Int J Clin Exp Med 2019;12(4):3095-3106
www.ijcem.com /ISSN:1940-5901/IJCEM0078581

Review Article

Endoplasmic reticulum stress in adipose tissue at the intersection of childhood obesity-associated type 2 diabetes/insulin resistance and atherosclerosis

Mingxia Wang[1*], Zhao Li[3*], Chuntao Li[2], Yamin Liu[5], Hongkun Jiang[4], Lihong Jia[1], Lingling Zhai[1], Qi Sun[1], Wei Wei[1], Yinglong Bai[1]

[1]Department of Child and Adolescent Health, School of Public Health, China Medical University, Shenyang, Liaoning, China; [2]Information Center, Departments of [3]Cardiology, [4]Pediatrics, The First Hospital of China Medical University, Shenyang, Liaoning, China; [5]Department of Cardiology, University of California, San Francisco, CA, USA. [*]Equal contributors.

Received April 26, 2018; Accepted December 6, 2018; Epub April 15, 2019; Published April 30, 2019

Abstract: Childhood obesity contributing to the development of metabolic diseases is a serious public health challenge on a global scale. Abnormal or excessive fat accumulation is obvious in children who are overweight or obese. As a complicated endocrine organ, adipose tissue is a predominant site of endoplasmic reticulum stress (ERS) that is induced by obesity. ERS is aggravated in obese adipose tissues, which are recognized as a molecular link between obesity and the development of metabolic diseases, such as type 2 diabetes/insulin resistance (T2D/IR) and atherosclerosis. Moreover, T2D increases the risk of atherosclerotic cardiovascular diseases (CVDs). In this review, the role of ERS in adipose tissues is analyzed, particularly regarding the initiation and exacerbation of T2D/IR and atherosclerosis. These findings indicate that it is necessary to devote more resources to the development of promising therapeutics and effective drugs to relieve ERS for the treatment of T2D and atherosclerosis, especially in children who are overweight or obese.

Keywords: Adipose tissue, atherosclerosis, childhood obesity, diabetes mellitus, endoplasmic reticulum stress

Introduction

Obesity is characterized as abnormal or excessive fat accumulation, which is most often defined by body mass index (BMI), which presents a risk to health. Per the World Health Organization (WHO), the number of people with obesity worldwide has nearly tripled since 1975 [1]. Childhood obesity is also a global problem of the 21st century, and represents a serious public health challenge, such as the continuous rise in the number of children and adolescents with obesity in many countries around the world [2-4]. The prevalence of obesity is approximately 17% and affects approximately 12.7 million children and adolescents in the United States [5]. The most recent results from the National Survey on Students Constitution and Health in China indicate that the prevalence of overweight and obesity in 2014 was 19.4% among children and adolescents aged 7-18 years [4]. Overall, children with combined obesity demonstrated a higher prevalence of metabolic disorders, and a study in Beijing showed that the prevalence of types of obesity and obesity-related metabolic disorders among children aged 6-17 years has increased significantly in the past decade [6]. Obese children are also likely to stay obese into adulthood [7, 8] and to suffer from health risks for many comorbidities and complications, such as type 2 diabetes (T2D) and cardiovascular diseases (CVDs) [9, 10]. Physicians and policy experts are particularly concerned regarding the contribution of obesity to the development of T2D and atherosclerosis, as these diseases are serious health hazards, but the underlying mechanisms are not fully understood.

In the obese condition, excess adipose tissue is highly associated with the development of various metabolic diseases, such as cardiometa-

bolic and glucose metabolism perturbation. To this end, researchers have invested considerable energy into exploring the mechanisms of adipose tissue in the development of metabolic diseases. Adipose tissue has been identified as a special endocrine organ that produces a variety of adipocytokines [11], and in recent years, endoplasmic reticulum stress (ERS) has been thought to play a causal role in the development of obesity-associated metabolic disorders [12, 13].

To obtain as much literature as possible on childhood obesity-associated type 2 diabetes/insulin resistance and atherosclerosis, as well as information regarding endoplasmic reticulum stress in adipose tissues, PubMed, Web of Science, Google, the China National Knowledge Infrastructure, and the VIP paper check system were checked, and English and Chinese papers from the last 50 years were collected and analyzed. In the following sections, T2D and atherosclerosis as related to obesity in childhood, focusing on the role of ERS in adipose tissues.

