NIH Public Access
Author Manuscript
Nature. Author manuscript; available in PMC 2014 November 19.

Published in final edited form as:
Nature. 2011 February 17; 470(7334): 338–339. doi:10.1038/470338a.

Genomics: Drugs, diabetes and cancer

Morris J. Birnbaum[1] and **Reuben J. Shaw**[2]

[1]University of Pennsylvania Medical School, Philadelphia, PA 19104-6148, USA

[2]Salk Institute for Biological Studies, Molecular and Cell Biology Laboratory, 10010 N. Torrey Pines Road, La Jolla, 92037 CA, USA

Summary

Variation in a genomic region that contains the cancer-a ssociated gene ATM affects a patient's response to the diabetes drug metformin. Two experts discuss the implications for understanding diabetes and the link to cancer.

A clue to metformin action, Morris J. Birnbaum

Let me start on a positive note. The genetic association between *ATM* and metformin sensitivity[1] represents a triumph of modern pharmacogenetics, and it is reasonable to hope that it will lead to fundamental insights into metformin's mechanism of action and the regulation of carbohydrate metabolism.

You might ask how a rare variation linked to *ATM* could possibly be related to the treatment of a common disease such as diabetes. After all, given the prevalence of diabetes, it would be reasonable to assume that it takes only slight disruptions in nutritional intake or energy expenditure to shift the balance between health and metabolic disease.

This is in fact far from the truth. To contract an illness with the serious consequences of type 2 diabetes, not only must there be disturbances in energy balance, but the normal homeostatic mechanisms that regulate metabolism must also be impaired. In other words, if the regulatory system fails to respond to caloric overload, disease ensues. With the relative uniformity of the Western — and increasingly global — lifestyle, a major determinant of susceptibility to type 2 diabetes must therefore be an individual's genetic make-up, which dictates the response to nutritional overload or therapeutic intervention.

Metformin works mainly by reducing glucose production by the liver, but there is still uncertainty about its mechanism of action at a molecular level. The drug blocks a step in the aerobic production of the cellular energy molecule ATP, activating a signalling pathway in which the enzyme AMPK senses energetic stress within the cell. Nonetheless, despite activating AMPK, metformin actually works independently of the enzyme[2,3]. The discovery of a role for *ATM* in modulating metformin responsiveness might provide a clue to the mechanism of action of this drug.

Unfortunately, however, it could equally well be a false lead. Classic genetic screens have taught us that some candidate genes can exert very indirect effects, providing little information about crucial signalling pathways. For example, variations in another gene also

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

affect metformin responsiveness, but that gene's product, OCT1, influences the rate of uptake of metformin by cells, rather than any major signalling pathway[4].

Another possibility is that ATM influences blood glucose levels through pathways parallel to — but not the same as — those modulated by metformin, and that its effects become apparent only with synergistic input from the drug. Indeed, 40 years ago, it was noted 5 that patients with ataxia telangiectasia often display a type-2-diabetes-like syndrome characterized by an insulin resistance too severe to be caused just by changes in liver glucose production.

With the genetic clues now to hand, careful biochemical and cell-biological studies should be performed to figure out the nature of the interaction between *ATM* and the beneficial effects of metformin. Most crucial will be to find out whether there are other molecules, apart from AMPK, that both control metabolism and are influenced by *ATM*.

The cancer connection, Reuben J. Shaw

A tumour-suppressor protein that mediates DNA repair and has ties with a metabolic disorder[1] — this might sound far-fetched. But in fact the reported link between responsiveness to metformin and a cancer gene is not without precedent.

Previous work has shown that activation of AMPK by metformin requires the activity of the kinase enzyme LKB1. The gene encoding LKB1 was originally identified for causing an inherited cancer disorder, and is one of the most commonly mutated genes in human lung cancer[6]. Animal studies also point to a role for this gene in a variety of spontaneously arising cancers. Notably, deletion of Lkb1 in mouse liver leads to loss of AMPK activity in that organ and to the development of metabolic dysfunction, including hyperglycaemia and hepatic steatosis — symptoms resembling those of type 2 diabetes[7]. Furthermore, a genetic survey revealed that DNA-base variations in LKB1 affect how women with polycystic ovary syndrome respond to treatment with metformin[8].

The fact that the present study (the first GWAS to find a locus that 'dictates' metformin response) has identified a possible role for ATM — which is also a kinase enzyme — could fit in with several earlier observations. For instance, patients with ataxia telangiectasia show insulin resistance and are at a higher risk of developing diabetes, and mice with defective ATM activity show insulin resistance and abnormal glucose homeostasis[9].

How might ATM be involved at a molecular level? The present work[1] hypothesizes that this enzyme modulates patients' responsiveness to metformin by affecting the drug's ability to activate AMPK. Indeed, ATM is known to phosphorylate LKB1 — AMPK's key activator[10, 11] — thereby affecting various cellular processes. ATM might also regulate AMPK independently of LKB1. Furthermore, it may affect metformin responsiveness by regulating other relevant targets that are independent of AMPK (Fig. 1). Indeed, ATM is known to phosphorylate other components of the insulin signalling pathway[12, 13].

