Cellular stress response pathways and diabetes mellitus

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Type 2 diabetes, insulin resistance, and heat shock proteins

Type 2 diabetes mellitus is a typical lifestyle-related disease, caused by impaired insulin secretion and insulin resistance. Both of these abnormalities are influenced by environmental and genetic factors. Insulin resistance is caused by impaired insulin signaling pathways, and recent studies have shown that increased inflammatory signals are involved in this phenomena [1].

In conditions with increased visceral fat accumulation, increased stress signals and increased inflammatory cytokines activate stress-induced kinases, such as c-Jun N-terminal kinase (JNK). JNK is reported to induce serine phosphorylation of insulin receptor substrate (IRS)-1, one of the major substrates of the insulin receptor tyrosine kinase, which results in reduced tyrosine phosphorylation of the substrate and finally causes impaired insulin signaling. JNK also activates NF- κ B (nuclear factor kappa-B) signals and increases the expression of tumor necrosis factor (TNF)- α and C-reactive protein (CRP). Since TNF- α

is known to stimulate JNK, vicious cycles to increase insulin resistance thus are enhanced [2].

Heat shock proteins (HSPs) are molecular chaperones induced by various environmental changes such as elevated temperature, toxins, oxidants and bacterial/viral infections, and they play essential roles in the proper synthesis, transport and folding of proteins [3]. The induction of this cellular stress response pathway (heat shock response pathway) is mainly mediated through the activation of a transcription factor termed heat shock factor-1 (HSF-1). Under stressed conditions, HSF-1 forms a trimer and accumulates in the nucleus, and it binds to its cis-acting element, termed the heat shock element (HSE) or heat response element (HRE), which is located in the 5'-flanking region of heat shock-responsive genes including the HSP70 family [4].

It was reported that the expression of HSP72 mRNA, a member of the HSP70 family, was reduced in subjects with type 2 diabetes [5]. The detailed mechanism of the decreased expression of HSP72 in subjects with type 2 diabetes has not been clarified yet, but it was reported that the trimer formation of HSF-1 is dependent, at least in part, on the inactivation of glycogen synthase kinase (GSK)-3 β . Because the inactivation of GSK-3 β depends on the activation of phosphatidylinositol (PI)-3 kinase and the Akt pathway, which is located downstream of insulin signaling, an impaired insulin signal may suppress the trimer formation of HSF-1 and result in decreased expression of the HSP72 gene [6] (Fig. 1).

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Increased expression of HSP72 ameliorates insulin resistance in animal models of type 2 diabetes

We and others have reported previously that an increased expression of HSP72 could ameliorate insulin resistance and improve glycemic control in animal models of obese type 2

Fig. 1 Insulin signaling pathway and induction of HSP 72 gene, and those under stressed conditions. Under normal conditions, insulin binds to the insulin receptor and activates its tyrosine kinase, which in turn causes the tyrosine phosphorylation of IRS-1. The p85 regulatory subunit of PI-3 kinase recognizes and binds to the specific tyrosine residues of IRS-1, which leads to the activation of PI-3 kinase and the following PDK-1/Akt signaling cascade. Activation of Akt causes the serine phosphorylation and inactivation of GSK-3 β , which results in the dephosphorylation and trimerization of HSF-1 followed by transcriptional activation of the HSP72 gene (shown by light green lines). Under conditions of type 2 diabetes or metabolic syndrome,

chronic inflammation and stress signals are activated, and the stress-induced activation of JNK causes the serine phosphorylation and inhibits the tyrosine phosphorylation of IRS-1, which finally suppresses the insulin signaling pathway mentioned above and attenuates HSP72 gene expression. JNK also activates the NF- κ B pathway and causes the induction of TNF- α and CRP, which further activates stress signals (shown by red lines). Because HSP72 protects cells in part by suppressing the JNK and/or NF- κ B activity, decreased expression of HSP72 under such conditions could cause a vicious cycle