T2D/IR in childhood

Diabetes is now recognized as a syndrome - a collection of disorders with hyperglycemia and glucose intolerance as their hallmark, due to either insulin deficiency, impaired effectiveness of insulin, or a combination of the two. Diagnoses of diabetes are made using fasting plasma glucose with a 2-hour post-challenge of glucose or hemoglobin A1c (HbA1c) [14]. The number of people with T2D is growing rapidly worldwide, which is associated with aging populations, economic development, increasing urbanization, less healthy diets, and reduced physical activity [15]. With increasing levels of obesity and physical inactivity among children in many countries, T2D in childhood has the potential to become a global public health issue that leads to serious health outcomes. Although reliable data are sparse, there is evidence that T2D in children and adolescents is increasing in certain countries [16-19]. An analysis of data from 14 Chinese medical centers shows that the prevalence of childhood diabetes has increased dramatically, the growth of T2D has exceeded that of type 1 diabetes, and the incidence rate of abnormal glucose metabolism in children with obesity has reached 28.26% [20].

People with diabetes are also at higher risk for developing a number of disabling and life-threatening health problems. Consistently high blood glucose levels can lead to serious diseases affecting, for instance, heart and blood vessels, eyes, and kidneys [21]. Furthermore, the prevalence of complications and comorbidities are higher among those with T2D compared with type 1 [22]. T2D in adolescents becomes a severe phenotype that poses major clinical challenges and public health burdens [23].

Hyperinsulinemia and IR, in particular, are common among adolescents with obesity. A recent meta-analysis that evaluates insulin resistance in adolescents aged 12-18 years observed that certain components defining IR - for example circulating insulin, C-peptide levels, and homeostatic model assessment-insulin resistance-IR values-are significantly higher in adolescents with obesity than those who are non-obese [24]. Typically, a patient with T2D is able to produce insulin but becomes resistant, such that the insulin becomes ineffective.

Atherosclerosis in childhood

Atherosclerosis is the underlying process that ultimately leads to clinical CVDs, and severe obesity has been strongly associated with increased cardiometabolic risk. Several studies on children and adolescents have concluded that there is a relevant association between excess weight and certain cardiometabolic risk factors-for example, high low-density lipoprotein cholesterol (LDL-C) level, low high-density lipoprotein cholesterol level, high systolic and diastolic blood pressures, and high triglyceride [25, 26]. As such, to prevent or better manage clinical diseases in children with elevated BMI and/or central obesity, all of the above recommended laboratory tests are warranted in practice [27]. According to the WHO, over three-quarters of CVD deaths take place in low-and middle-income countries [28]. Further, CVDs are already among the top health problems of the Chinese population, and both the prevalence and mortality of CVDs in China are still rising. Recent data from the China Cardiovascular Disease Report 2016 show that CVDs remain the leading cause of death (higher than tumors and other diseases) and are responsible for over 42% of all deaths in China, and billions of dollars in economic losses [29].

Body weight control and correcting dyslipidemia are important strategies for preventing and treating atherosclerosis in children and adolescents [30]. Early stages of the atherosclerotic process are detectable in children with obesity [31], an early pathological finding of which is the presence of fatty streaks in the arterial intima at three years of age, and in the coronary arteries during adolescence [32]. Intima media thickness (IMT) evaluated by ultrasonography is a noninvasive indicator of the atherosclerosis process [33]. Dyslipidemia is one of the strongest traditional risk factors for the development of CVDs, and often emerges during childhood and adolescence [34]. Adolescents with dyslipidemia have an increased risk of developing high carotid IMT in adulthood, and if overweight or obese they have higher carotid intima thickness in adulthood compared with those who did not exhibit both risk factors [35]. Researchers measured the serum lipid concentrations of representative school-age children in Beijing and observed a higher prevalence of hyperlipidemia and dyslipidemia in children and adolescents with obesity and adverse trends of serum lipid concentrations compared with that of 10 years ago [36]. A cohort study has demonstrated that LDL-C levels during childhood are associated with carotid artery IMT in adults [37]. Further, exposure to high levels of LDL-C in childhood can contribute to the development of atherosclerosis in adulthood [38].

