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Involvement of Regucalcin in Lipid Metabolic Disorder and Diabetes

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I was much pleasured to prepare inaugural editorial for a new Journal "International Journal of Diabetes and Clinical Research". In this editorial, I prefer to describe an involvement of regucalcin in lipid metabolic disorder and diabetes, which is a recent topic. Regucalcin, which was discovered in 1978 [1,2], plays a multifunctional role as a suppressor protein in signal transduction in various types of cells and tissues and plays a cell physiologic role in maintaining cell homeostasis for various stimuli [3-9]. The regucalcin gene (*rgn*) is localized on the X chromosome and is identified in over 15 species consisting of regucalcin family [3]. Regucalcin has been demonstrated to play a multifunctional role in cell regulation of calcium homeostasis, signal transduction, protein synthesis and proteolysis, nuclear gene expression, cell proliferation and apoptosis in various types of cells and tissues including liver, kidney, heart, brain and bone [3-9]. Moreover, regucalcin was shown to play a pathophysiologic role in hyperlipidemia and diabetes. We generated regucalcin transgenic rats that reveal overexpression of endogenous regucalcin, and this animal was found to induce hyperlipidemia associated with osteoporosis [10-12]. Regucalcin was suggested to be a key molecule in lipid metabolic disorder implicated in obesity and diabetes.

Obesity and diabetes are currently a major health problem worldwide with growing in prevalence. The incidence of metabolic disease, including type 2 diabetes with obesity, is increased to epidemic levels. Obesity and diabetes induce secondary diseases with various pathophysiologic states, which are important in clinical aspects including cardiovascular disease, neural disturbance, kidney disease, osteoporosis and cancer. Obesity is based on stimulation of adipogenesis. Bone marrow mesenchymal stem cells are multipotent cells, which among other cell lineages, and give to differentiate into adipocytes, osteoblasts, chondrocytes and myoblasts [13]. This occurs through cross talk between complex signaling pathways including those derived from bone morphogenic proteins, winglesstype MMTV integration site (Wnt) proteins, hedgehogs, delta/jagged proteins, fibroblastic growth factors, insulin, insulin-like growth factors, and transcriptional regulators of adipocyte and osteoblast differentiation including peroxisome proliferators-activated receptor-gamma (PPARγ) and runt-related transcription factor 2 (Runx2) [13-15]. Insulin, which is secreted by feeding, stimulates adipogenesis from bone marrow mesenchymal stem cells. Bone marrow adiposity and mature adipocytes with obesity greatly produces tumor necrosis factor-α (TNF-α), an inflammatory cytokine [16]. This TNF-α may cause insulin resistance that leads to type 2 diabetes. Various hormones and cytokines, which include leptin, adiponectin, insulin, epinephrine, cortisol, glucagon, TNF-α and other factors, are well known as key molecules that relate to obesity and diabetes. Disturbance of these factors may play an important role in pathophysiologic conditions of obesity and diabetes.

Regucalcin was demonstrated to stimulate adipogenesis in mouse bone marrow cell culture *in vitro* [17], suggesting an involvement as a stimulatory factor in adipogenesis. Interestingly, exogenous regucalcin was found to suppress osteoblastogenesis and stimulate adipogenesis in mouse bone marrow culture *in vitro* [17,18]. Regucalcin may stimulate differentiation from bone marrow mesenchymal stem cells to adipocytes; supporting the view that regucalcin plays a regulatory role in adipogenesis. Regucalcin Transgenic (TG) rats, which overexpress endogenous regucalcin, induced a remarkable bone loss associated with increase in serum triglyceride and high-density lipoprotein (HDL)-cholesterol concentrations at the age of 36 weeks *in vivo* [10-12]. Serum free fatty acid, triglyceride, cholesterol or HDL-cholesterol concentrations were markedly increased in regucalcin TG male and female rats at 14-50 weeks of age [11]. This animal may be a useful tool in the aspects of lipid metabolic disorder and osteoporosis. Hyperlipidemia has been reported to induce in various animal models; lipoprotein lipase-deficient mice [19], low-density lipoprotein (LDL) receptor-deficient mice [20], apolipoprotein C3-KO mice [21], apolipoprotein C1 TG mice [22], very LDL lipoprotein receptor KO mice [23], cholesterol 7 alpha-hydroxylase-deficient mice [24], apoE-deficient mice [25] and hepatic myr-Akt overexpressing mice [26]. These animal models for hyperlipidemia are based on molecules that are regulated to lipid metabolism. Regucalcin is a novel protein molecule that regulates lipid metabolism [18].

Regucalcin was showed to express in the adipose tissues of normal rats [27]. Triglyceride content in the adipose tissues was increased in regucalcin TG rats with aging [27]. Liver triglyceride, total cholesterol, free fatty acid and glycogen contents were decreased in regucalcin TG rats [27]. The expression of regucalcin in the liver tissues was enhanced in regucalcin TG rats [27]. Regucalcin suppressed the activations of glycogen particulate phosphorylase a, cytoplasmic pyruvate kinase, and fructose 1,6-diphosphatase in rat

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liver [3]. Regucalcin may suppress glycogen synthesis in the liver and stimulate glycogenolysis in regucalcin TG rats. As the result, lipid synthesis may be stimulated in the liver tissues of the TG rats *in vivo*. Leptin and adiponectine are adipokines that are involved in lipid metabolism. Leptin mRNA expression in the adipose or liver tissues was found to decrease in regucalcin TG rats with aging [27]. Adiponectin mRNA expression was not changed in the adipose tissues of the TG rats, while its level was decreased in the liver tissues [27]. These decreases may be partly involved in hyperlipidemia induced in regucalcin TG rats. Thus, regucalcin may play an important role in the disorder of lipid metabolism in the liver.

