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EDITORIAL COMMENT

MicroRNA-24 and the Diabetic Heart*



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Patients with diabetes are at risk of vascular complications, leading to cardiovascular, renal, and neurological disease. In this issue of *JACC: Basic to Translational Science*, Wang et al. (1) suggest that impaired infarct healing in diabetics results from a hyperinsulinemia- and hyperglycemia-induced down-regulation of microRNA (miRNA)-24 (miR-24). The authors ascribe the protective effect of miR-24 to repression of protein targets involved in apoptosis, autophagy, and protein O-GlcNAcylation. Raising miR-24 is proposed as a potential therapeutic approach for improving post-infarct healing in patients with type 2 diabetes (T2D).

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In contrast with the absence of a preventative benefit of intense glucose control in a primary prevention setting (2), incident acute myocardial infarction (MI) in diabetic patients is associated with increased subsequent heart failure and mortality (3), both during initial hospitalization and long-term follow-up. However, early enthusiasm for intensive insulin treatment has given way to an agnostic

approach, as large studies found benefits and potential harm associated with these strategies (4). The higher mortality and complication rates in T2D patients are multifactorial and probably related to the duration of glycemic dysregulation. Why do T2D patients treated with insulin fail to show an improved clinical outcome?

Wang et al. (1) suggest that insulin therapy, added to higher baseline insulin levels reduces miR-24 levels, with adverse effects after ischemic injury. According to the authors, this may, at least in part, explain the lack of therapeutic efficacy of insulin treatment in T2D patients post-MI.

A strength of this study is the use of 2 murine models, one akin to T2D and type 1 diabetes (T1D). Although insulin use increased mortality post-MI in db/db mice (T2D), insulin use decreased mortality in mice treated with streptozotocin (T1D). Wang et al. demonstrate a reduction in infarct size after ischemia reperfusion in db/db mice after systemic administration of nanoparticles containing miR-24 as well as in transgenic mice that have cardiomyocyte-specific overexpression of miR-24. O-GlcNAc transferase, Bcl-2-like protein 11, and autophagy-related 4A cysteine peptidase are the proposed targets of miR-24 responsible (Figure 1). Similar to most miRNAs, miR-24 is ubiquitously expressed (5). Qian et al. (6) have previously shown that in vivo administration of miR-24 nanoparticles inhibited cardiomyocyte apoptosis in a mouse model of MI, thereby attenuating infarct size and reducing cardiac dysfunction by directly acting on Bcl-2-like protein 11.

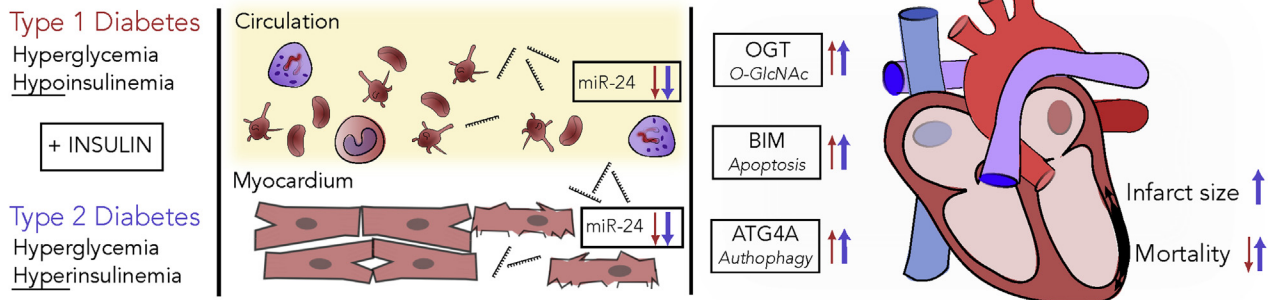
MiR-24 is also part of a pri-miR cluster, together with miR-23 and miR-27 (7). Increased expression of miR-24 but also of miR-27b has been associated with cardiac dysfunction (8,9). Previously, the authors reported that hyperglycemia represses miR-24 in endothelial cells. Reduced miR-24 was associated with increased von Willebrand factor secretion by endothelial cells (10). Notably, Fiedler et al. (11)

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All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* [author instructions page](#).

FIGURE 1 MiR-24 and the Diabetic Heart



The infarct size after ischemia-reperfusion is reduced in a mouse model of type 2 diabetes upon microribonucleic acid 24 (miR-24) overexpression. O-GlcNAc transferase (OGT), Bcl-2-like protein 11 (BIM), and autophagy-related 4A cysteine peptidase (ATG4A) are proposed as targets of miR-24. Insulin treatment reduced mortality in a mouse model of type 1 diabetes, but not type 2 diabetes. The observed plasma changes in miR-24 may not be connected to myocardial tissue.

revealed that miR-24 is up-regulated after MI and enriched in cardiac endothelial cells under normoglycemia. Blocking endothelial miR-24 using antagonists limited infarct size by preventing endothelial cell apoptosis and enhancing vascularity (6). Thus, miR-24 appears to affect both endothelial cells and cardiomyocytes, with opposite outcomes in post-MI remodeling

Wang et al. further demonstrate a decrease in miR-24 in response to hyperinsulinemia in a clamp study in 5 T1D patients. A significant decrease in miR-24 levels was observed in the plasma of T2D compared with T1D patients. We have recently identified miR-24 as an abundant miRNA in platelets. Its plasma levels are reduced by antiplatelet therapy (12). Diabetics are known to have increased platelet reactivity (13). Reduced platelet miRNAs, including miR-24, were among the predominant changes in circulating miRNAs in patients with T2D (14,15). Insulin antagonizes platelet activation, but platelets from T2D are less sensitive to this effect due to their insulin resistance (15). Therefore, differential miR-24 detection in the plasma of T2D may reflect differential platelet reactivity,

especially as the plasma isolation protocol in Wang et al. does not prevent pre-analytic platelet activation (16). The rapid reduction of plasma miR-24 seen in Wang et al.'s glucose clamp experiment supports this suggestion; as insulin levels increase, platelet reactivity is reduced and platelet "poor" plasma subsequently demonstrates reduced miR-24 levels (17).

Although it would be an oversimplification to attribute myocardial dysfunction after MI in T2D to the dysregulation of an individual miRNA such as miR-24, the study by Wang et al. emphasizes the significance of miR-24 in the ischemic diabetic heart (Figure 1). Also, the proposed role for circulating miRNAs such as miR-24 in the pathophysiology of infarct healing in diabetics in relation to insulin sensitivity and production as demonstrated by this study encourages further exploration.

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