T2D increases risk of atherosclerotic CVDs

As a consequence of the global rise in the prevalence of childhood obesity, T2D has emerged at an unprecedented rate. Researchers have reached a consensus that increases in BMI in childhood and adolescence are closely associated with a higher incidence of T2D and atherosclerotic CVDs in young adults [39]. Starting in the mid-19th century, CVDs have been perceived as a major complication of diabetes. When Kannel et al. used data from the Framingham Heart Study in 1979, a twofold to threefold increased risk of clinical atherosclerotic disease was reported, and diabetes was identified as a major cardiovascular risk factor [40]. In following decades, the growth of diabetes worldwide has been termed an epidemic, and diabetes-associated CVDs have become a major health care issue.

T2D increases the risk of CVDs and associated mortality, largely due to increased atherosclerosis [40]. T2D in adolescence manifests as a severe progressive form of diabetes that frequently presents with complications, responds poorly to treatment, and results in rapid progression of microvascular and macrovascular complications [23]. Patients have a higher cardiovascular morbidity and mortality, and are disproportionately affected by CVDs compared with nondiabetic subjects [41].

The role of diabetes in the pathogenesis of CVDs has received a great deal of research interest in recent years. In summary, CVD is elevated in T2D due to a complex combination of traditional and nontraditional risk factors that play a role in the beginning and in the evolution of atherosclerosis over its long natural history, from endothelial function to clinical events [42]. Traditional risk factors-including obesity, dyslipidemia, hypertension, family history, and cigarette smoking-do not fully account for this excess risk, and nontraditional factors, such as IR, endothelial dysfunction, impaired fibrinolysis, inflammation, microalbuminuria, hyperhomocysteinemia, postprandial abnormalities, and vascular wall abnormalities, might also be important.

Diabetes has adverse effects on the initiation, progression, and regression of the lesions associated with atherosclerosis. A significant recent research advancement is that genetically engineered mouse models provide important insights into the mechanisms through which diabetes promotes atherosclerotic lesions of different maturity. Consistent results from different mouse models show that during the initial stage, diabetes can accelerate the formation of atherosclerotic lesions by promoting macrophage accumulation in the brachiocephalic artery and aorta [43, 44]. Diabetes does not increase the size of advanced lesions, but rather causes increased intra-plaque hemorrhaging in the macrophage-rich areas in these lesions [45]. Diabetes also hinders the regression of such lesions through hyperglycemia and increases monocyte recruitment into regressing lesions [46].

Many of the metabolic and cardiovascular complications of obesity are already present during childhood, and are closely related to the presence of IR and hyperinsulinemia. In the obese

state, adipose tissues release increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines, and other factors that are involved in the development of IR [47]. While most insulin-resistant individuals with obesity are able to maintain the degree of hyperinsulinemia required to prevent the manifest decompensation of glucose homeostasis, T2D develops when IR individuals cannot secrete the increased amounts of insulin needed to compensate for the insulin resistance [48]. Atherosclerosis starts in childhood, and manifests in clinical diseases in certain individuals. IR per se is related to diabetes-accelerated atherosclerosis, which induces endothelial dysfunction and is perhaps the most important among a cluster of pathophysiological factors that are associated with early/accelerated atherosclerosis [49].

ERS in adipose tissues at the intersection of T2D/IR and atherosclerosis

ERS is aggravated in obese adipose tissues

Adipocytes have emerged as an important player in the pathogenesis of both T2D/IR and atherosclerosis. In addition to adipocyte hypertrophy [50], local tissue hypoxia [51], and macrophages and other immune-cell infiltration [52], ERS has attracted increasing attention among a variety of theories [53]. Accumulating evidence shows that some ERS markers of phosphorylation-such as a subunit of the eukaryotic translation initiation factor 2 (eIF2), double-stranded RNA-activated protein kinase-like endoplasmic reticulum kinase (PERK), c-Jun N-terminal kinase (JNK), and inositol-requiring kinase 1α (IRE-1α) - are significantly increased in the adipose tissues of obese humans and animals [54-56]. Further, the effects of different ERS inducers on endocrine function were not found to be the same, although all could induce ERS in adipocytes [57].

