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The Role of the Heme Oxygenase System in the Metabolic Syndrome

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Abstract: Molecular chaperones and the heat shock response play a major role in the maintenance of cellular homeostasis under various pathological conditions. In particular, their role is to regulate protein conformation, protect proteins from misfolding and aggregation, and maintain signalling and organellarnetworks. Among variousheat shock proteins, Hsp32 also known as heme oxygenase-1 (HO-1), has demonstrated an important role in metabolic syndrome. In particular, the HO system seems to play a major role in the complex pathophysiological cascade involved in insulin resistance mechanisms, and adipocyte functions as measured by the release of important adipokynes. The aim of the present review is to point out the role of HO-1 in metabolic syndrome, and how to exploit its beneficial effects as a therapeutic strategy to prevent complicationsof andto improve insulin sensitivity.

Keywords: Metabolic syndrome, heme oxygenase, insulin sensitivity, adiponectin, heat shock proteins.

INTRODUCTION

The prevalence of obesity, sedentary lifestyle, and the ageing of the population is on the rise globally [1], leading to an increased risk of cardiovascular disease and type 2 diabetes. The metabolic syndrome represents a clustering of pathologic factors including central obesity, glucose intolerance, hypertension, and dyslipidemia, with the underlying common thread of insulin resistance. Several expert groups have suggested in the last few years diagnostic criteria to be used in clinical practice to identify patients with metabolic syndrome, and these definitions have been somewhat different [2].

As stated by the joint American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement on "Diagnosis and Management of the Metabolic Syndrome" III [3], all the proposed classifications have in common the concept that the metabolic syndrome represents a constellation of interrelated risk factors of metabolic origin ("metabolic risk factors") that appear to directly promote the development of atherosclerotic cardiovascular disease. The metabolic risk factors include elevated blood pressure, elevated plasma glucose, and atherogenic dyslipidemia, which consists of an aggregation of lipoprotein abnormalities including elevated plasma triglyceride levels, increased small, dense low-density-lipoproteins (LDL), and reduced high-density-lipoproteins (HDL)-cholesterol concentrations [4].

The pathophysiology of the metabolic syndrome results from a complex genetic and environmental interaction, contributing to atherosclerosis and increasing the risk of glucose intolerance and diabetes [5, 6] through a process of chronic and incremental damage to the arterial wall. The mechanisms underlying atherosclerosis are incompletely understood. In addition to the aforementioned risk factors, a number of other processes including hypercoagulability, oxidative stress, endothelial dysfunction, chronic infection, and inflammation have been proposed.

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Recent studies have also suggested the role of heat-shock proteins (HSP)s in cardio-metabolic risk [7-10].The Aim of this review article is to discuss the role of HSPs in the metabolic syndrome and its associated cardiovascular risks.

HEAT SHOCK PROTEINS, MOLECULAR CHAPERONES AND CHAPERONOPATHIES

Heat shock proteins (Hsps) are ubiquitous proteins, highly conserved during evolution that are involved in many vital functions such as gene expression regulation, cell differentiation, DNA replication, signal transduction, programmed apoptosis, cellular senescence and immortalization [11-13]. Since there are several groups of Hsps, a classification of practical value in research and practice is that based on molecular weight (Table **1**).

Many members of the Hsp families are present constitutively in cells while some are expressed only after stress [11, 14]. Several mechanisms exist to regulate the abundance of cytosolic and nuclear chaperones, and activation of heat shock transcription factor 1 (HSF1) is an essential aspect of the heat shock response. In higher eukaryotes, triggering of the heat-shock response is mediated by this master regulator, HSF1 [11, 15]. The activated HSF enters the nucleus and binds to heat-shock elements (HSE) in the promoter region of the selected Hsp gene [11]. Inthe absence of stressors, Hsp-chaperones have multiple housekeeping functions, such as folding and translocation of newly synthesized proteins, protein degradation, and activation of transcription factors, and they also participate in determining tumour immunogenicity and antigenic presentation [11, 13, 16].