In light of these intriguing connections, it is essential to rigorously examine whether the rs11212617 variant serves to modulate ATM activity, towards AMPK activation or that of

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

other downstream targets. From the present data, it is not clear whether ATM activity is even perturbed by this variant.

As for metformin's relevance to cancer therapy, patients with diabetes who take this drug have a lower risk of developing cancer than those on other anti-diabetes medications[14]. Whether metformin is a general activator of ATM and its targets in the DNA-damage-response pathway should therefore be thoroughly investigated. Although LKB1 and AMPK are good candidates for mediating some of the beneficial effects of metformin on cancer risk, the involvement of the broader tumour-suppressor pathways controlled by ATM is an intriguing possibility. Future studies dissecting the relationship between metformin action, ATM, LKB1 and AMPK should shed light on the intersection between suppression of the risk of cancer and that of diabetes.

References

1. Zhou K, Bellenguez C, Spencer CC, Bennett AJ, Coleman RL, Tavendale R, Hawley SA, Donnelly LA, Schofield C, Groves CJ, Burch L, Carr F, Strange A, Freeman C, Blackwell JM, Bramon E, Brown MA, Casas JP, Corvin A, Craddock N, Deloukas P, Dronov S, Duncanson A, Edkins S, Gray E, Hunt S, Jankowski J, Langford C, Markus HS, Mathew CG, Plomin R, Rautanen A, Sawcer SJ, Samani NJ, Trembath R, Viswanathan AC, Wood NW, investigators, M. Harries LW, Hattersley AT, Doney AS, Colhoun H, Morris AD, Sutherland C, Hardie DG, Peltonen L, McCarthy MI, Holman RR, Palmer CN, Donnelly P, Pearson ER. GoDarts, Group, U.D.P.S., Wellcome Trust Case Control, C. Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes. Nat Genet. 2011; 43:117–120. [PubMed: 21186350]
2. Foretz M, Hebrard S, Leclerc J, Zarrinpashneh E, Soty M, Mithieux G, Sakamoto K, Andreelli F, Viollet B. Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway via a decrease in hepatic energy state. J Clin Invest. 2010; 120:2355–2369. [PubMed: 20577053]
3. Miller RA, Birnbaum MJ. An energetic tale of AMPK-independent effects of metformin. J Clin Invest. 2010; 120:2267–2270. [PubMed: 20577046]
4. Shu Y, Brown C, Castro RA, Shi RJ, Lin ET, Owen RP, Sheardown SA, Yue L, Burchard EG, Brett CM, Giacomini KM. Effect of genetic variation in the organic cation transporter 1, OCT1, on metformin pharmacokinetics. Clin Pharmacol Ther. 2008; 83:273–280. [PubMed: 17609683]
5. Schalch DS, McFarlin DE, Barlow MH. An unusual form of diabetes mellitus in ataxia telangiectasia. N Engl J Med. 1970; 282:1396–1402. [PubMed: 4192270]
6. Shackelford DB, Shaw RJ. The LKB1-AMPK pathway: metabolism and growth control in tumour suppression. Nat Rev Cancer. 2009; 9:563–575. [PubMed: 19629071]
7. Shaw RJ, Lamia KA, Vasquez D, Koo SH, Bardeesy N, Depinho RA, Montminy M, Cantley LC. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. Science. 2005; 310:1642–1646. [PubMed: 16308421]
8. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, Steinkampf MP, Coutifaris C, McGovern PG, Cataldo NA, Gosman GG, Nestler JE, Giudice LC, Ewens KG, Spielman RS, Leppert PC, Myers ER. Reproductive Medicine, N. Ovulatory response to treatment of polycystic ovary syndrome is associated with a polymorphism in the STK11 gene. J Clin Endocrinol Metab. 2008; 93:792–800. [PubMed: 18000088]
9. Schneider JG, Finck BN, Ren J, Standley KN, Takagi M, Maclean KH, Bernal-Mizrachi C, Muslin AJ, Kastan MB, Semenkovich CF. ATM-dependent suppression of stress signaling reduces vascular disease in metabolic syndrome. Cell Metab. 2006; 4:377–389. [PubMed: 17084711]
10. Sapkota GP, Deak M, Kieloch A, Morrice N, Goodarzi AA, Smythe C, Shiloh Y, Lees-Miller SP, Alessi DR. Ionizing radiation induces ataxia telangiectasia mutated kinase (ATM)-mediated phosphorylation of LKB1/STK11 at Thr-366. Biochem J. 2002; 368:507–516. [PubMed: 12234250]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