The endoplasmic reticulum (ER) is a membrane-bound and structurally intricate organelle that is present in all eukaryotic cells. Most secreted and transmembrane proteins fold and mature in the lumen of the ER after these proteins enter the ER as unfolded polypeptide chains. The protein-folding machinery of the ER is composed of molecular chaperones, foldases, and the lectins that maintain the ER quality-control system [58]. Many conditions that perturb cellular-energy levels, the redox state or Ca^{2+} concentration, and even mutations within proteins, can reduce the protein-folding capacity of the ER or impede further processing or transport within the ER. When the folding capacity of the ER fails to accommodate the load of unfolded proteins, the ER homeostasis is perturbed to the condition described as endoplasmic reticulum stress [59]. To combat the deleterious effects of ERS, an adaptive mechanism called the unfolded protein response (UPR) is implemented [60]. The ubiquitin-proteasome and the autophagy-lysosome systems are the two main degradation systems involved in this defense [61, 62]. If the stress cannot be resolved, both proteasomal degradation and autophagy fail, the damage continues, and the cell switches to the apoptotic pathway [63].

Our current level of understanding is that this concerted and complex UPR is mediated through three ER transmembrane receptors, which are classified into types I and II [64]. IRE1 and PERK are type I proteins that possess protein kinase activities, and activating transcription factor 6 (ATF6) is a type II transmembrane protein that encodes a transcription factor. In addition, the long-lived type III, which includes functional cytoplasmic proteins, has also been used as a parameter for assessing autophagic activity. From a functional perspective, the proteasome degrades type I and type II proteins and autophagy degrades type II and type III proteins as well as damaged or excess organelles [65]. Additionally, in resting cells the three ERS receptors are maintained in an inactive state through their association with the ER chaperone, the glucose-regulated protein 78 (GRP78, also known as BiP). Upon accumulation of unfolded proteins, GRP78 dissociates from the three receptors, which leads to their activation and triggers the UPR [66]. The overall consequence of the UPR is the suppression of the global protein expression, but the upregulation of ER chaperons and proteins is involved in degradation pathways. ER homeostasis is maintained by the concerted work of these receptor proteins and the unfolded protein/chaperone system.

ERS in adipose tissues is related to T2D/IR

IR is the condition of the body that does not respond appropriately to circulating insulin [47], which is a common denominator for many

metabolic and cardiovascular complications of obesity that typically precede the onset of T2D. In addition to liver and muscle, IR can occur in adipose tissues, especially [67].

Obesity contributes to many metabolic diseases, although the underlying mechanisms of this contribution have not been thoroughly elucidated to date. However, white adipose tissue emerges as a primary peripheral organ that plays an important role in the initiation and exacerbation of IR, T2D, and atherosclerosis. Ozcan et al. observed that PERK phosphorylation, JNK activity, and GRP78 expression were all significantly increased in the adipose tissue of obese mice compared with lean controls [54]. The results indicate that adipose tissue is a predominant site of ERS, which is induced by obesity. Further, this stress leads to the suppression of insulin receptor signaling through the hyper-activation of JNK and the subsequent serine phosphorylation of insulin receptor substrate-1 (IRS-1) [54]. ERS is now recognized as a molecular link among obesity, the deterioration of insulin action, and the development of T2D.

Insulin activates cellular events by binding to its membrane receptor, which leads to insulin receptor tyrosine kinase activation and the subsequent tyrosine phosphorylation of downstream signaling molecules, such as IRS-1 and IRS-2 [68]. Phosphorylation of IRS-1 on tyrosine residue is required for insulin-stimulated responses, but increased phosphorylation of specific serine residues can render IRS-1 inactive [69]. Insulin action is inhibited by ERS in liver cells and ERS induces insulin receptor signaling by increasing serine phosphorylation and decreasing the tyrosine phosphorylation of IRS-1, which led to IR [54, 55, 70].

Additional JNK-independent mechanisms involved in obesity-induced IR have also been identified. ERS and impaired insulin signaling have been observed in the adipose tissues of obese human subjects and mice fed with a high-fat diet. Zhou et al. found that ERS-induced insulin receptor dysfunction and downregulation in adipocytes is not mediated by the tyrosine phosphorylation of the receptor, per se, but rather by autophagy-dependent ER-associated degradation [71]. The adaptive role of autophagy in response to ERS-induced IR is also seen in another research study on pro-granulin [72].

