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PERSPECTIVE AND REFLECTION ARTICLE

Inflammation, heat shock proteins, and type 2 diabetes

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Abstract We propose that type 2 diabetes results from a vicious cycle of metabolically induced inflammation, impaired insulin responsiveness, and subsequent loss of homeostatic signaling. A crucial and previously underrecognized event contributing to this loss of homeostasis is a reduction in heat shock proteins (HSPs, or stress proteins). The central causal pathways of this cycle are the following: (a) obesity-driven inflammation promotes insulin resistance; (b) impaired insulin signaling in turn reduces the expression of HSPs, leaving tissues vulnerable to damage and allowing the accumulation of harmful proteins aggregates; and (c) resulting damage to the pancreatic beta-cell leads to further losses in insulin signaling, while a decline in anti-inflammatory HSPs allows inflammation to expand unhindered. Obesity and sedentary lifestyle perpetuate this cycle, while dieting and exercise forestall it by raising HSPs, reducing inflammation, and improving insulin signaling. Because HSP expression carries substantial metabolic costs, it is likely that an evolutionary history of high activity levels and resource scarcity selected for more conservative HSP expression than is appropriate for our current environment of caloric abundance.

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As type 2 diabetes mellitus (T2DM) figures more prominently in the future of mankind, an integrated perspective is needed to both understand and subsequently treat this indolent, progressive disease. Here, we integrate the results of recent experimental research to present a new perspective on the disease's pathogenesis. We propose that type 2 diabetes is a vicious cycle of metabolically induced inflammation, impaired insulin responsiveness, and loss of homeostatic signaling. A key, and previously underrecognized, event contributing to this loss of homeostasis is a reduction in heat shock proteins (Fig. 1). While each of the steps in this cycle leads directly to the next, all three are modulated by environmental factors.

The following observations support this mechanistic understanding:

Inflammation alone can cause insulin resistance. In the past several years, research has established a clear causal relationship between chronic inflammation, obesity, and insulin resistance. Adipocytes and macrophages secrete inflammatory cytokines (like TNF-α) which activate the serine-threonine kinases—c-jun amino terminal kinase (JNK) and inhibitor of κ B kinase (IKK)—in insulin sensitive organs—liver, skeletal muscle and adipose tissue. JNK and IKK both impair function of the insulin receptor and interfere with downstream signaling. One consequence of impaired insulin action is excess lipid deposition in liver and adipocytes, which elevates lipid metabolites (ceramide and diacylglycerol). These lipids directly activate JNK and IKK, further amplifying the defect in

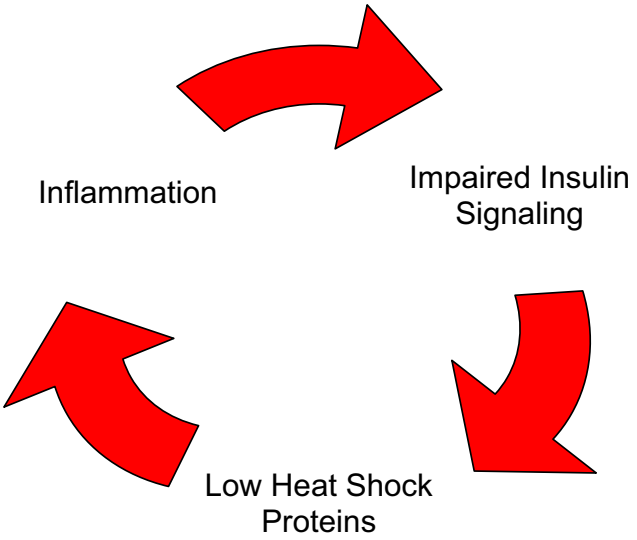

Fig. 1 Type 2 diabetes mellitus and the vicious, progressive cycle

insulin signaling. Interfering with JNK or IKK genetically, with a pharmacologic agent (e.g. salicylates, statins, or thiazolidinedions), or through exercise protects against obesity-induced insulin resistance (Hotamışlıgil 2006; Shoelson et al. 2006).

Impaired insulin signaling reduces heat shock proteins. T2DM is associated with low heat shock factor-1 (HSF-1), low HSP expression, and low HSP levels in insulin-sensitive tissue (Atalay et al. 2004; Bruce et al. 2003: Kavanagh et al. 2008). Furthermore, impaired wound healing of the diabetic state is associated with a delayed HSP response (Bitar et al. 1999). Restoring insulin action raises HSPs in diabetic animal models, whereas interruption of the insulin signaling cascade results in activation of glycogen synthase kinase-3 (GSK-3). When activated, GSK-3 prevents nuclear translocation of HSF-1 by phosphorylating HSF-1's ser 303 and 307, thereby lowering HSPs (Chu et al. 1998). Additionally, loss of insulin signaling represses HSF-1 activity through expression of MAP kinase pErk1 (mitogen activated kinase extra-cellular regulated kinase) (Wigmore et al. 2007). Relevantly, JNK itself deactivates HSF-1 (Park and Liu 2001).