Fasting induced a decrease in regucalcin mRNA expression in rat liver *in vivo*, and this decrease was restored after re-feeding in rats *in vivo* [28]. Oral administration of glucose to fasted rats caused a significant increase in hepatic regucalcin mRNA expression [28], suggesting an involvement of insulin secreted from pancreatic cells after glucose administration. Hepatic regucalcin mRNA expression was elevated administration of insulin to fasted rats *in vivo* [28]. Insulin was demonstrated to directly stimulate regucalcin mRNA and protein expressions in human hepatoma cells (HepG2) *in vitro* [29]. Thus, insulin stimulated regucalcin gene expression in liver cells. Hepatic regucalcin expression was markedly decreased after a single subcutaneous administration of streptozotocin that induces type 1 diabetes [21]. These findings support the view that regucalcin gene expression is enhanced by insulin, and that regucalcin may be involved in liver metabolic disorder related to diabetes.

Deficiency of regucalcin has been reported to cause an impairment of glucose tolerance in regucalcin knockout (KO) mice [22,30]. Regucalcin KO mice caused a significant increase in blood glucose concentration and a decrease in serum insulin levels after glucose administration compared with wild-type mice *in vivo* [29]. Regucalcin deficiency in mice caused an accumulation of neutral lipids and phospholipids in the liver and shortens the life span [22]. Regucalcin was not expressed in hepatic stellate cells (HSCs) of both wild type and regucalcin KO mice [31,32]. Numerous HSCs was hypertrophic and contained abundant microvesicular lipid droplets in the liver cytoplasm of aged regucalcin KO mice [32]. Deficiency of regucalcin may lead to accumulation of liver lipid components.

Insulin resistance may be modeled in culture system by using cloned rat hepatoma H4-II-E cells cultured with insulin and TNF-α *in vitro* [33]. This *in vitro* model nicely mimicsed insulin resistance in human type 2 diabetic mellitus. When H4-II-E cells were cultured in the presence of TNF-α plus insulin *in vitro*, regucalcin was identified as an important protein, which is involved in insulin resistance, by proteome analysis [33]. Regucalcin may be a key molecule that is related to insulin resistance. Regucalcin, moreover, has been demonstrated to stimulate glucose utilization and lipid production in H4-II-E cells *in vitro* [34]. Overexpression of endogenous regucalcin was found to stimulate the production of triglyceride and free fatty acid in H4-II-E cells cultured with or without the supplementation of glucose in the absence of insulin [34]. Regucalcin may stimulate lipid production that is linked to glucose metabolism in liver cells *in vitro*. The effect of insulin, which enhances medium glucose consumption, triglyceride and free fatty acid productions in liver cells cultured with glucose supplementation, was suppressed by overexpression of regucalcin *in vitro* [35]. Insulin resistance in the liver is associated with the pathogenesis of Nonalcoholic Fatty Liver Disease (NAFLD). Patients with NAFLD had a significant lower level of hepatic regucalcin [36]. Hepatic regucalcin levels were decreased in a fibrosis stage-dependent manner and were correlated negatively with the homeostasis model assessment of insulin resistance, the net electronegative charge modified-LDL, and type IV collagen 7S [36]. Whether or not the decrease in hepatic regucalcin in human patients is a result or a cause of cirrhosis remains to be elucidated [36].

Regucalcin was showed to regulate the genes expression of various proteins that are related to glucose and lipid metabolism in liver cells. Overexpression of regucalcin did not reveal stimulatory effects on the gene expression of enzymes including acetyl-CoA carboxylase, HMG-CoA reductase, glucokinase and pyruvate kinase in liver cells after culture with or without glucose supplementation in the presence of insulin [34]. Overexpression of regucalcin increased the expression of glucose transporter 2 (GLUT 2) mRNA to enhance glucose utilization in the liver cells [34,35], and it was found to suppress the expression of insulin receptor (Insr) or phosphatidylinositol 3-kinase (PI3K) mRNAs that are an insulin signaling-related protein [34,35]. Regulatory effects of regucalcin on these gene expressions may play an important role in insulin resistance in liver cells. In addition, regucalcin may suppress signal transduction pathways that are related to insulin action in liver cells.

As described above, regucalcin may play a physiological role in lipid and glucose metabolism in the adipocytes and liver cells. Regucalcin was identified to be a molecule related to insulin resistance in liver cells. Deficiency of regucalcin impaired glucose tolerance and induces liver lipid accumulation. Overexpression of regucalcin was found to stimulate hepatic glycolysis and lipid production. Disturbance of hepatic regucalcin gene expression may lead to disorders of lipid metabolism and insulin resistance in the liver tissues, leading a hyperlipidemia. Regucalcin may play a potential pathophysiologic role as a regulatory protein implicated in lipid metabolic disorder and diabetes. Regucalcin may be a target molecule for therapy of these diseases. In this aspect, clinical studies will be expected.

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