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COMMENTARY

Endoplasmic reticulum stress epigenetics is related to adiposity, dyslipidemia, and insulin resistance

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ABSTRACT

Unresolved ER stress is involved in the onset and progression of several obesity-related metabolic disorders, including dyslipidemia and insulin resistance. Different epigenetic modifications may regulate ER stress response and consequently disease risks. These epigenetic phenomena encompass DNA and histone methylation patterns in ER stress genes and downstream signaling molecules, as well as microRNA expression. Our results suggest potential associations of methylation signatures at ER regulatory genes in white blood cells with an abdominal/central obesity marker (waist circumference), dyslipidemia, and insulin resistance. Interestingly, most of these genes were implicated in ER stress, as revealed by pathway enrichment analysis. Together, these findings add knowledge into the current understanding of relationships between obesity and accompanying complications with epigenetics and ER stress. Here, we comment about the implication of ER stress in central/abdominal adiposity, dyslipidemia, and insulin resistance, with an emphasis on the role that epigenetics may play on these pathological processes.

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Introduction

Overweight and obesity are two pathological conditions characterized by excessive general body fat accumulation, with important adverse effects on health status [1]. In particular, increased central fat distribution, also known as abdominal obesity, is significantly associated with metabolic disturbances, including insulin resistance (IR), dyslipidemia, and inflammation [2]. Indeed, waist circumference (WC), an anthropometric marker of central/abdominal adiposity, is an accepted criterion for the diagnosis of metabolic syndrome [3]. Moreover, the measurement of WC has been suggested to assess obesity-related mortality in adults in addition to body mass index (BMI), as revealed by meta-regression analyses [4].

The relationship between excessive adiposity and metabolic dysfunctions involve multiple cellular mechanisms. One of them appears to be endoplasmic reticulum (ER) stress [5,6] which results from ER protein folding disruption, leading to abnormal accumulation of misfolded proteins within this organelle [7]. As a consequence, eukaryotic cells activate the unfolded protein response (UPR) aimed to restore ER homeostasis by increasing both degradation of misfolded proteins and, concomitantly, reducing protein translation [8]. However, under chronic ER stress, UPR trigger a set of prodeath signals such as mitochondrial-mediated apoptosis and autophagy that are involved in several obesity-related metabolic disorders [9].

Besides environmental factors, different epigenetic modifications may regulate ER stress response and consequently disease risks [10]. These included DNA and histone methylation patterns in or near ER stress gene promoters and interconnected downstream signaling molecules [10–12]. Also, microRNA (miRNA) expression constitutes a fine-tuning mechanism for optimal ER activity during stress conditions [13,14]. Thus, epigenetic phenomena may help to explain, at least in part, inter-individual differences in the susceptibility to developing excessive adiposity and associated comorbidities [15–17]. Moreover, these insights may lead to the search for epigenetic biomarkers to predict metabolic risk and to personalize therapeutic strategies for obesity prevention and management [18,19]. Here, we give a general overview about the potential implication of ER stress in abdominal adiposity, dyslipidemia, and IR, with an

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emphasis on the role that epigenetics play on these pathological processes.

Obesity, ER stress, dyslipidemia, and insulin resistance

Early experiments using cell culture and mouse models have demonstrated that excessive adiposity results in chronic ER stress, particularly in liver and adipose tissues [20]. Further studies have indicated a significant increase of ER stress in adipose tissue of obese subjects [21,22]. In turn, this adverse cellular event appears to be involved in the development of IR and progression to type 2 diabetes mellitus, where multiple mechanisms have been hypothesized [23]. In this context, ER stress can disrupt insulin receptor signaling through enhanced activation of c-Jun N-terminal kinase (JNK) and subsequent serine-phosphorylation of the insulin receptor substrate-1 (IRS-1), leading to decreased insulin action [20]. Moreover, it has been reported that ER stress state induces lipolysis in adipocytes, which primarily could respond to an adaptive response regulating energy homeostasis [24]. Nevertheless, sustained ER stress triggers an accelerated free fatty acid efflux from adipocytes to the bloodstream and other tissues, thus eventually contributing to lipotoxicity, dyslipidemia, and IR [24]. In addition, obesity-induced ER stress has been linked to autophagy, chronic inflammation, and β-cell apoptosis, all of which are key components implicated in the pathogenesis of IR and metabolic syndrome [25,26]. Furthermore, ER-stress-induced IR may also be the result of increased lipogenesis in the liver and the subsequent intracellular lipid accumulation as well as upregulation of gluconeogenic gene expression [23]. Interestingly, caloric restriction reduced ER stress and improved hepatic insulin action by suppressing JNK-mediated IRS-1 serine-phosphorylation in obese mice [27]. Also, exercise training ameliorated ER stress and IR in high-fat-induced obese rats [28]. Furthermore, markers of ER stress in adipose tissue significantly decreased after surgery-induced weight loss [29].

