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Commentary

Mysterious Metformin

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Patients with diabetes are at a higher risk for cancer. Numerous meta-analyses have demonstrated that they have a higher incidence of cancers of the liver [1], pancreas [2], endometrium [3], breast [4], colon [5], and bladder [6], and non-Hodgkin's lymphoma [7], with a relative risk in the range of 1.2–2.5. Potential mechanisms to explain this greater risk include the mitogenic effects of insulin (baseline hyperinsulinemia, exogenous insulin) and underlying metabolic abnormalities such as increased oxidative stress, hyperglycemia, hyperlipidemia, and obesity [8]. When diabetic patients get cancer, the prognosis is unfavorable compared with nondiabetics. A recent meta-analysis found a 1.4-fold higher risk for all-cause mortality for diabetic subjects [9].

A surprising finding in recent epidemiological studies was that metformin (Fig. 1) lowers the risk for several types of cancer in type II diabetics (Table 1). A case–control study of patients in Scotland showed that metformin usage decreased the risk for any cancer diagnosis [10]. The authors identified a dose–response relationship between higher metformin use, duration of use, number of prescriptions, and amount dispensed and lower rates of cancer [10]. A follow-up cohort study among new metformin users with type II diabetes over a 10-year period revealed a 37% lower adjusted incidence of cancer, with one less cancer per 23 patients treated with metformin [11, 12]. Compared with sulfonylureas and insulin, metformin was linked to either a lower cancer incidence or lower mortality in two studies, although sulfonylurea-treated patients were older than metformin-treated subjects in both studies [13, 14]. The apparent protective effect of metformin has been demonstrated in pancreatic and prostate cancer as well [15, 16].

It remains unclear whether metformin exerts an actual protective effect, blocks a potential mitogenic property of insulin, or is primarily used in patients with less severe diabetes. Controversy erupted recently over claims that insulin glargine may raise the risk for cancer over that seen with other insulins [17, 18] and metformin [13]. These reports were criticized as methodologically flawed [19], and other studies failed to show a specific greater risk with insulin glargine than with other insulins [20, 21]. (For a detailed cogent analysis of this controversy, see Ehninger and Schmidt [22] and the perceptive commentary by de Miguel-Yanes and Meigs [23].)

Not only have epidemiological studies indicated a cancer-preventive effect of metformin, but there has emerged intriguing evidence that metformin may enhance chemotherapy for established tumors. In a study of diabetic, early-stage breast cancer patients treated with neoadjuvant chemotherapy, metformin users had a higher pathologic

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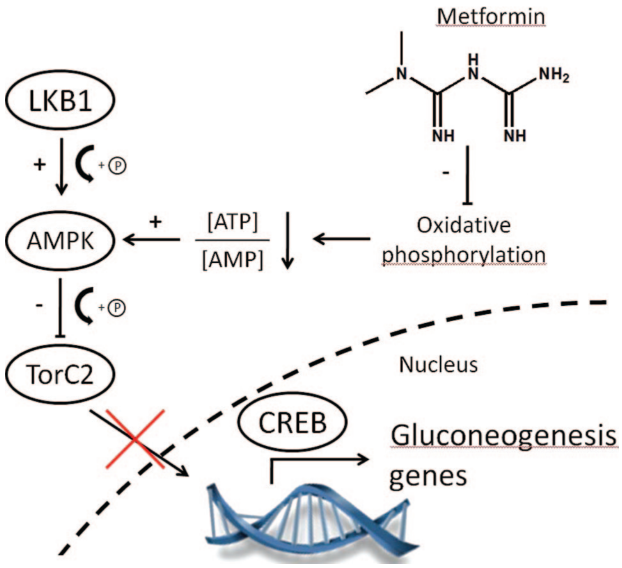

Figure 1. Mechanism of metformin action in diabetes. Metformin is thought to partially inhibit oxidative phosphorylation, altering the ATP–AMP ratio [28]. This activates AMP kinase (AMPK), which phosphorylates TorC2, blocking its nuclear translocation and transcription of genes involved in gluconeogenesis [29]. The kinase and tumor suppressor LKB1 is essential for the activity of AMPK [32].

Abbreviation: CREB, cAMP-response element binding protein.

complete response rate, defined as the absence of invasive carcinoma of the breast or axillary lymph nodes at the time of surgery [22]. The idea that metformin may somehow protect against cancer has led to initiation of ongoing clinical trials of metformin in breast cancer treatment and prevention [25, 26].