Treatment of chemical chaperones-such as 4-phenyl butyric acid (4-PBA) and taurine-conjugated ursodeoxycholic acid (TUDCA), which are currently approved by U.S. Food and Drug Administration for use in humans-can potentially reduce ERS, normalize hyperglycemia, restore systemic insulin sensitivity, resolve fatty liver disease, and enhance insulin action in adipose tissues, as well as in the murine model's liver and muscle tissues [55]. The effect of PBA reducing ERS to prevent lipid-induced β-cell dysfunction has been seen in nondiabetic overweight or obese humans [73]. Although the effect of TUDCA increasing insulin sensitivity was not found to be significant in adipose tissue in men and women with obesity [74], ongoing research on chemical chaperones that ameliorate ERS and modulate UPR will potentially be of considerable help in identifying therapeutic targets for human metabolic diseases. The response of relevant biomarkers in the mechanism of ERS-induced T2D is shown in **Table 1**.

ERS in adipose tissues is related to atherosclerosis

There is now ample evidence for the role of ERS in the progression of atherosclerosis. Some ERS and UPR activation markers-such as GRP78, phospho-PERK, and C/EBP homologous protein (CHOP) - have been observed in both human [75] and animal [76] atherosclerotic lesional cells, particularly macrophages and endothelial cells. Notably, only after human blood monocytes were differentiated into macrophages have UPR markers been found in lesions [77]. Several athero-relevant inducers, including oxidative stress, oxysterols, and high levels of intracellular cholesterol and saturated fatty acids, can lead to the prolonged activation of the UPR [78], particularly in the context of obesity, insulin resistance, or diabetes.

It is currently accepted that in addition to lipid disorders, inflammation, and macrophages are an integral part of atherosclerosis pathology [79]. Adipose tissue is composed of not only adipocytes but also a number of other cell types, including pre-adipocytes, macrophages, and vascular cells. Adipose tissue macrophage accumulation is directly proportional to adiposity in humans, and while the macrophages ratio is under 10% in lean adipose tissue, during

Table 1. Response of relevant biomarkers in the mechanism of ERS-induced T2D

Markers	Biological responses	Cells/tissues (Ref.)	Species (Ref.)
GRP78	Expression increased, dissociation from ERS receptors	Adipose tissue [54], 3T3-L1 adipocytes [57], liver tissue [54], HepG2 cells [70]	ob/ob mice [54], murine [57], human [70]
eIF2	Phosphorylation, a key indicator of the presence of ERS	Liver tissue [54], adipose tissues [54], 3T3-L1 adipocytes [57], HepG2 cells [70]	ob/ob mice [54], murine [57], human [70]
PERK	Phosphorylation, a key indicator of the presence of ERS	Liver tissue [54], adipose tissues [54], adipocytes [56]	ob/ob mice [54], human [56]
JNK	Phosphorylation	Adipose tissue [54], Liver tissue [54], adipocytes [56], HepG2 cells [70], 3T3-L1 adipocytes [71]	ob/ob mice [54], human [56], human [70], murine [71]
IRE-1α	Phosphorylation	Mouse embryonic fibroblasts [54], HepG2 cells [70]	ob/ob mice [54], human [70]
ATF6	Expression increased	3T3-L1 adipocytes [57], HepG2 cells [70]	Murine [57], human [70]
IRS-1	Serine phosphorylation, inactive in response to insulin	Liver cells [54], adipose tissues [55], HepG2 cells [70], 3T3-L1 adipocytes [71]	ob/ob mice [55], Rat [54], human [70], murine [71]
CHOP	Expression increased	HepG2 cells [70], 3T3-L1 adipocytes [71]	Human [70], murine [71]

ERs = endoplasmic reticulum stress; GRP78 = glucose-regulated protein 78; eIF2 = subunit of eukaryotic translation initiation factor 2; PERK = double-stranded RNA-activated protein kinase-like endoplasmic reticulum kinase; JNK = c-Jun N-terminal kinase; IRE-1α = inositol-requiring kinase 1α; ATF6 = activating transcription factor 6; IRS-1 = insulin receptor substrate-1; CHOP = C/EBP homologous protein.

obesity, this ratio rises to 50% [80]. Similarly, macrophages comprise only 10-15% of stromal vascular cells (SVCs) in the visceral adipose tissue of lean subjects, but this increases to 40-50% of SVCs in the visceral adipose tissue of humans with obesity [81].