Many Hsps are molecular chaperones, and here we will use the terms, Hsp and molecular chaperone, interchangeably. Molecular chaperones assist in protein folding, degradation, and intracellular trafficking [11, 12, 17]. As a consequence, aberrant expression of chaperone genes may cause various disorders. A group of pathologies, due to congenital or acquired malfunction of chaperones, has been described as chaperonopathies [12, 17-19]. The number of papers demonstrating a link between Hsps dysfunction and metabolic syndrome is growing [20-22], and hence this syndrome is expected to be included soon among chaperonopathies.

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Table 1. Subpopulations of Hsp-chaperones.

NAME	OTHER NAMES	MW (kDa)
Super-Heavy	Sacsin	200 or higher
Heavy High	Hsp100	100–199
Hsp90	HSP86; HSP89A; HSP90A; HSP90N; HSPC1; HSPCA; LAP2; FLJ31884	81–99
Hsp70	Chaperones; DnaK	65–80
Hsp60	Chaperonins (Groups I and II); Cpn60 and CCT	55–64
Hsp40	DnaJ	35–54
Small Hsp	sHsp; alpha-crystallins; Hsp10	34 or less
Other Proteases;	isomerases; AAA + proteins (e.g., paraplegin [SPG7]; spastin [SPG4]; torsin A); Alpha Hemoglobin-Stabilizing Protein (AHSP); clusterin; PPI (cyclophilin); etc	Various
Hsp32	Heme oxygenase-1	32

However, an important issue is that many other Hsps are not chaperones (and vice versa). Unfortunately, these distinctions have not been made in the great majority of published work on these molecules that use the names Hsp and chaperones interchangeably. Hsp32, also named Heme-oxygenase-1 (HO-1), is one of the most important Hsp's without achaperoning function. HO-1 is the inducible isoform of heme oxygenase, which catalyzes the NADPH, O_2 and cytochrome P450 reductase dependent oxidation of heme to carbon monoxide, iron and biliverdin that is immediately reduced to bilirubin [23, 24]. another inducible protein by heat shock is Heme Oxygenase –1 (HO-1), and therefore has also been referred to as heat shock protein (hsp) 32 [25]. Heme oxygenase 1 or heat shock protein 32 is a member ofthe heme oxygenase (HO) protein family. Heme oxygenase (HO) catalyzes the rate-limiting step in heme degradation, yielding biliverdin IX [alpha], iron, and carbon monoxide (CO) . The HO enzyme system comprises two isoenzymes, namely HO-1 and HO-2, which are encoded by distinct genes. Although HO-2 appear to be constitutively expressed, HO-1 is highly inducible under a variety of conditions associated with oxidative stress, i.e., glutathione depletion [26], ischemia/reperfusion [27], hyperoxia [28], hypoxia [29], endotoxemia [30], in cell lines derived from a variety of species. The heme–heme oxygenase (HO) system serves as an important cellular antioxidant defense system in obesity, diabetes and generally ina metabolic syndrome.

Another important issue is that researchhas recently shown various ways by which cells are able to actively secrete Hsps, i.e., using the classic Golgi's or the alternative lipid rafts-exosome pathways [16, 31-33].

HEME OXYGENASE 1 AND METABOLIC SYNDROME

Oxidative stress has long been implicated in the pathogenicity of insulin resistance in Type 2 Diabetes and of with cardiovascular complications [34]. Oxidative stress is one of the underlying mechanisms in the pathogenesis of hyperglycemia-inducedtissue damage, β cell dysfunction, and endothelial dysfunction. Hyperglycemia increases O_2^- production, culminating in oxidative tissue damage within multiple organ systems, and chronic oxidative stress has also been linked to glucose toxicity and cellular destruction of β cells in Type 2 Diabetes [35].

Thus, it is not surprising that HO-1, as a Key antioxidant enzyme, has consistently been shown to protect against the development of diabetes [36].

