FORUM Genomics

Drugs, diabetes and cancer

Variation in a genomic region that contains the cancer-associated 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.

THE PAPER IN BRIEF

- The authors[1] analyse genomic variation among a large group of patients who respond differently to metformin — the most commonly used drug for treating type 2 diabetes.
- This genome-wide association study (GWAS) involved 1,024 Scottish patients, as well as a further 2,896 patients to check for replication of the results.
- Treatment success was significantly linked to the presence of a single nucleotide-base variation designated rs11212617.
- This variation occurs in a genomic region (locus) that also contains the gene *ATM*. *ATM* encodes a tumour-suppressor protein involved in DNA repair and cell-cycle control that is mutated in ataxia telangiectasia, a neurodegenerative disease associated with a predisposition to cancer.
- The authors further show, in a rat cancer cell line, that inhibition of *ATM* weakens metformin-mediated activation of a metabolic enzyme, AMPK.

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 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*.

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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

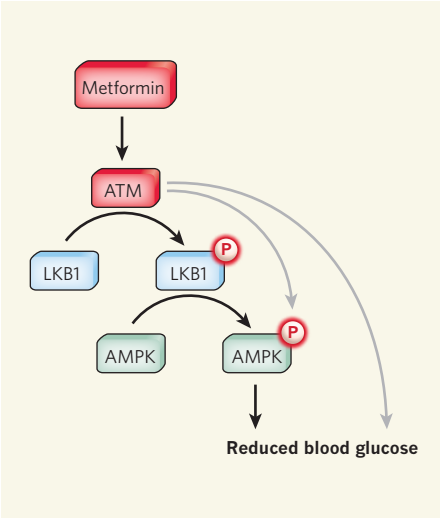

Figure 1 | Possible mechanisms of the anti-diabetic effects of ATM. In response to metformin, ATM could mediate the phosphorylation (P), and so the activation, of AMPK by phosphorylating LKB1. Alternatively, ATM might activate AMPK independently of LKB1, or reduce blood glucose levels through pathways entirely independent of AMPK.

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 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. ■

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EVOLUTIONARY BIOLOGY

When life got big

Deposits in China dating to about 600 million years ago contain carbon compressions of algae and other organisms. The fossils provide a new window into the early evolution of complex multicellular life. SEE LETTER P.390

GUY M. NARBONNE

The Ediacaran period (635 million to 542 million years ago) represents a watershed in the history of life, when 'life got big' after nearly 3 billion years of microbial evolution[1]. The early fossil record of large, architecturally complex, multicellular life has generally been regarded as starting with the Avalon assemblage of the Ediacara biota, known from Newfoundland, England and northwest Canada. The assemblage consists of centimetre- to metre-scale impressions of soft-bodied, fractal organisms (rangeomorphs) that first appeared 579 million years ago and dominated deep-water environments throughout the latter half of the Ediacaran[2]. On page 390 of this issue, Yuan and colleagues[3] describe centimetre-scale algal compressions and other fossils from the early Ediacaran. They provide both a different fossil search-image and a probable extension of the oldest record of macroscopic and morphologically complex life.

The fossils occur in huge numbers as carbon compressions on bedding surfaces in black shales in the Lantian Formation of southern China. Many of the fossils show branching patterns and other features typical of macroscopic fleshy algae, some of them comparable with modern kelp. Yuan *et al.* informally compare other examples of the fossils to cnidarians and bilaterian worms, but more work is needed before such connections can be established firmly.

The Lantian biota was discovered more than a decade ago, but in the absence of definitive age indicators it was originally regarded as correlating with the Miaohe biota of central China (now dated at 551 million years old[4]). Revision of its age by Yuan and colleagues substantially increases its importance. The Lantian succession is highly condensed, with less than 150 metres of strata representing more than 90 million years, requiring great care in identifying subdivisions and correlations. Setting this caveat aside, new carbon-isotope data permit robust correlations that imply that the Lantian biota is much older than previously thought, probably between 577 million and 635 million years old.

The younger part of this range is indistinguishable from the 579-million-year date for the oldest occurrence of the Avalon assemblage of the Ediacara biota, and would suggest that complex macroscopic multicellularity occurred synchronously in both algae and rangeomorphs at the end of the Gaskiers glaciation 582 million years ago[5]. However, it is more likely that the Lantian algae are older than that, and that they appeared soon after the end of the Marinoan glaciation (635 million years ago[4]). If so, it implies a staggered acquisition of large, complex multicellularity by different groups of Ediacaran life in response to sequential global glaciations and changes in ocean chemistry[6].

The Lantian biota offers a window into early complex multicellularity that superbly complements the view provided by the Avalon assemblage: there is little similarity between them other than their age. They have no taxa in common, possibly even at the kingdom level. Lantian fossils were preserved as carbon compressions that are broadly similar in preservational style to the Burgess Shale and other exceptional fossil deposits of Cambrian