How might metformin exert its mysterious effects in both diabetes and cancer? In 2001, Zhou and colleagues found that metformin indirectly activates AMP kinase, a key sensor of the balance of cellular ATP and AMP concentrations [27]; this activation of AMP kinase possibly results from the drug's partial inhibition of the mitochondrial respiratory chain (Fig. 1) [28]. Once activated, AMP kinase phosphorylates the transcriptional activator TorC2, blocking its nuclear translocation and inhibiting expression of genes involved in gluconeogenesis [29]. This mechanism is thought to underlie the ability of metformin to lower glucose and insulin levels, explaining its therapeutic effect in diabetes [30]. There is evidence that AMP kinase may play a role in tumor suppression. AMP kinase is activated by the product of the Peutz-Jegher tumor suppressor gene *LKB1*. Loss of *LKB1* function is a frequent finding in lung adenocarcinoma and squamous cell carcinomas [31]. Mice deficient in hepatic LKB1 develop hyperglycemia and are resistant to the glucose-lowering effects of metformin [32].

Table 1. Studies showing metformin reduces cancer risk in type II diabetics

Type of study	Subjects	Findings
Case–control [10]	11,876 patients newly diagnosed with type II diabetes in Scotland in 1993–2001	Patients who took metformin during the 8-year study period had a lower risk for hospital admissions for cancer (adjusted odds ratio, 0.77). A dose–response effect was observed for duration of metformin treatment and number of prescriptions/ total amount of metformin dispensed.
Observational cohort [12]	4,085 type II diabetics in Scotland treated with metformin compared with diabetic comparators who never used the drug in 1994–2003	Cancer diagnosed in 7.3% of metformin users versus 11.6% of controls, adjusted for age, body mass index, smoking status, A1c.
Case–control [15]	973 patients with pancreatic adenocarcinoma and 863 controls in Texas in 2004–2008	Diabetic patients treated with metformin had a lower risk for pancreatic cancer (odds ratio, 0.38).
Case–control [16]	1,001 prostate cancer patients and 942 controls in Washington state in 2002–2005	Metformin use was associated with a 44% lower risk for prostate cancer, although the adjusted odds ratio was 0.56 with a 95% confidence interval of 0.32–1.0.
Retrospective cohort [14]	10,309 patients treated with metformin or sulfonylureas in 1991–1996 in Saskatchewan	Sulfonylurea and insulin users had a higher cancer mortality (hazard ratio, 1.3 and 1.9, respectively). Confounding factors include insulin use associated with more severe disease.
Retrospective cohort [24]	2,529 patients with early-stage breast cancer receiving neoadjuvant chemotherapy in 1990–2007	Metformin users had a 24% pathologic complete response rate, compared with 8% of diabetics not on metformin. No differences in disease recurrence or overall survival were observed.
Retrospective cohort [13]	62,809 diabetics in the U.K. treated with metformin, sulfonylureas, and insulin	Metformin decreased the risk for colon or pancreatic cancer but not breast or prostate cancer. The combination of metformin with insulin reversed the higher rates of malignancy.

The involvement of a tumor suppressor pathway as a target for metformin's action in glucose homeostasis prompted studies of possible effects in tumor cells and animal cancer models. Metformin exerts in vitro inhibition of the proliferation of prostate [33], ovarian [34], and breast [35–37] cancer cells. This inhibitory effect is seen, however, at concentrations ($\geq$100–500 μM) that are at least tenfold higher than the peak plasma concentration attained with typical dosing in diabetics ($\sim$10 μM) [38]. Mouse xenograft models demonstrate in vivo antitumor effects of metformin against pancreatic [39], prostate [33], and *p53* mutant colon [40] cancers. Metformin delays the onset of tumors in mice deficient in the PTEN tumor suppressor [41] and prevents pancreatic cancer in hamsters fed a high-fat diet and exposed to a pancreatic carcinogen [42].