11. Sherman MH, Kuraishy AI, Deshpande C, Hong JS, Cacalano NA, Gatti RA, Manis JP, Damore MA, Pellegrini M, Teitell MA. AID-induced genotoxic stress promotes B cell differentiation in the germinal center via ATM and LKB1 signaling. Mol Cell. 2010; 39:873–885. [PubMed: 20864035]
12. Yang DQ, Kastan MB. Participation of ATM in insulin signalling through phosphorylation of eIF-4E-binding protein 1. Nat Cell Biol. 2000; 2:893–898. [PubMed: 11146653]
13. Matsuoka S, Ballif BA, Smogorzewska A, McDonald ER 3rd, Hurov KE, Luo J, Bakalarski CE, Zhao Z, Solimini N, Lerenthal Y, Shiloh Y, Gygi SP, Elledge SJ. ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage. Science. 2007; 316:1160–1166. [PubMed: 17525332]
14. Pollak M. Metformin and other biguanides in oncology: advancing the research agenda. Cancer Prev Res (Phila). 2010; 3:1060–1065. [PubMed: 20810670]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

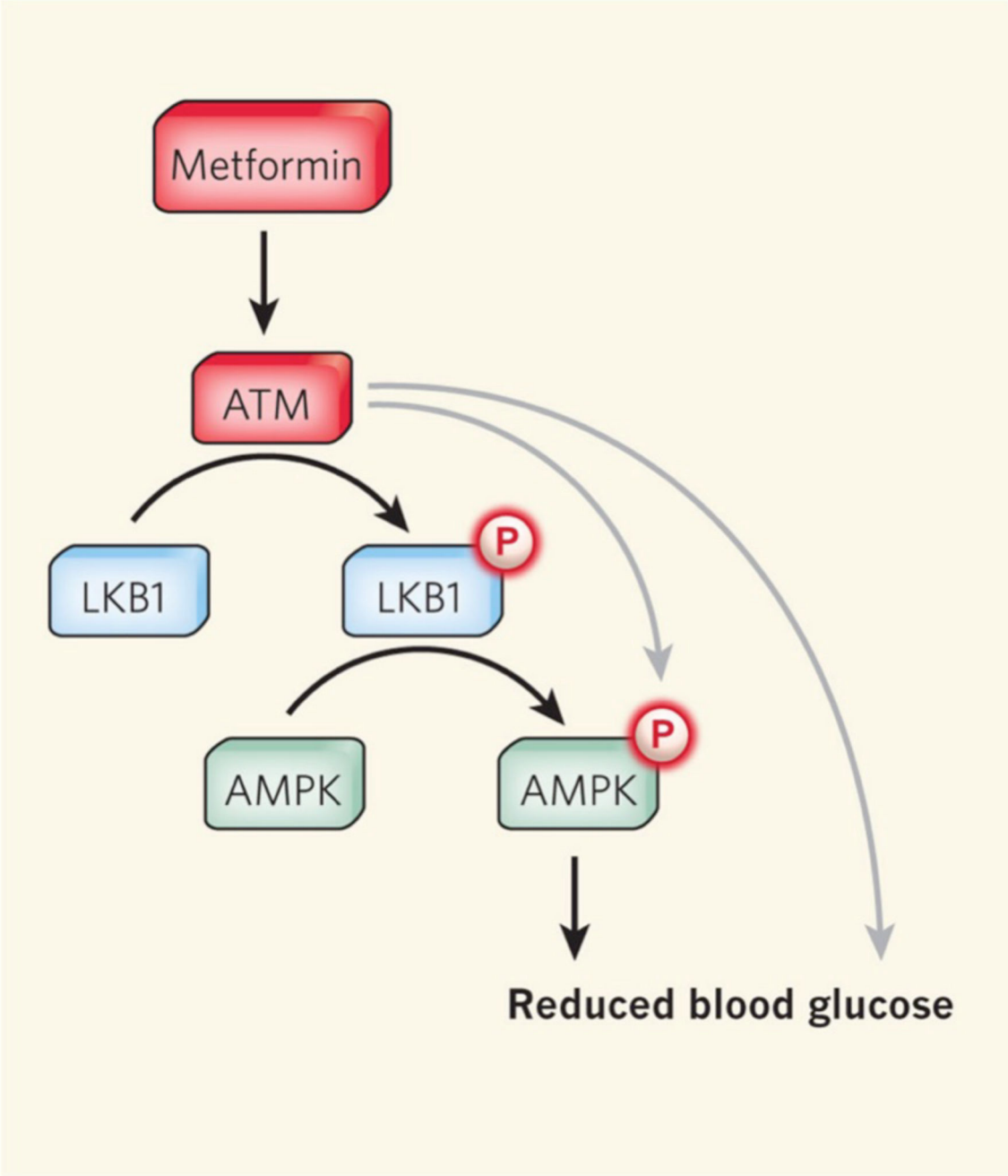

Figure 1. Possible mechanisms of the anti-diabetic effects of ATM

In response to metformin, ATM could mediate the phosphorylation (P), and so the activation, of AMPK by phosphorylating LKB1. Alternatively, ATM might activate AMPK independently of LKB1, or reduce blood glucose levels through pathways entirely independent of AMPK.