Editorial Commentary

Down-regulation of miR-24 in diabetes: a novel insight into the mechanism of diabetic exacerbation of myocardial ischaemia-reperfusion injury

Robert M. Bell, Derek M. Yellon

Hatter Cardiovascular Institute, University College London, London, UK

Correspondence to: Professor Derek Yellon. Director of the Hatter Cardiovascular Institute, UCL, London, UK. Email: d.yellon@ucl.ac.uk.

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Diabetes is an important cardiovascular risk factor, contributing to the development of arterial atherosclerosis. Consequently, approximately 20% of all patients experiencing an acute coronary syndrome also suffer from this debilitating disorder of glucose homeostasis (1). Unfortunately, diabetes represents much more than a simple cardiovascular risk factor: diabetic patients not only experience more recurrent acute coronary syndromes than non-diabetics, but also suffer larger myocardial infarcts and greater morbidity and mortality, even following expedient and successful percutaneous intervention.

Current clinical management of diabetes to date remains focused upon the most easily measured derangement of normal physiology: hyperglycaemia. Pharmacological interventions have therefore concentrated upon augmenting insulin release, supplementing insulin exogenously or augmenting tissue sensitivity to insulin in an attempt to overcome the evolved insulin resistance characterised by type 2 diabetes mellitus. While this approach is effective in attenuating the microvascular complications of diabetes, until very recently, management of hyperglycaemia alone has proven disappointing in avoiding the macrovascular complications with negligible impact upon cardiovascular outcomes. Moreover, while mortality and morbidity from coronary artery disease has been in decline for the last five decades, this hard-won battle is currently under threat from the worldwide diabetic pandemic. Given the inflationary pressures upon mortality and morbidity posed by diabetes, understanding the mechanisms underlying the interaction between diabetes and cardiovascular disease is essential. Recent favourable data from the clinical outcome trials of sodium-glucose co-transporter (SGLT) inhibition (2,3) and glucagon-like peptide-1 (GLP-1) receptor agonists (4) is a pleasing, if a somewhat unexpected finding; the mechanisms underlying their cardiovascular mortality benefits remain unclear, although a number of mechanisms have been speculated (5). Notwithstanding, identifying the deleterious mechanisms and attempting to break the dangerous circle of diabetes, coronary artery disease and acute myocardial ischaemia resulting from coronary syndromes, and thus identifying potential targets for therapeutic intervention in diabetes beyond pure sugar control, remain an urgent clinical need.

Micro-ribonucleic acids (miRNAs), small 21-23 nucleotide non-coding RNAs, are well recognised in their role in both physiological and pathophysiological processes to control cellular differentiation, proliferation and survival. In the context of myocardial ischaemia-reperfusion injury (6), miRNAs have been widely been shown to impact on pro-cell death pathways (necrosis, apoptosis, pyroptosis, necroptosis) and canonical cardioprotective pathways, including the reperfusion injury salvage (RISK) pathways (PI3K/Akt, MEK/ERK) and survivor activating factor enhancement (SAFE) pathway (Jak/STAT), in either a positive or deleterious fashion, as reviewed (7,8). Similarly, diabetes also impacts miRNA expression in the heart, implicated for example, in the evolution of diabetic cardiomyopathies (9) and cardiovascular disease (10). Interestingly, the detrimental diabetic phenotype is characterised by deleterious regulation of miRNAs that have

the potential to augment myocardial ischaemia-reperfusion injury and down-regulate endogenous cardioprotective mechanisms. In a recent issue of the *Journal of the American College of Cardiology*, Wang *et al.* (11) report of one such diabetes-miRNA interaction that falls into the latter camp. Their principle finding is down-regulation of miR-24 in diabetes, with a consequent exacerbation of myocardial infarct size in *in-vivo* murine heart following injurious ischaemia-reperfusion injury.

miR-24 is part of a primary miRNA cluster comprising of miR-23 and miR-27 on chromosome 9 (9q22.32, miR-24.1) and 19 (19p13.13, miR-24.2), that is highly conserved across mammalian species (12,13). Interestingly, miR-24 has previously been shown to be important in the evolution of adverse remodelling to pressure overload and myocardial injury following ischaemia-reperfusion injury [including after remote ischaemic conditioning (14)], although not always in a beneficial way (15-17). While miR-24 may exacerbate myocardial fibrosis, it also attenuates apoptosis (18-20), and the latter attenuation of cell death may be particularly useful in the context of acute myocardial ischaemia-reperfusion injury. miR-24 expression is also significantly regulated by diabetes, and while there is some controversy in this area, circulating and tissue miR-24 appears suppressed in patients with, and in animal models of type 2 diabetes (21-24) [reviewed (12)].