Epigenetics of ER stress and obesity phenotypes

In a previous study [10], 15 differentially methylated CpG sites within ER regulatory genes in white blood cells that were associated with general obesity (BMI) in an adult population: cg08188400 (*MAP2K7*), cg20541779 (*CASP12*), cg24776411 (*EIF2AK1*), cg14190817 (*HSPA5*), cg21376454 (*ERN1*), cg06666486 (*EIF2AK1*), cg03211481 (*DNAJC1*), cg18357645 (*OS9*), cg05801879 (*MBTPS1*), cg20964082 (*ERO1LB*), cg17300868 (*NFE2L2*), cg03384128 (*EIF2AK4*), cg02712587 (*EIF2AK4*), cg04972384 (*SELS*), and cg02240686 (*EIF2AK2*). In addition to BMI, methylation signatures at cg20964082 (*ERO1LB*), cg17300868 (*NFE2L2*), cg05801879 (*MBTPS1*), and cg03384128 (*EIF2AK4*) similarly correlated with total fat mass [10].

In a new analysis, methylation patterns at the abovementioned 15 CpGs also correlated with an abdominal obesity marker such as WC (Fig. 1). Interestingly, obesity-associated genes affected key cellular processes in the ER including protein recognition (*DNAJC1, HSPA5*), protein targeting (*ERO1LB, OS9*), and ER-induced