Finally, *HSF-1 activation and subsequent HSP expression yield a broad anti-inflammatory state*. In particular, HSP-70 and hemeoxygenase block the activation of inflammatory kinases (Gabai et al. 1997; Li et al. 2008). Importantly, HSPs block pro-inflammatory transcription factors (like nuclear factor κβ) by blocking their targets, activation, and binding (Stice and Knowlton 2008).

The cyclical model proposed here generates the prediction that raising HSPs should decrease inflammation and improve insulin action. Indeed, Özcan et al. (2006) observed that chemical chaperones reduce inflammation and restore glucose homeostasis in a mouse model of T2DM. More recently, Chung et al. (2008) demonstrated that overexpression of HSP-70 in fat-fed mice prevented activation of JNK and the development of insulin resistance, as did a weekly regime of heat shock itself. They also observed that a GSK-3 inhibitor, BGP-15, increased HSF-1 and HSP-70 levels, reduced JNK activity, and improved insulin signaling and metabolism in ob/ob mice. Like HSP-70, the chaperone hemeoxygenase is low in tissues of diabetic animals and is regulated by insulin signaling (including GSK-3) and HSF-1 (Bruce et al. 2003; Ferrándiz and Devesa 2008; Lu et al. 2002; Salazar et al. 2006). Li and colleagues recently observed that CoPP, a hemeoxygenase stimulating agent, reduced the inflammatory cytokines IL-6 and TNF-α and improved insulin signaling (Li et al. 2008).

The metabolic vicious cycle paradigm permits a functional understanding of T2DM pathogenesis. Obesity, sedentary lifestyle, and high fat calorie diet accelerate this cycle by reducing insulin signaling, increasing inflammatory cytokines, and inducing a low HSP state. Similarly, prolonged stress raises stress hormones (cortisol, catecholamines, and glucagon), which eventually impair insulin signaling and result in depressed HSPs levels. These acquired defects in HSP signaling lead to unmodulated inflammation and more insulin resistance.

The low HSP state of diabetes makes tissues vulnerable to stress, which could lead to the excessive mortality and organ failure associated with this disease. Furthermore, the essential cellular functions of HSPs such as aiding protein folding, "life guarding" organelles like mitochondria, reducing apoptosis, and diminishing endoplasmic reticulum stress become impaired in T2DM (Hooper 2007).

The paradigm proposed here may also explain emerging observations concerning cellular viability, particularly in tissues where insulin signaling occurs but does not result in glucose uptake, such as the pancreatic β-cell and neurons. T2DM, Alzheimer's disease, and other neurodegenerative diseases all entail a loss of insulin signaling and accumulation of protein aggregates (phosphorylated Tau proteins and amyloid precursors) leading to cellular damage and death (Hayden et al. 2005). We propose that insulin resistance in these tissues yields a low HSP state that leads to increased intracellular protein aggregation, which may further increase tissue vulnerability. Supporting this hypothesis is the observation that GSK-3 inhibitors can raise HSPs and protect the brain from ischemia (Ren et al. 2004). Other HSP-raising drugs also delay the disease progression of amyotropic lateral sclerosis, which, like Alzheimer's, develops through a process of deleterious protein aggregation (Brown 2007). The loss of pancreatic β-cells due to a low HSP state and the intracellular amyloid accumulation

that results lead to a further loss of insulin signaling. The observation that the HSP response declines with age can help explain the increased risk for the development of T2DM and dementia in older age.

Dieting and exercise raise HSPs, reduce inflammation, and improve insulin signaling, and thus reverse the cycle that leads to type 2 diabetes. The reason that T2DM has become so prominent in the present and future of mankind is because we no longer hunt and gather our food; instead, we live a sedentary and overfed lifestyle. Why didn't our species evolve with higher levels of HSPs? In the study referred to above, the overexpressing HSP-70 mice had only one-quarter the body fat as the wild mice, and had increased mitochondrial oxidative metabolism (Chung et al. 2008). While such a phenotype would prove healthy and beneficial in today's world, it would not have survived the famines of our evolutionary past. On the shorter time scale of phenotypic development, cues of potential resource scarcity in utero may prompt more conservative expression of HSPs, which, in an environment of actual resource abundance, leaves the organism vulnerable to the metabolic syndrome and T2DM.

The self-perpetuating cycle model proposed here provides an integrated framework for understanding the source of the fundamental defects of type 2 diabetes, and clearly expands our potential for therapeutic intervention at each step in the cycle.

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