Wang *et al.* (11) demonstrate, as expected, that myocardial ischaemia-reperfusion injury is exacerbated by diabetes. Interestingly, the largest infarcts were found in the type2 diabetic db/db mice compared to the streptozotocin type1 diabetic animals or controls. Somewhat intriguingly, 28-day post infarct survival was worst in type 2 diabetic animals concomitantly treated with insulin but conversely, insulin therapy had a survival benefit in type 1 diabetic animals. These data suggest that insulin therapy to replace insufficient insulin production is likely beneficial, but detrimental when used under circumstances of high insulin resistance.

Disappointingly, in this study, the authors have not measured the circulating or tissue levels of miR-24 in these diabetic animals to correlate to final infarct size and survival, but they did examine circulating miR-24 in human subjects. In diabetic patients, miR-24 levels were lower in type2 diabetics compared to type 1, and lower still in type 2 subjects treated with insulin. The logical hypothesis from these data is that insulin therapy in type 2 diabetics has the potential to exacerbate myocardial injury through augmented depletion of miR-24. Certainly, despite the encouraging data from the DIAGAMI-1 study (25), subsequent insulin-based interventions designed to manage hyperglycaemia in patients presenting with an acute coronary syndrome, have proven disappointing. Whether the benefits of controlling hyperglycaemia by intensive insulin therapy following myocardial ischaemia-reperfusion are entirely countered by pro-injurious depletion of miR-24 in patients with established type 2 diabetes is unclear, but it does represent an intriguing hypothesis that can be tested.

To demonstrate causality between miR-24 and myocardial resistance to injurious ischaemia-reperfusion injury, the authors adopted two approaches: pharmacological and genetic. Administering exogenous miR-24 to type2 diabetic db/db mice 2-week prior to subjecting the animals to coronary occlusion not only restored tissue miR-24 levels, but also abrogated the excess myocardial injury associated with the type 2 diabetic phenotype. Remarkably, the exogenous miR-24 also led to a fall of circulating glucose and insulin levels, suggesting that miR-24 may have a role in regulating tissue insulin sensitivity.

The genetic manipulation approach applied is interesting: a cardiomyocyte-specific up-regulation of miR-24, thus avoiding whole-body effects of increased tissue expression. Compared to wild-type littermates, over-expression of miR-24 led to a 40% reduction of infarct size. miR-24 has already been associated with the regulation of a large number of important cell-death pathways, including BIM and Bcl-2 (13), but Wang *et al.* (11) also identify additional, novel targets relevant to their diabetic models, including the autophagic pathway regulator, ATG-4a and the O-GlcNAc transfer protein, OTG. Transfection of isolated primary mouse cardiomyocytes with the miR-24-mimic (Ambion mirVana) significantly suppressed expression of BIM, ATG-4a and OTG. Moreover, miR-24 also abrogated the upregulation of OGT by insulin in high-glucose cell culture and, in the miR-24 over-expressing mice, attenuated OGT expression and O-GlcNAcylation in heart lysates.

Thus, Wang *et al.* reveal a novel paradigm of miR-24 suppression in diabetic subjects with concomitant increases in O-GlcNAcylation and dysregulation of pro-death pathways. That these deleterious pathways may potentially be further augmented by insulin therapy in type2 diabetic patients strikes a potentially cautionary note in the management of these patients that deserves further scrutiny. However, it would seem that miR-24 is a potential pharmacological target for future drug development, and it would be fascinating to see whether the recent remarkable improvements in cardiovascular outcomes resulting from

the outcome trials in SGLT2 inhibitors and the GLP-1 receptor agonists are also associated with alterations in miR-24 expression.

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Footnote

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