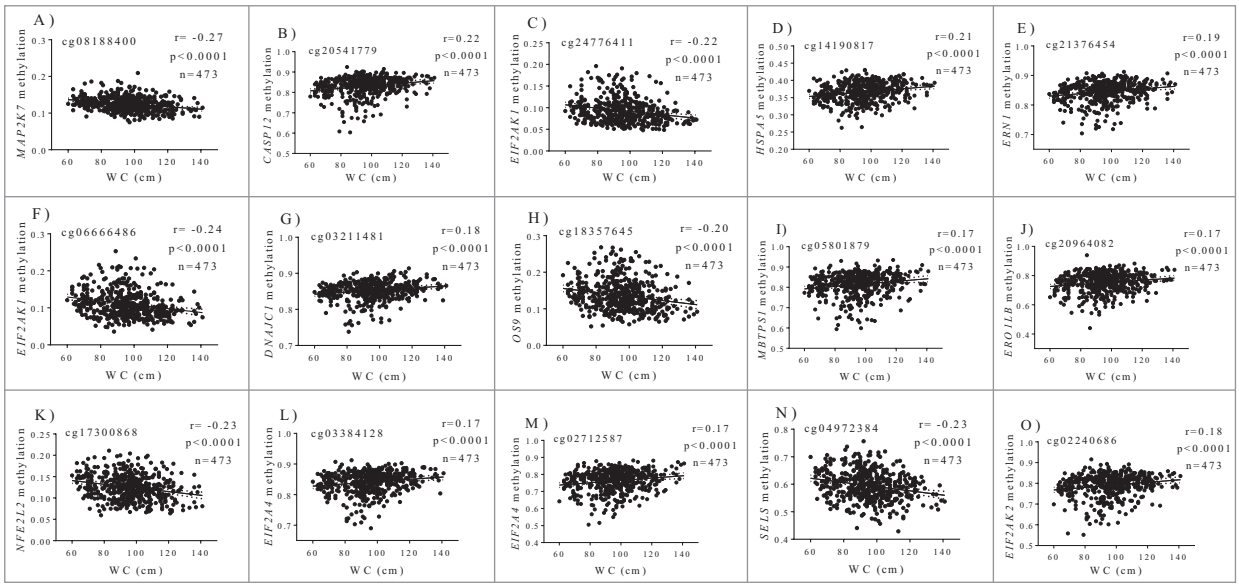

Figure 1. Correlations between methylation levels (beta values) at ER stress genes and WC after adjustments for age and sex. (A) cg08188400, *MAP2K7* (B) cg20541779, *CASP12* (C) cg24776411, *EIF2AK1* (D) cg14190817, *HSPA5* (E) cg21376454, *ERN1* (F) cg06666486, *EIF2AK1* (G) cg03211481, *DNAJC1* (H) cg18357645, *OS9* (I) cg05801879, *MBTPS1* (J) cg20964082, *ERO1LB* (K) cg17300868, *NFE2L2* (L) cg03384128, *EIF2AK4* (M) cg02712587, *EIF2AK4* (N) cg04972384, *SELS* (O) cg02240686, *EIF2AK2*.

degradation (*SELS*). More importantly, most of them were implicated in ER stress, including the master stress sensors *ERN1, EIF2AK1, EIF2AK2, EIF2AK4*, and downstream regulators such as *MAP2K7, CASP12, MBTPS1*, and *NFE2L2*, as revealed by pathway enrichment analysis. In agreement with our findings, a transgenerational set of epigenetic modifications (mainly reduced accumulation of methylated histones in *Lxrα/ Nr1h3* and *Ero1*-α gene promoters) led to up-regulation of lipogenesis and ER stress pathways in the liver of C57BL/6 mice fed a high-fat diet [11]. Additionally, the combination of offspring exposure to maternal obesity and the consumption of an obesogenic diet in mice triggered altered UPR signaling rhythmicity, cellular apoptosis, and hypermethylation of *GRP78*, a chaperone protein and a master regulator of ER homeostasis [12]. Furthermore, treatment of hepatocytes from high-fat diet obese mice with the specialized pro-resolving lipid mediator maresin 1 (MaR1) protected cells from lipotoxic and hypoxia-induced endoplasmic reticulum stress via specific miRNA signatures targeting both protein folding and apoptosis [30]. Also, MaR1 ameliorated liver steatosis by reducing lipogenesis, while promoting fatty acid oxidation and autophagy [31].

It is important to highlight that methylation signatures in blood cells concerning obesity features have been consistently reflected in other tissues. For instance, a methylation map in blood leukocytes mirrored methylation marks found in subcutaneous adipose tissue, which efficiently discriminated obesity from non-obesity status [32]. Moreover, gene methylation parallelisms between white blood cells and oral mucosa samples in relation to overweight and insulin sensibility have been reported [33].

Epigenetics of ER stress, dyslipidemia, and insulin resistance

In a previous investigation [10], statistically significant associations between methylation patterns at cg20964082 (*ERO1LB*) and cg17300868 (*NFE2L2*) and insulin and HOMA-IR index were found, whereas cg05801879 (*MBTPS1*) and cg03384128 (*EIF2AK4*) were specifically associated with serum triglyceride levels. In a new approach, the methylation status of the aforementioned 4 CpG sites was compared by categories of metabolic markers (Fig. 2). In this sense, increased concentrations of insulin and HOMA-IR index were accompanied by lower methylation levels at cg20964082 (*ERO1LB*) and cg17300868 (*NFE2L2*), while a reduced methylation at cg05801879 (*MBTPS1*), and cg03384128 (*EIF2AK4*) was found in subjects with higher serum triglyceride levels (Fig. 2). Consistently, impaired glucose homeostasis was found in F2 mice progeny from male founder obesity, which was partially influenced by hepatic ER stress in a sex-specific manner as well as by altered DNA methylation at the *Nr1h3* locus, a nuclear factor involved in metabolic syndrome [34]. *In vitro* and *in vivo* experiments revealed that ER stress plays an important role in the increase of hepatic glucose production in obesity and diabetes partially by decreasing STAT3 deacetylation [35]. In addition, exposure to the high-fat diet led to hyperacetylation of proteins involved in gluconeogenesis, liver injury and the ER stress response [36].

