival, due in part to the problem of "confounding by indication". Of the diabetic pancreatic cancer patients studied, some were treated with metformin and some with other agents, but this was not a randomized decision. We cannot exclude the possibility that patient characteristics that lead to a decision to treat diabetes with metformin rather than another agent are associated with a relatively favorable pancreatic cancer prognosis. In such a situation, metformin use would be associated with favorable outcome but not be responsible for it.

Diabetes is associated with pancreatic cancer more frequently than would be expected by chance alone, but the basis of this association remains an active research topic (2). The simplistic view that the association can be accounted for by destruction of pancreatic β cells by the neoplasm is not consistent with all the available data, and there is evidence for secretion by some pancreatic cancers of a soluble factor that increases insulin resistance, causing hyperglycemia (2). Whatever the mechanism, it is possible that more aggressive pancreatic cancers are associated with more severe diabetes, and that this leads to a decision to use an antidiabetic regimen that is likewise more aggressive than metformin. In this situation, better outcome is associated with metformin use but not attributable to metformin.

However, the story should not end with this consideration of the limitations of the methods employed. The fact that we cannot be certain that the association of metformin use with improved pancreatic cancer survival is causal does not demonstrate that metformin is without antineoplastic activity. Especially in pancreatic cancer, where the clinical need for improved therapies is extreme, it would be an error to fail to follow up the clue provided by the study of Sadeghi and colleagues (1). This is particularly true because completely independent laboratory studies provide biologic plausibility of antineoplastic activity of metformin and related biguanides (3).

Mechanisms by which metformin could influence neoplastic growth have recently been reviewed (3) and are depicted in Fig. 1. It is of interest that although this agent has been widely used in diabetes treatment for decades, key aspects of its mode of action for this indication have only recently been elucidated. Partial overlap may exist between the mechanisms established to contribute to antidiabetic properties and those speculated to underlie any antineoplastic activity the compound may have.

Most proposed mechanisms of metformin and other biguanides can be attributed to a primary action of the drug as a weak inhibitor of respiratory complex I of the mitochondria (4). Complex I is required for mitochondrial ATP generation, consumes NADH, and generates reactive oxygen species (ROS); thus, cells exposed to sufficient concentrations of metformin show reduced ATP levels, altered NAD^+/NADH ratio in mitochondria, and at least in some experimental systems, reduced ROS production (5). It is critical to consider cellular and whole-organism pharmacokinetic factors that determine where these actions occur *in vivo*. Following oral ingestion, the portion of metformin that is absorbed is delivered to the liver via the portal circulation, so this organ is exposed to a higher