The discovery that metformin selectively kills cancer stem cells adds further interest and may explain its antineoplastic properties. Hirsch and colleagues genetically manipulated human breast epithelial cells to enrich for stem cells, and tested these along with three distinct breast tumor cell lines [43]. Using flow cytometry to track the effects of metformin, researchers found that the drug is selectively toxic to cancer stem cells. Whereas the lowest concentration of metformin tested in vitro on stem cells (100 μM) is considerably less than the concentration used in other in vitro studies, it is still at least tenfold above the steady-state concentrations achieved with typical dosing in diabetics ($\sim$10 μM) [38]. To test metformin's action in vivo, mice were implanted with transformed mammary epithelial cells and treated with three cycles of metformin and with the anthracycline doxorubicin. When combined with doxorubicin, metformin wiped out tumors and prevented recurrence. Metformin alone had no effect, and doxorubicin as a single agent initially shrank tumors but they later regrew. Virtually no cancer stem cells were recovered immediately after treatment, and the complete response was sustained for nearly 2 months. Further studies will delineate whether the AMP kinase pathway is important in cancer stem cells, and if the synergistic effect of metformin and anthracyclines is generalized to other types of cancer and to its combination with other drugs.

Metformin is a relative of isoamylene guanidine, the active ingredient in the French lilac (*Galega officinalis*), used for centuries to treat polyuria in diabetics [44]. The related compounds phenformin and buformin were withdrawn from clinical use in the 1970s after association with lactic acidosis [45], which occurs much less frequently with metformin. The risk–benefit ratio of phenformin or buformin in treating malignancy supports resurrecting these drugs and congeners for preclinical studies on the AMP kinase pathway and cancer stem cells. Metformin is also used to treat polycystic ovary syndrome, by increasing insulin sensitivity [46], and it will be interesting to follow the rate of malignancy in this treatment group. If metformin ultimately helps cancer patients, it will join drugs such as thalidomide, retinoic acid, and arsenic, which have unique, if not exotic, mechanisms of action and were first used elsewhere in medicine but found their way into the arsenal of anticancer drugs.

Author Contributions

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References

1 El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: A systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol 2006;4:369–380.

2 Huxley R, Ansary-Moghaddam A, Berrington de González A et al. Type-II diabetes and pancreatic cancer: A meta-analysis of 36 studies. Br J Cancer 2005;92:2076–2083.

3 Friberg E, Orsini N, Mantzoros CS et al. Diabetes mellitus and risk of endometrial cancer: A meta-analysis. Diabetologia 2007;50:1365–1374.

4 Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: A meta-analysis. Int J Cancer 2007;121:856–862.

5 Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: A meta-analysis. J Natl Cancer Inst 2005;97:1679–1687.

6 Larsson SC, Orsini N, Brismar K et al. Diabetes mellitus and risk of bladder cancer: A meta-analysis. Diabetologia 2006;49:2819–2823.

7 Mitri J, Castillo J, Pittas AG. Diabetes and risk of non-Hodgkin's lymphoma: A meta-analysis of observational studies. Diabetes Care 2008;31: 2391–2397.

8 Vigneri P, Frasca F, Sciacca L et al. Diabetes and cancer. Endocr Relat Cancer 2009;16:1103–1123.

9 Barone BB, Yeh HC, Snyder CF et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: A systematic review and meta-analysis. JAMA 2008;300:2754–2764.

10 Evans JM, Donnelly LA, Emslie-Smith AM et al. Metformin and reduced risk of cancer in diabetic patients. BMJ 2005;330:1304–1305.

11 Duncan BB, Schmidt MI. Metformin, cancer, alphabet soup, and the role of epidemiology in etiologic research. Diabetes Care 2009;32:1748–1750.

12 Libby G, Donnelly LA, Donnan PT et al. New users of metformin are at low risk of incident cancer: A cohort study among people with type 2 diabetes. Diabetes Care 2009;32:1620–1625.

13 Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009;52:1766–1777.

14 Bowker SL, Majumdar SR, Veugelers P et al. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care 2006;29:254–258.

15 Li D, Yeung SC, Hassan MM et al. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology 2009;137:482–488.

16 Wright JL, Stanford JL. Metformin use and prostate cancer in Caucasian men: Results from a population-based case-control study. Cancer Causes Control 2009;20:1617–1622.

17 Jonasson JM, Ljung R, Talbäck M et al. Insulin glargine use and short-term incidence of malignancies—a population-based follow-up study in Sweden. Diabetologia 2009;52:1745–1754.

18 Hemkens LG, Grouven U, Bender R et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: A cohort study. Diabetologia 2009;52:1732–1744.

19 Pocock SJ, Smeeth L. Insulin glargine and malignancy: An unwarranted alarm. Lancet 2009;374:511–513.

20 Rosenstock J, Fonseca V, McGill JB et al. Similar risk of malignancy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: Findings from a 5 year randomised, open-label study. Diabetologia 2009;52:1971–1973.