diabetes. Chung J et al. reported that transgenic overexpression of HSP72 protein in skeletal muscle or pharmacological means to induce HSP72 protein could protect against the insulin resistance and hyperglycemia in high-fat fed mice, or in ob/ob mice [7]. Henstridge et al. further showed that such induction of HSP72 increased the skeletal mitochondria number and oxidative capacity, and resulted in the amelioration of insulin resistance [8]. Gupte et al. showed that a heat treatment improved glucose tolerance and insulin resistance in high-fat-fed rats [9]. We have shown that a combination of heat shock treatment (HS) and mild electrical stimulation (MES) [42 °C pads and 12-V direct current (55 pulses/s with 0.1-ms duration) for 10 min, twice per week] could effectively induce HSP72 mRNA and protein in high-fat-fed mice, which resulted in improved insulin signaling and glycemic control with decreased visceral fat [10]. In this method, MES (12-V direct current, 55 pulses/s with 0.1-ms duration) enhances heat induction of HSP72 at least in part by a suppression of HSP72 degradation [11] and may also activate insulin signaling by modulating the membrane

localization of the insulin receptor [12]. We also showed that oral administration of geranylgeranylacetone (GGA), a chemical inducer of HSP72, induced HSP72 protein in liver and amelioration of insulin resistance and hyperglycemia in high-fat-fed mice [13]. In addition to the amelioration of glucose tolerance, we reported an improved β -cell function, assessed by endoplasmic reticular (ER) stress markers, apoptosis signals and insulin content, in db/db mice treated with HS + MES [14]. These reports suggest the possibility of activation of the heat shock response pathway and/or HSP72 induction for the treatment of type 2 diabetes in humans.

Human subjects with metabolic syndrome or type 2 diabetes and HSP72

In 1999, Hooper et al. reported an improvement of glycemic control in subjects with type 2 diabetes after 3 weeks of hot tub therapy (30 min for 3 weeks, 6 days in a week)

[15]. Obese subjects also showed a decrease in fasting blood glucose after sauna therapy for 2 weeks, 15 min/day at 60 °C [16]. These reports together with our animal studies mentioned above encouraged us to apply MES + HS treatment for human subjects with type 2 diabetes.

First, the safety of the HS + MES treatment [42 °C pads and 12-V direct current (55 pulses/s with 0.1-ms duration) for 30 min, four times per week for 8 weeks] was investigated in healthy volunteers. As a result, not only the safety of the method but also reduced inflammatory markers (TNF- α and CRP) were confirmed in ten healthy Japanese males [17]. In 40 Japanese male subjects with metabolic syndrome, treatment with HS + MES [42 °C pads and 1.4 ± 0.1 V/cm direct current (55 pulses/s with 0.1 ms duration) for 60 min, four times per week for 12 weeks] significantly reduced fasting blood glucose and insulin levels, visceral fat, circulating inflammatory markers and blood pressure [18]. Moreover, in 40 Japanese male subjects with type 2 diabetes, the same treatment with HS + MES significantly reduced HbA1c levels by -0.43% in addition to the improvements of various metabolic parameters as observed in the subjects with metabolic syndrome [18]. Although we could not investigate the impact of HS + MES treatment in either the liver or fat of these subjects, increased expression of HSP72, decreased activation of JNK and decreased mRNA expression of CRP, NF- κ B and TNF- α were confirmed in monocytes after the treatment with HS + MES in the subjects with type 2 diabetes.

Future perspectives

We and others have previously reported that overburdening the endoplasmic reticulum (ER) stress response pathway, which is another cellular stress response pathway, is involved in the development and progression of diabetes [19, 20]. Induction of a molecular chaperone to reduce the overburdening on ER stress was reported to ameliorate the diabetic phenotype in an animal model of diabetes [21]. Both the ER stress response and heat shock response pathways are essentially involved in the defense to protect us from various stresses; therefore, the approaches to strengthen such cellular response pathways could provide us with novel therapeutic strategies to prevent the development and progression of type 2 diabetes.

Compliance with ethical standards

Human rights statement and informed consent This article does not contain any original studies with human or animal subjects performed by any of the authors.

Conflict of interest Eiichi Araki has received speaker honoraria from Astellas Pharma Inc. and Mitsubishi Tanabe Pharma Co. as well as scholarship grants from Astellas Pharma Inc., Daiichi-Sankyo Co., Ltd., AstraZeneca K.K. and Takeda Pharmaceutical Co. Tatsuya Kondo and Hirofumi Kai have no conflict of interest.

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