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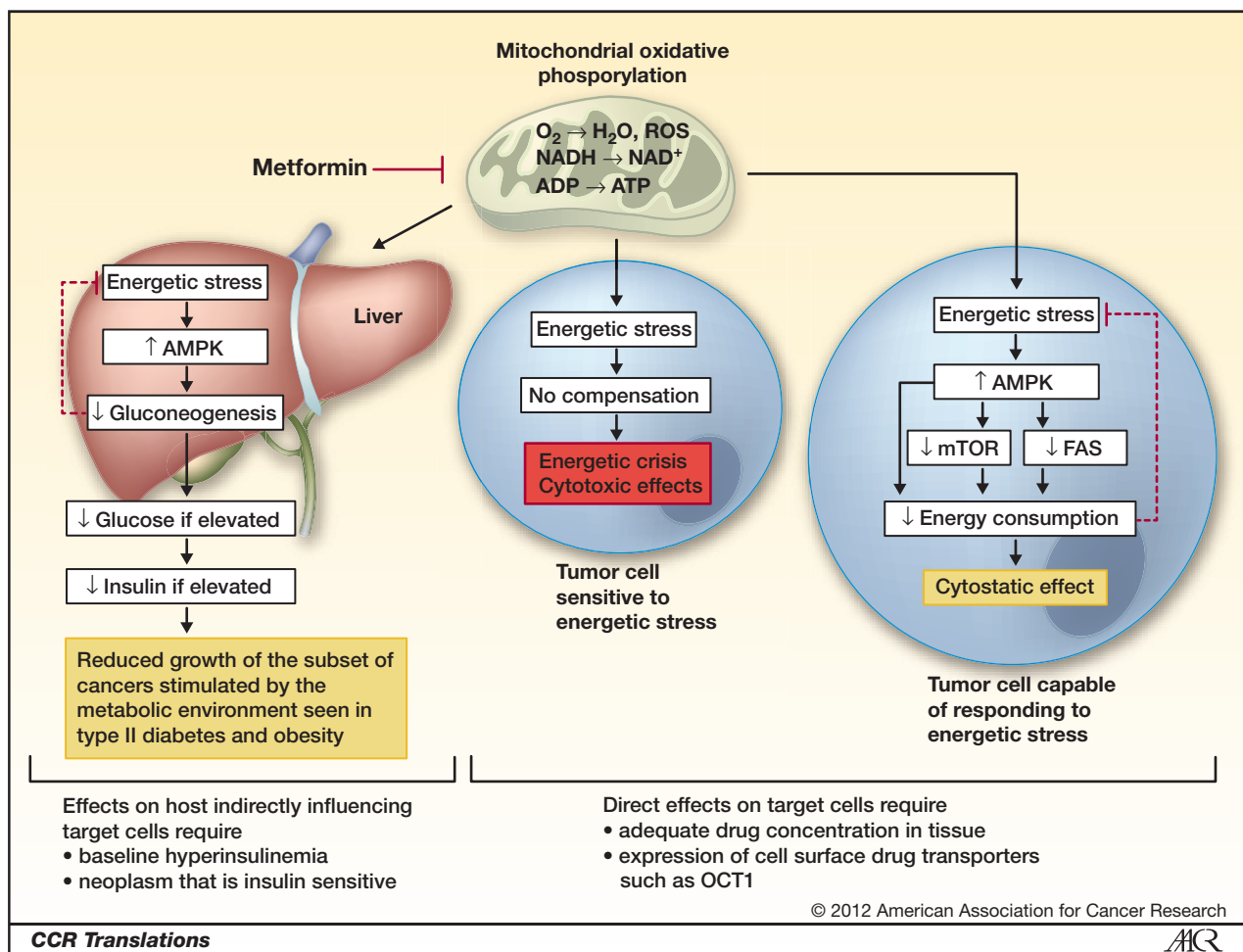
Figure 1. Proposed mechanisms of metformin action as an antineoplastic agent. Dozens of mechanisms have been proposed, with key examples shown here. A fundamental action of the drug is to reduce mitochondrial oxidative phosphorylation, and this can alter the host metabolic environment in ways that influence target cells, even if the target cells are not exposed to an effective concentration of the compound. An example of this indirect action of metformin involves the liver, and this action is also important in the antidiabetic action of the drug. Metformin-induced energy stress inhibits hepatic gluconeogenesis, which represents the export of energy (as glucose) from the liver. This ameliorates the energetic stress of the hepatocyte but also lowers circulating glucose levels, causing a fall in insulin levels (provided insulin is elevated at baseline, which is often the case in type II diabetes or obesity). This can have a cytostatic effect on the subset of tumors that thrive in a high-insulin environment. Similar processes have been proposed for hormones other than insulin. In contrast, metformin may also act directly on target cells, provided that whole-organism and cellular pharmacokinetic conditions are satisfied. Normal cells and some transformed cells are able to cope with the modest degree of energy stress induced by metformin, in part by reducing, in an AMPK-dependent fashion, energy-consuming biosynthetic functions such as protein synthesis (via AMPK-dependent mTOR inhibition) and lipid synthesis (via AMPK-dependent FAS inhibition). This relieves the energetic stress but obliges the cell to adopt the restrictions of a "low-energy" lifestyle, leading to a cytostatic effect. In contrast, certain tumors have defects that make them incapable of compensating for the energetic stress induced by metformin, leading to a cytotoxic effect on the tumor, with no important effect on the host and a favorable therapeutic index. Pharmacokinetic properties of metformin may not be optimal for the "direct" mechanisms, and in this sense it may be regarded as a "lead compound" requiring optimization. Phenformin is an example of a biguanide that may have pharmacokinetic advantages over metformin for certain indications.

concentration than most of the body. Furthermore, hepatocytes express OCT1, a transport molecule that facilitates cellular uptake of metformin. Thus, the liver is an important site of metformin action, and this organ is important in its antidiabetic activity.