The mechanisms by which HO-1has mediated these effects are various, and besides its antioxidant action, HO-1 also directly affects glucose metabolism, which might be due to the presence of a binding site for a glucocorticoid-responsive element in the HO-1 gene promoter [37]. In fact, HO-1 was shown to stimulate insulin production in experimental animal models [36], at least partially, via the release of carbon monoxide [38], which is an immediate product of HO-1. Indeed, HO-1 induction by hemin has been demonstrated to improve insulin signaling and glucose metabolism, and to have lowered insulin resistance in various animal models, including streptozotocin-induced diabetes[39], insulin-resistant type 2 diabetes [40], as well as essential hypertension[41].

Besides improving insulin sensitivity, HO-1 induction has been reported to reduce visceral and subcutaneous obesity in diabetic and obese mice [42, 43] through mechanisms involving the attenuation of the inflammatory processes, as well as modulation of PPARγ signaling [44]. Furthermore, chronic HO-1 induction has been shown to increase metabolic turnover, heat production, and physical activity in an experimental model of obesity [45], suggesting the complexityofthebeneficialeffectsofHO-1inductionuponthese metabolic disorders.

Early studies demonstrated thata decrease in HO-1 gene expression observed with hyperglycemia in experimental diabetes was associated with an increase of endothelial cells into the circulation, presumably reflecting cell damage and an elevation of oxidant production *in vivo*. These findings were reversed bya human HO-1 gene transfer, suggesting that heme-HO-1 system appears to be significantly involved in vascular endothelial cell physiology [46, 47].

Ndisang and colleagues showed that up-regulation of the heme oxygenase system with hemin improves insulin sensitivity and glucose metabolisms pontaneously in adult Hypertensive Rats (SHRs) [48], representing a model of essential hypertension with characteristics ofa metabolic syndrome. In particular, the authors showed that hemin treatment enhanced the antioxidant status in SHRs, and reduced oxidative stress by an increment of bilirubin, ferritin, SOD, and catalase, and reverted proinflammatory/oxidative transcription factors as AP-1, AP-2, NF-kB, and JNK. Moreover, elevated oxidative stress depletes insulin levels [49] and activates JNK, causing insulin resistance [49, 50], whereas the suppression of JNK leads to improved glucose tolerance for the increased insulin production in SHRs.

Furthermore, Abraham *et al*. demonstrated that upregulation of HO-1, in association with increased levels of adiponectin ,prevented vascular and cardiac dysfunction in SHRs fed a high fat diet, a phenotype designed to mimica metabolic syndrome. In par-

ticular, the authors have shown that the inhibition of HO activity prevented the beneficial effects of HO-1 induction in obese SHR with regard to blood pressure, adiponectin, pAKT and pAMPK [51]. These data support the beneficial role of pharmaco-genetic interventions targeted towards HO-1-adiponectin axis in patients with metabolic syndrome. Such patients often exhibit chronic energy imbalance, along with a wide array of cardiovascular abnormalities amenable to aggravation by confounding factors such as diet induced obesity. Restoration of metabolic homeostasis by activationof the HO-1-adiponectin axis could not only improve the energy profile, but also attenuate associated cardiovascular pathophysiological alterations observed in patients withmetabolic syndrome.

On the other hand, adipose tissue dysfunction has been shown to be a mediator in the development of obesity-associated complications and metabolic syndrome [52]. Several studies have demonstrated that HO-1 induction improves insulin sensitivity, reduces adipose tissue volume and causes adipose tissue remodeling in a model of obesity-induced insulin resistance, suggesting that HO-1 could be used as potential therapeutic target for obesity and its associated health risks [53]. In addition, it has been demonstrated that HO-1 expression increases mesenchymal stem cell-derived osteoblasts, but decreases adipocyte lineage [54, 55] suggesting that targeting HO-1 gene expression attenuates the hyperglycemia-mediated decrease in MSC-derived osteoblast differentiation [56].

