Commentary

MicroRNA and hyperglycemic memory in the diabetic heart

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"Hyperglycemic memory" is an interesting term. This hypothesis was first put forward in 1990 by Roy *et al*. (1), after which this phenomenon was named "metabolic" or "hyperglycemic" memory (2,3). Recently, two-meta analyses showed that intensive glycemic control had no impact on the risk of heart failure in patients with diabetes mellitus (4,5). It is possible that the small benefit on non-fatal myocardial infarctions and microalbuminuria may be offset by a significant increase in the risk of severe hypoglycemia (4), and the detrimental effects of hyperglycemia may persist even after restoration of normal glucose levels, that is, "hyperglycemic" or "metabolic" memory. Collectively, these data suggest that such memories are stored early in the course of diabetes, supporting the hypothesis of hyperglycemic memory.

Chronic hyperglycemia is a major initiator of diabetic vascular complications. Indeed, high glucose, mediated via various mechanisms such as increased production of advanced glycation end products, activation of protein kinase C, stimulation of the polyol pathway and enhanced reactive oxygen species generation, regulates vascular inflammation, altered gene expression of growth factors and cytokines, and platelet and macrophage activation, thus playing a central role in the development and progression of diabetic vascular complications (6). In turn, this results in diabetic cardiomyopathy. Diabetic cardiomyopathy is characterized by myocardial hypertrophy, fibrosis, and impairment of the left ventricular performance occurring independently of a recognized cause, namely myocardial ischemia (7,8). Oxidative bursts, in turn, are capable of amplifying maladaptive signaling, including of protein kinase C, mitogen-activated protein kinases, advanced glycation end products, and aldose reductase, consequently leading to apoptosis, hypertrophy, fibrosis, impaired calcium homeostasis, and contractile dysfunction (8).

Recently, Costantino *et al*. suggested that glycemic control is not able to rescue hyperglycemia-induced alterations of microRNAs (miRNAs) in the diabetic heart. The authors showed that 316 out of 1,008 total miRNAs were dysregulated in the diabetic heart (9). Notably, 268 of those miRNAs remained significantly altered after 3 weeks of intensive glycemic control with insulin. miRNAs represent a class of small non-coding RNAs that control the expression of entire networks of complementary transcripts. In the heart, miRNAs are critically involved in the maintenance of tissue homeostasis (10). In 1990, Roy *et al*. found that the fibronectin mRNA levels were increased in the kidney cortex and heart in streptozotocin-induced diabetic rats (1). Subsequently, in 2007, He *et al*. revealed that overexpression of miRNA-29, which is highly up-regulated in diabetic rats, leads to insulin resistance in 3T3-L1 adipocytes (11).

The findings by Costantino *et al*. are very interesting; if these kinds of changes in miRNAs occur in the early phase of diabetes mellitus, these findings may impact on the appropriate glucose lowering therapy. Especially, the notion that lower is better in terms of the glucose level may collapse in the near future. Indeed, glycemic control was unable to restore the expression of relevant downregulated miRNAs, such as the anti-fibrotic miRNA-29b, as well as miRNA-30a and miRNA-1, potent inhibitors of mitochondrial fission, apoptosis, and hypertrophy, in previous reports (12-14). Furthermore, miRNA-1 replacement therapy has recently been shown to revert cardiac hypertrophy and fibrosis by targeting Fibulin-1, a secreted protein implicated in extracellular matrix remodeling (15). Taken together, these findings indicate that now is the time to review the current glucose lowering therapy strategies and focus on gene therapy.

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Footnote

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