Obese adipose tissue is further characterized by the enhanced infiltration of macrophage and various T-lymphocytes, and the release of abundant pro-inflammatory cytokines - for example, interleukin-6 (IL-6) and the tumor necrosis factor (TNF) [82]. During obesity, the immune cell population differs, both in number and in inflammatory phenotypes. A classically activated macrophage (ATM1) produces large amounts of pro-inflammatory mediators, such as TNF-α, IL-1β, and IL-6, which cause IR in adipose tissue [83]. An alternatively activated macrophage (ATM2) promotes local insulin sensitivity through the production of anti-inflammatory cytokines [84]. Available results have shown that any impairment of macrophage alternative activation can potentially exacerbate the expression of inflammatory markers within adipose tissue [83]. The phenotypic switch in macrophage polarization elicited by diet-induced obesity is widely apparent [83]. Obesity induced by a high-fat diet can also induce depot-specific inflammation in white adipose tissues with the decreased expression of the ATM2 feature [85]. The ratio of ATM1/ATM2 is pivotal in the pathologies of atherosclerosis [86], and a recent comparison study identified that atherosclerotic patients had a higher ATM1/ATM2 ratio and elevated serum M1-related chemokines. It is speculated that the ATM1/ATM2 profile changes are likely to contribute to atherosclerotic progression [87].

As sentinel cells, macrophages use various surface receptors and secreted molecules to monitor and respond to local microenvironmental signals [88]. In adipose tissue, many bioactive molecules called adipokines are produced and secreted in peripheral and visceral adipocytes [89]. Following the onset of obesity, the expression and secretion of adipokines are modified, which leads to the secretory profile of adipocytes shifting towards the pro-inflammatory spectrum. Evidence shows that adipokines and chemokines are key mediators that play crucial roles in crosstalk between adipocytes and macrophages and in the regulation of adipose tissue inflammation. A co-culture system of adipocytes and macrophages *in vitro* is therefore a good model for examining the molecular mechanism through which these cells communicate. TNF-α is a major macrophage-derived mediator of inflammation in adipocytes, and free fatty acids might be important adipocyte-derived mediators of inflammation in macrophages; as

Table 2. Response of relevant biomarkers in the mechanism of ERS-induced atherosclerosis

Markers	Biological responses	Cells/tissues (Ref.)	Species (Ref.)
CHOP	Expression increased; expression downregulated by an adipokine (vaspin)	Histological sections from atherosclerotic coronary artery lesions [75, 76], macrophages [95]	Human [75, 95], E-deficient (apoE$^{-/-}$) mice [76]
GRP78	Expression increased	Histological sections from atherosclerotic coronary artery lesions [75-77], macrophages [77]	Human [75, 77], E-deficient (apoE$^{-/-}$) mice [76, 77]
eIF2	Phosphorylation	Macrophages [77]	Human [77]
PERK	Phosphorylation	Histological sections from atherosclerotic coronary artery lesions [76, 77]	E-deficient (apoE$^{-/-}$) mice [76, 77]
ATF6	Expression downregulated by an adipokine (vaspin)	Macrophages [95]	Human [95]
JNK	Phosphorylated expression downregulated by an adipokine (vaspin)	Macrophages [95]	Human [95]

ERS = endoplasmic reticulum stress; CHOP = C/EBP homologous protein; GRP78 = glucose-regulated protein 78; eIF2 = subunit of eukaryotic translation initiation factor 2; PERK = double-stranded RNA-activated protein kinase-like endoplasmic reticulum kinase; ATF6 = activating transcription factor 6; JNK = c-Jun N-terminal kinase; vaspin = visceral adipose tissue-derived serine protease inhibitor.

such, a paracrine loop involving free fatty acids and TNF-α is postulated to build a cycle that aggravates inflammatory changes in the adipose tissue [90].