The deregulated expression of adipokines and inflammatory cytokines by adipocytes and infiltrating macrophages in adipose tissue contributes to obesity-induced insulin resistance [57, 58]. Several chemotactic factors, including monocytic chemotactic protein-1 (MCP-1), osteopontin, CXC motif chemokine ligand-14, and angiopoietin-like protein 2, are upregulated in adipose tissue during the early phase of obesity, and mediating the recruitment of monocytes to adipose tissue, andthe genetic ablation of these genes ameliorates obesity-induced adipose inflammation and insulin resistance in animals [59-62]. These findings emphasize the significance of adipose macrophage infiltration in the development of theobesity-associated metabolic syndrome. Recent studies[63]have identified a novel function of HO-1 in macrophages. Although it is regarded as an anti-inflammatory enzyme which suppresses the production of proinflammatory cytokines in macrophages, HO-1 can impact the migration response of macrophages through modulating p38 and FAK activations. HO-1 expression in hematopoietic cells promotes the migration of macrophages toward the adipose tissue during obesity, and exacerbates the development of metabolic disease. This finding is contradictory to the other reports showing that systemic induction of HO-1 in diabetic animals reduced adiposity and improved insulin sensitivity [43, 64]. In this regard, the salutary effects of HO-1 on adipocytes and skeletal muscles as demonstrated in these studies might overpower the effect of HO-1 on macrophage migration toward obese adipose tissue, and the down-regulation of chemokine expression induced by HO-1 in adipocytes might restrict the adipose macrophages recruitment .

Furthermore, it has beendemonstrated that HO-2 deletion leads to manifestations of the metabolic syndrome, including obesity, hypertension, and insulin resistance. These changes in the HO-2-null mouse were associated with impaired vascular function, increased inflammatory signals, and alterations in cytoprotective circuits, including HO-1, epoxygenase-derived EETs, and adiponectin [65]. In this study, the first cytoprotective circuit that was altered by HO-2 deletion was the HO system. The authors showed that HO-2 deletion leads to reduced HO-1 expression and a decrease in HO activity.HO-2 deficiency enhanced diabetes-induced renal dysfunction and morphologic injury, and HO-1 up-regulation in the HO-2-null mouse rescued and prevented the morphologic damage [66]. HO-2 is critical for HO-1 expression andto illustrate the fact that the subsequent failure to up-regulate the HO system may contribute to unresolved inflammation, and the development of chronic inflammatory conditions [67]. HO-1 induction or overexpression abrogates the injurious consequences of obesity and hypertension, whereas inhibition of HO activity exacerbates these conditions [68]. Therefore, it is notsurprising that HO-2-null mice exhibited similar characteristics as obmice in which the HO-1 suppression displays metabolic syndrome [64, 69]. Furthermore, the diminished activity of the HO system in metabolic syndrome may contribute to increased oxidative stress and inflammatory conditions, and consequently to derangements in the regulation of adipogenesis, increased blood pressure. Finally, Vanella L. *et al* showed that HO-2 plays a major role in adiponectin release by a protein-protein interaction mechanisms thus further suggesting that the HO system may serve as chaperone proteins (LUCA BBRC 2013).

CONCLUSIONS AND FUTURE PERSPECTIVES

HO-1 plays an important role in contributing to metabolic control in *in vitro* and *in vivo* models. These results were also confirmed in human research suggesting that HO-1 may serve as a potential target for metabolic control and metabolic syndrome-related complications. Finally, future studies are now warranted in order to fully elucidate how to exploit HO-1 byproducts for their beneficial and therapeutic effects in themetabolic syndrome.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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All the authors contributed in the design and writing of this paper according to their specializationand specific field of research.

ABBREVIATIONS

HO-1	=	Heme Oxygenase-1
LDL	=	Low-density-lipoproteins
HDL	=	High-density-lipoproteins
HSP	=	Heat-shock proteins
HSF1	=	Heat shock transcription factor 1
HSE	=	Heat-shock elements
MCP-1	=	Monocytic chemotactic protein-1

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