ANTIOXIDANTS & REDOX SIGNALING
Volume 9, Number 3, 2007

DOI: 10.1089/ars.2006.1486

# Forum Editorial

# Metabolic Disorders in Diabetes Mellitus: Impact of Mitochondrial Function and Oxidative Stress on Diabetes and Its Complications

EIICHI ARAKI[1] and JUN-ICHI MIYAZAKI[2]

## PATHOGENESIS OF DIABETES MELLITUS

DIABETES MELLITUS is caused by impaired insulin secretion from pancreatic β cells and/or impaired insulin action in peripheral tissues, such as skeletal muscles and liver. Genetic and environmental factors are known to be involved in the development of the disease. Genetic mutations (for example in the insulin, insulin receptor, glucokinase, HNF1α, and mitochondrial genes) are known to cause diabetes directly. However, the genetic factors that lead to common type 2 diabetes are largely unknown.

When blood glucose is not well enough controlled in a diabetic patient, microvascular complications, such as retinopathy, neuropathy, and nephropathy, and macrovascular complications, such as coronary heart disease and cerebral infarction, can occur. Because the microvascular complications are specific for diabetes, no doubt exists that they are caused by hyperglycemia and related metabolic disorders. Conversely, the macrovascular complications are not specific for diabetes but are accelerated in the diabetic state. Amelioration of the metabolic disorder can prevent the development and progression of diabetic complications (14, 16, 18). However, putting this solution into practice has been difficult, and many patients continue to have diabetic complications. Therefore, investigations to resolve the mechanisms underlying diabetic complications and to identify novel therapeutic targets are urgently needed.

## MITOCHONDRIAL FUNCTION, OXIDATIVE STRESS, AND DIABETES MELLITUS

Mitochondria play an important role in many cell functions, mainly through the production of ATP through their electron-transport chain. Disruption of mitochondrial function leads to the development of several diseases, including mitochondrial encephalomyopathy, Parkinson disease, and diabetes. Pancreatic β cells function in glucose metabolism through their glucose-induced insulin secretion, which requires ATP synthesized by the mitochondrial electron-transport system. Therefore, impaired mitochondrial function leads to the development of diabetes owing to impaired insulin secretion (4, 17). In addition, prolonged hyperglycemia is now thought to cause the apoptosis of β cells. This could create a vicious cycle in which reduced insulin secretion from β cells worsens the glycemic control of the patients, which leads to more β cell apoptosis and an even greater reduction in insulin secretion (2). Insulin resistance is also deeply involved in the development of type 2 diabetes, and increased oxidative stress is reported to cause insulin resistance by various mechanisms (6, 7, 15).

Finally, overwork of the mitochondrial electron-transport system owing to the increased flux of glucose in various cells leads to the overproduction of reactive oxygen species (ROS), increases oxidative stress, and may cause various disorders, including diabetic microvascular and macrovascular complications (1, 12). Oxidative stress in diabetic subjects is induced not only by mitochondria-derived ROS but also by other mechanisms, including the increased production of inflammatory cytokines, advanced glycation end product (AGE), and NAD(P)H oxidase–related pathways.

## FOCUS OF THIS ISSUE

In this issue, we focus on how impairments at the molecular level affect the pathogenesis of diabetes and diabetic complications, giving special attention to the role of oxidative stress from mitochondria and other sources.

Martens *et al*. (11) argue that hyperglycemia contributes to β cell apoptosis. They propose that impaired glucose sensing

[1]Department of Metabolic Medicine, Faculty of Medical and Pharmaceutical Sciences, Kumamoto University, Kumamoto, Japan.
[2]Division of Stem Cell Regulation Research, Osaka University Graduate School of Medicine, Osaka, Japan.

and metabolism may decrease β cell viability, rather than β cell viability decreasing because of being overactivated by high glucose levels.

An interesting feature in glucose metabolism has been reported for embryonic stem (ES) cells, which can differentiate into many cell types, including insulin-producing cells. Kondo *et al.* (9) suggest that elevated glycolysis and reduced mitochondrial oxygen consumption are important for the proliferation of murine ES cells. They found that the glycolytic flux was high in murine ES cells, probably through the increased activities of glycolytic enzymes, and suggest that these metabolic phenotypes may be related to the immortality of ES cells.

Oxidative stress has been implicated in the development of insulin resistance in peripheral tissues (6, 7). In addition, nitrosative stress may be involved in the pathogenesis of insulin resistance and diabetes mellitus. Kaneki *et al*. (5) describe the effects on insulin signaling of the nitrosylation of molecules that are important for this signaling pathway, including the insulin receptor, insulin receptor substrate-1, and Akt/PKB.

Nishikawa *et al*. (13) describe the impact of mitochondria-derived ROS on diabetes and its complications and propose that mitochondrial ROS are important not only for the development of diabetic complications but also for the development of diabetes itself. Furthermore, Kaneto *et al*. (6, 7) suggest that oxidative stress caused by hyperglycemia as well as by the activation of several cytokine networks and the subsequent activation of Jun N-terminal kinase (JNK) is involved in the development of both type 1 and type 2 diabetes and in the progression of macrovascular complications.

Diabetic nephropathy is a microvascular complication and the leading cause of chronic renal failure in developed countries. Coughlan *et al*. (3) describe the role of the AGE and RAGE (receptor for AGE)-mediated pathway in the development of diabetic nephropathy and other vascular diseases, and suggest the RAGE as a potential therapeutic target for nephropathy treatment.

A transcriptional cofactor of peroxisome proliferator-activated receptor-γ (PPAR-γ), called peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1α), is also implicated in the regulation of ROS levels (10, 19). One possible mechanism is the induction of manganese superoxide dismutase (MnSOD) and a subsequent incremental increase in mitochondrial biogenesis (10). Kim *et al*. (8) looked at the effects of overexpressing PGC-1α. They found that it suppressed a tumor necrosis factor-α (TNF-α)–induced increase in the expression of monocyte chemoattractant protein-1 (MCP-1) and vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells and smooth muscle cells, both products of NF-κB–dependent genes. These results led the authors to suggest that the activation of PGC-1α might be one way to suppress vascular disease.

Although several biomarkers for oxidative stress exist, no definitive method for measuring it *in vivo* has been developed. Yamato *et al*. (20) developed a new way to measure oxidative stress in the eye of model diabetic mice using electron spin resonance spectroscopy and applying carbamoyl-PROXYL as a spin probe, although further investigation is needed to confirm the accuracy of this approach.

## FUTURE DIRECTIONS

No question exists that the oxidative stress and metabolic disorders caused by the impaired function or overwork of mitochondria and by other mechanisms profoundly contribute to diabetic complications. In addition, as described in the articles in this issue, cellular stresses lead to the development of diabetes itself, through impaired β cell function and decreased response to insulin signals. Several potential therapeutic targets also are suggested in this issue, which include antioxidants, suppression of the JNK and RAGE pathways, and the activation of AMP-activated protein kinase (AMPK) and the PGC-1α signal cascade. We sincerely hope and believe that the translation of such investigations into the development of new therapeutic agents will provide better therapy and, eventually, cures for diabetes and diabetic complications.

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Address reprint requests to:
*Dr. Eiichi Araki*
*Department of Metabolic Medicine*
*Faculty of Medical and Pharmaceutical Sciences*
*Kumamoto University*
*1-1-1 Honjo, Kumamoto 860-8556, Japan*

*E-mail:* earaki@kaiju.medic.kumamoto-u.ac.jp

Date of first submission to ARS Central, October 13, 2006; date of acceptance, October 15, 2006.

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