Nevertheless, no differences in the methylation status of CpG islands located in the *NFE2L2* gene promoter (encoding Nrf2) were found between normal and gestational diabetic mellitus cells [37]. Notably, demethylation of the *KEAP1* gene promoter, a negative regulator of *NFE2L2*, was evidenced in some diabetic complications such as cardiomyopathy and cataracts [38,39]. Consequently, decreased *NFE2L2* activity by *KEAP1*-mediated proteosomal degradation may lead to transcription repression of antioxidant enzymes and alteration of redox-balance up on diabetes. Moreover, hyperglycemia altered the transcriptional function of *NFE2L2* to promote antioxidant gene expression through enhance histone methylation at crucial binding element regions [40].

Of note, the administration of sodium butyrate, a known activator of *NFE2L2*, increased Nrf2 expression at the transcriptional level to ameliorate diabetic nephropathy in mice, possibly by the epigenetic inhibition of histone deacetylase activity [41]. Also, upregulation of *NFE2L2* by increasing miR-200a protected against diabetic nephropathy in mice treated with an analogue of curcumin [42]. Similarly, miR-708 was potently upregulated by triggering ER stress in pancreatic islets of *ob/ob* mice, whose overexpression suppressed β-cell proliferation and induced β-cell apoptosis [43]. Additionally, it was demonstrated that a modest increase in maternal dietary fat in mice programmed triglyceride storage in the liver of their offspring at the adult stage that was controlled by the eIF2α kinase Gcn2 (*Eif2ak4*), which stimulated epigenetic modification (trimethylation of lysine 4 of histone 3) at the *Pparγ2* gene in the neonatal liver [44]. Although the Gcn2-dependent perinatal programming of liver triglyceride storage was proposed as an early nutrition adaptation, this event could predispose individuals to develop liver steatosis in adults. Interestingly, novel regulatory functions of miR-128-2 in cellular cholesterol homeostasis and induction of ER stress response were reported [45]. Likewise, miRNA-induced mitochondrial dysfunction and ER stress are engaged in diverse lipid and lipoprotein disorders by deregulating genes involved in control of intracellular lipid synthesis, fatty acid oxidation, and lipoprotein assembly [46].

Because ER stress is related to inflammation [47], associations between methylation levels at ER stress