What are the consequences of metformin-induced inhibition of oxidative phosphorylation in the liver? The decline in oxidative phosphorylation leads to a decrease in mitochondrial ATP production, which triggers the activation of AMPK, a cellular "energy thermostat" that plays a key role in regulating energy metabolism (6).

Activation of AMPK downregulates energy consuming processes and upregulates processes that facilitate generation of ATP, such as glucose uptake. A major process by which hepatocytes consume energy is by exporting it to the circulation as glucose, and this is inhibited by metformin (7). This process, known as gluconeogenesis, plays a key role in blood glucose homeostasis. In type II diabetes, excessive gluconeogenesis contributes to hyperglycemia. By reducing gluconeogenesis, and stimulating cellular glucose uptake, metformin lowers the hyperglycemia of type II diabetes. This reduction, in turn,

allows normalization of the hyperinsulinemia that is a consequence of insulin resistance and hyperglycemia. These actions of metformin may be sufficient to reduce proliferation of the subset of cancers that proliferate more aggressively in a high insulin environment (8, 9). Interestingly, this mechanism does not require metformin to have access to neoplastic cells; by acting on the liver, metformin alters the metabolic environment in a way that could have an inhibitory effect on a subset of cancers. It is also important to note that this mechanism is unlikely to operate in patients who do not show metabolic abnormalities at baseline, because metformin does not lower glucose or insulin levels unless they are elevated, and even among patients who are hyperinsulinemic, metformin is unlikely to affect cancers with PTEN loss or phosphoinositide 3-kinase–activating mutations, either of which would be expected to remove any growth advantage associated with hyperinsulinemia.

"Direct" actions of metformin that require uptake of the drug by neoplastic cells have been described (3), but it is unclear if these operate *in vivo*, as there are gaps in knowledge concerning metformin pharmacokinetics. Some tumors do not express the required transport molecules, and for these cancers, it is unlikely that metformin would accumulate to a concentration that would allow for direct action following conventional doses used in diabetes treatment. However, other biguanides, such as phenformin, have less stringent requirements for active transport and may have more favorable tissue distribution.

Among the many direct effects of metformin that arise in a cell-autonomous fashion as a consequence of inhibition of oxidative phosphorylation by metformin are inhibition of mTOR and fatty acid synthase, both of which are mediated by AMPK activation, and lead to a predominantly cytostatic effect (3). A direct cytotoxic effect related to an energetic crisis caused by metformin in those cancers where mutations such as loss of LKB1 or p53 impairs their ability to constrain energy consumption when mitochondrial ATP production falls is of particular interest (10).

In sum, we have clinical, pharmacologic, and biologic clues concerning potential roles for biguanides in cancer prevention or treatment and hypotheses concerning both host and tumor characteristics that may identify situations where these drugs are most likely to be of value. Clinical trials that simply use metformin at antidiabetic doses in unselected cancer patients may or may not reveal benefit, so carefully designed preclinical and clinical studies are needed for rigorous investigation of important details. Whether or not metformin has activity as a single agent, rational combinations need study, including synthetic lethality approaches that exploit metabolic vulnerabilities of neoplastic cells (11). Perhaps metformin will show utility at conventional antidiabetic doses, but it is possible that metformin should be regarded as a lead compound requiring pharmacologic optimization for oncologic indications, for example by improving accumulation in neoplastic tissue. This will be an exciting dossier in "repurposing" research (12), but the complexities must not be underestimated.

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