21 Colhoun HM; SDRN Epidemiology Group. Use of insulin glargine and cancer incidence in Scotland: A study from the Scottish Diabetes Research Network Epidemiology Group. Diabetologia 2009;52:1755–1765.

22 Ehninger G, Schmidt AH. Putting insulin glargine and malignancies into perspective. ***The Oncologist*** 2009;14:1169–1174.

23 de Miguel-Yanes JM, Meigs JB. When "flawed" translates into "flood": The unproven association between cancer incidence and glargine insulin therapy. ***The Oncologist*** 2009;14:1175–1177.

24 Jiralerspong S, Palla SL, Giordano SH et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol 2009;27:3297–3302.

25 Muti P, Berrino F, Krogh V et al. Metformin, diet and breast cancer: An avenue for chemoprevention. Cell Cycle 2009;8:2661.

26 Cazzaniga M, Bonanni B, Guerrieri-Gonzaga A et al. Is it time to test metformin in breast cancer clinical trials? Cancer Epidemiol Biomarkers Prev 2009;18:701–705.

27 Zhou G, Myers R, Li Y et al. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 2001;108:1167–1174.

28 Owen MR, Doran E, Halestrap AP. Evidence that metformin exerts its antidiabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem J 2000;348:607–614.

29 Koo SH, Flechner L, Qi L et al. The CREB coactivator TORC2 is a key regulator of fasting glucose metabolism. Nature 2005;437:1109–1111.

30 Pollak M. Insulin-like growth factor-related signaling and cancer development. Recent Results Cancer Res 2007;174:49–53.

31 Ji H, Ramsey MR, Hayes DN et al. LKB1 modulates lung cancer differentiation and metastasis. Nature 2007;448:807–810.

32 Shaw RJ, Lamia KA, Vasquez D et al. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. Science 2005; 310:1642–1646.

33 Ben Sahra I, Laurent K, Loubat A et al. The antidiabetic drug metformin exerts an antitumoral effect in vitro and in vivo through a decrease of cyclin D1 level. Oncogene 2008;27:3576–3586.

34 Gotlieb WH, Saumet J, Beauchamp MC et al. In vitro metformin antineoplastic activity in epithelial ovarian cancer. Gynecol Oncol 2008;110: 246–250.

35 Zakikhani M, Dowling R, Fantus IG et al. Metformin is an AMP kinase-dependent growth inhibitor for breast cancer cells. Cancer Res 2006;66: 10269–10273.

36 Zhuang Y, Miskimins WK. Cell cycle arrest in metformin treated breast cancer cells involves activation of AMPK, downregulation of cyclin D1, and requires p27Kip1 or p21Cip1. J Mol Signal 2008;3:18.

37 Liu B, Fan Z, Edgerton SM et al. Metformin induces unique biological and molecular responses in triple negative breast cancer cells. Cell Cycle 2009; 8:2031–2040.

38 Glucophage® package insert. Princeton, NJ: Bristol-Myers Squibb, 2009. Available at http://packageinserts.bms.com/pi/pi_glucophage.pdf, accessed December 4, 2009.

39 Kisfalvi K, Eibl G, Sinnett-Smith J et al. Metformin disrupts crosstalk between G protein-coupled receptor and insulin receptor signaling systems and inhibits pancreatic cancer growth. Cancer Res 2009;69:6539–6545.

40 Buzzai M, Jones RG, Amaravadi RK et al. Systemic treatment with the antidiabetic drug metformin selectively impairs p53-deficient tumor cell growth. Cancer Res 2007;67:6745–6752.

41 Huang X, Wullschleger S, Shpiro N et al. Important role of the LKB1-AMPK pathway in suppressing tumorigenesis in PTEN-deficient mice. Biochem J 2008;412:211–221.

42 Schneider MB, Matsuzaki H, Haorah J et al. Prevention of pancreatic cancer induction in hamsters by metformin. Gastroenterology 2001;120:1263–1270.

43 Hirsch HA, Iliopoulos D, Tsichlis PN et al. Metformin selectively targets cancer stem cells, and acts together with chemotherapy to block tumor growth and prolong remission. Cancer Res 2009;69:7507–7511.

44 Witters LA. The blooming of the French lilac. J Clin Invest 2001;108: 1105–1107.

45 Bailey CJ, Turner RC. Metformin. N Engl J Med 1996;334:574–579.

46 Nestler JE. Metformin in the treatment of infertility in polycystic ovarian syndrome: An alternative perspective. Fertil Steril 2008;90:14–16.