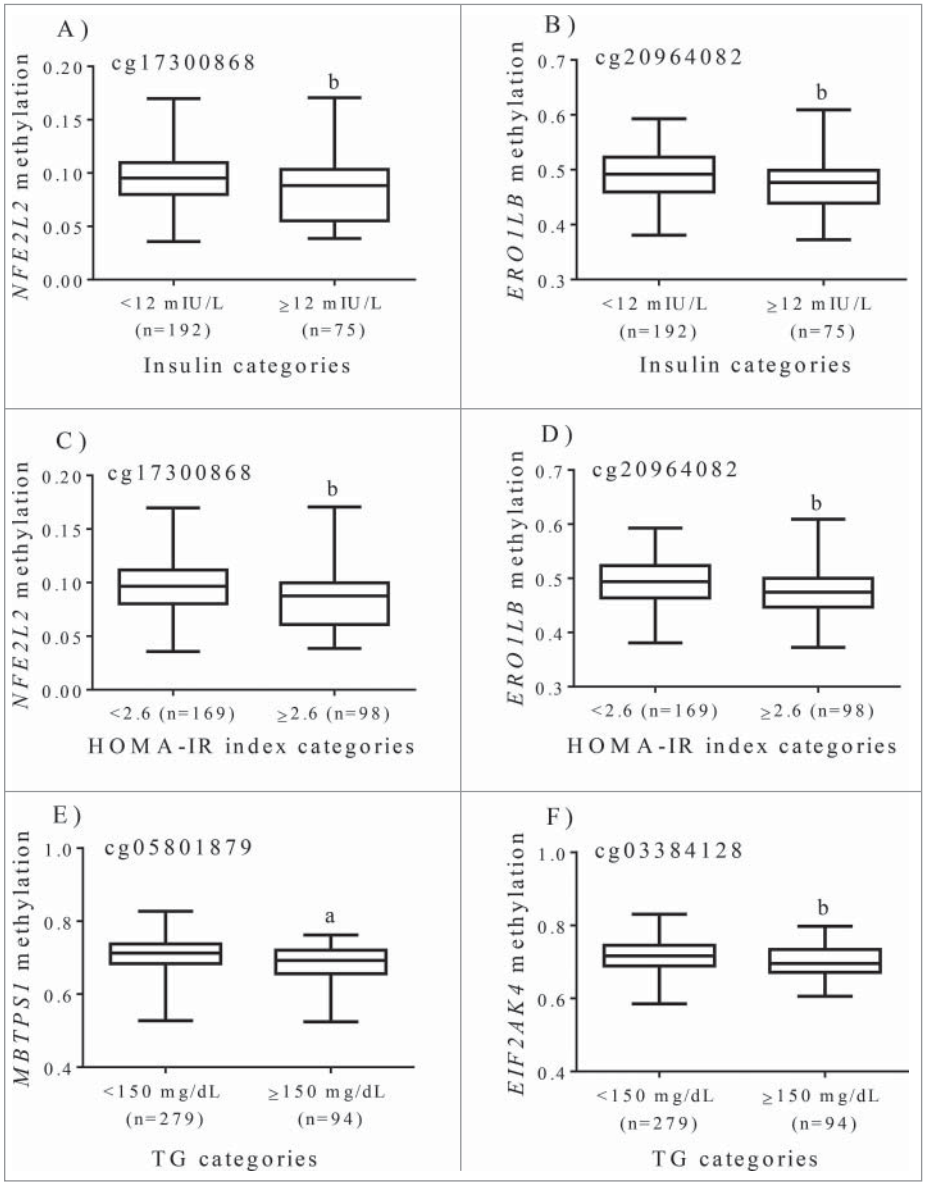

Figure 2. Tenth, 25th, 50th, 75th, and 90th percentiles of methylation levels (beta values) at ER regulatory genes by categories of insulin, HOMA-IR and triglycerides after adjustments for age and sex in subjects with excessive weight. (A) cg17300868, *NFE2L2* (B) cg20964082, *ERO1LB* (C) cg17300868, *NFE2L2* (D) cg20964082, *ERO1LB* (E) cg05801879, *MBTPS1* (F) cg03384128, *EIF2AK4*. [a]$p < 0.0001$. [b]$p < 0.05$.

genes and serum concentrations of inflammatory markers were evaluated in a subsample of the MENA cohort (n=80). A modest positive correlation between *HSPA5* methylation at cg14190817 and circulating C-reactive protein concentration was found (r=0.24, p=0.030), supporting a role of HSPA5 as a possible biomarker for inflammatory states [48].

Concluding remarks

Growing scientific evidence support the involvement of ER stress in the onset and progression of obesity-associated chronic diseases (Fig. 3). At the molecular level, ER stress response can be influenced by several epigenetic modifications. Together, our results suggest that methylation status at genes integrating the ER network could be an epigenetic mechanism underlying fat deposition, lipid metabolism, and insulin resistance. These findings contribute to the current understanding of relationships between obesity, epigenetics, and ER stress. Furthermore, this knowledge may favor the identification of potential ER targets as well as the implementation of precision medicine and nutrition strategies aimed to prevent and control excessive adiposity and related metabolic syndrome complications by targeting the epigenome.

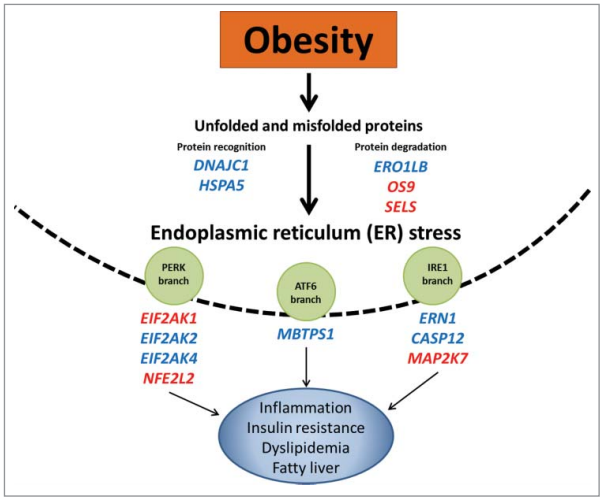

Figure 3. Epigenetic regulation of endoplasmic reticulum stress in obesity and associated metabolic diseases. Obesity induces a chronic activation of the unfolded protein response and consequently ER stress. Differentially methylated ER regulatory genes play a pivotal role in obesity-induced ER stress, leading to the development of metabolic disturbances. Hypomethylated (red color); hypermethyated (blue color).

Disclosure of potential conflicts of interest

No potential conflicts of interest to declare.

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