

Department of Internal Medicine

Division of Diabetes, Metabolism and Endocrinology

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General Summary

Physicians should practice patient-oriented medicine based on the concept of evidence-based medicine, which consists of research evidence, clinical expertise, and patients' preferences. To accomplish this goal, we encourage the members of our staff to do basic and clinical research. Areas of research include diabetes, metabolism, and endocrinology.

Research Activities

Epidemiology and evidence-based medicine

A nationwide epidemiologic study of mortality in approximately 3,500 patients with type 1 diabetes was started in 1986 and has continued to provide much information about the prognosis of Japanese children with type 1 diabetes. A population-based interventional study of childhood obesity and glucose intolerance has also continued. Several clinical trials of the treatment of type 2 diabetes using continuous glucose monitoring are being performed.

Molecular diabetology and islet medicine

Injuries to islet cells and their reduced regenerative capacity are novel therapeutic targets in the pathophysiology of diabetes are particular our interests in this field. Our study group has succeeded in the direct *in vivo* transfer of genes, including cell-cycle regulators, such as cyclin-dependent kinase 4. We confirmed that regulated proliferation of mature beta cells restores glucose metabolism in diabetic mice.

We have also begun to focus on peri-islet Schwann (PIS) cells to investigate their critical role in the protection of islet endocrine cells and islet development in fetal mice. By using developmental engineering techniques in mice, we found that PIS cells are derived from the neural crest. We also found that PIS cells regulate islet conformation and, probably, alpha/beta cell function via direct contact with alpha cells.

Insulin resistance and obesity

A series of basic research studies of insulin resistance were performed in Otsuka Long-Evans Tokushima Fatty rats. The effects of a new oral hypoglycemic agent (dipeptidyl peptidase IV inhibitor) on insulin resistance were investigated.

Dietary therapy

A highly monounsaturated enteral formula suppressed postprandial hyperglycemia without exaggerated insulin secretion compared with a high-carbohydrate enteral formula in patients with type 2 diabetes mellitus and in healthy subjects. By using continuous glucose monitoring, we found that a highly monounsaturated enteral formula significantly suppressed postprandial hyperglycemia and markedly reduced 24-hour glycemic variation in patients with type 2 diabetes receiving tube feeding to a greater extent than did a high-carbohydrate enteral formula, even if carbohydrate nutrients were adjusted to have a low glycemic index.

Diabetic vascular complications

We investigated the role of the Rho/Rho-kinase signaling pathway in the development of diabetic complications. We showed that the Rho/Rho-kinase signaling pathway plays a crucial role in macrophage accumulation in the kidney under diabetic conditions. We also demonstrated that Rho/Rho-kinase mediates thrombin-induced endothelial activation. Intriguingly, we found that the Rho/Rho-kinase signaling pathway is involved in the pathogenesis of diabetic neuropathy. These findings indicate that Rho/Rho-kinase is an important factor that links microvascular complications with macrovascular complications. We are now investigating molecular mechanisms underlying these observations.

Endocrinology

To identify and separate stem-like cells in human pituitary adenomas, we focused on the expression of CD133, a tumor stem-cell marker in brain tumors, and also examined the differences indicating the stem properties between CD133(+) cells and CD133(−) cells. The effects of Ca²⁺-channel antagonists on the expression of steroidogenic enzymes were evaluated using human adrenocortical carcinoma cell line NCI-H295R.

The 12-lipoxygenase pathway may play a part in the pathogenesis of diabetic cardiomyopathy. Therefore, the role of 12-lipoxygenase in cardiomyopathy was examined *in vivo* in diabetic cardiomyopathy model rats and *in vitro* in a primary cardiomyocyte culture system.

A possible direct effect of endotoxin on human stellate cells, which play a critical role in the progression of nonalcoholic steatohepatitis, was studied in the human hepatic stellate cell line LX-2.

A previous study has shown that ACTH secretion from the hearts of patients with hypertension is increased and suggest that ACTH is involved in the pathophysiology of cardiovascular diseases. Recently, pro-opiomelanocortin messenger RNA has been found to be expressed in the murine heart. Therefore, we designed a study to clarify the pathophysiological role of pro-opiomelanocortin using HL-1 cardiomyocytes.

Publications

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