To understanding the molecular basis of crosstalk between adipocytes and macrophage infiltration in obese adipose tissue, researchers screened adipocyte genes both *in vivo* and in 3T3-L1 adipocytes co-cultured with RAW264.7 macrophages *in vitro*. The Ras association domain family 6 (RASSF6) was identified, and its mRNA expression was seen to decrease, both in adipocytes conditioned by activated macrophages *in vitro* and in the adipose tissue of obese mice, which suggested that the cellular functions of RASSF6 in adipocytes are regulated through macrophage interactions. Researchers have speculated that the suppressive effect might be partially dependent on the TNF-α released from macrophages, and subsequent results confirmed that the dramatic decrease in the RASSF6 expression in obese adipose tissue can be involved in the control of the differentiation state and/or number of adipocytes during obesity [91]. Researchers later verified through its interaction with activated macrophages that IκB kinase ε expression in adipocytes is upregulated [92].

Another novel adipokine, visceral adipose tissue-derived serine protease inhibitor (vaspin), has been recognized for its potential insulin-sensitizing properties [93], and serum vaspin concentrations are higher in obese humans with T2D [94]. Researchers have observed that vaspin can significantly inhibit the expression levels of ATF6, CHOP, and JNK1/2 of microphages in vitro, and the CHOP expression and necrotic area were decreased in the atherosclerotic plaques of vaspin-transfected apoE$^{-/-}$ mice. These results confirm that vaspin can attenuate the progression of atherosclerosis by inhibiting ERS-induced macrophage apoptosis [95]. The response of relevant biomarkers in the mechanism of ERS-induced atherosclerosis is shown in **Table 2**.

Conclusions

The current epidemic of childhood obesity with the subsequent increasing risk of metabolic disorders has led to a new urgency in metabolic research. T2D increases the risk of atherosclerotic CVDs, and ERS in adipose tissues is aggravated in the initiation and exacerbation of T2D and atherosclerosis. As the largest endocrine organ, adipose tissue will be the key target for curing the metabolic diseases that are associated with obesity. Genetically engineered animal models and the adipocytes-macrophages I co-culture system *in vitro* have demonstrated the crosstalk between adipocytes and macrophages, and researchers are exploring the mechanism of ERS in the pathophysiological progression of T2D and atherosclerosis. Although it is not discussed in this review, other cells within adipose tissue (including pre-adipo-

cytes and SVCs), can also secrete an extensive range of protein signals and factors that are linked to the inflammatory response in the obese condition and might therefore also be sensitive to ERS. It is necessary to devote more energy to developing promising therapeutics and effective drugs to relieve ERS in adipose tissues for the treatment of T2D and atherosclerosis especially in children with obesity.

Acknowledgements

The work was supported by the National Natural Science Foundation Committee of China (No. 81373018 and 81172691).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yinglong Bai, Department of Child and Adolescent Health, School of Public Health, China Medical University, No. 77 Puhe Road, Shenyang North New Area, Shenyang 110122, Liaoning, China. Tel: +86 18900910667; Fax: +86 24 31939406; E-mail: ylbai@cmu.edu.cn

References

[1] World Health Organization. Obesity [Internet]. Geneva, Switzerland: World Health Organization 2017; Available from: http://www.who.int/topics/obesity/en/, accessed on 23/04/2018.

[2] Ogden CL, Carroll MD, Kit BK and Flegal KM. Prevalence of childhood and adult obesity in the united states, 2011-2012. JAMA 2014; 311: 806-814.

[3] Olds T, Maher C, Zumin S, Peneau S, Lioret S, Castetbon K, Bellisle, de Wilde J, Hohepa M, Maddison R, Lissner L, Sjoberg A, Zimmermann M, Aeberli I, Ogden C, Flegal K and Summerbell C. Evidence that the prevalence of childhood overweight is plateauing: data from nine countries. Int J Pediatr Obes 2011; 6: 342-360.

[4] Wang S, Dong Y, Wang Z, Zou Z and Ma J. Trends in overweight and obesity among Chinese children of 7-18 years old during 1985-2014. Zhonghua Yu Fang Yi Xue Za Zhi 2017; 51: 300-305.

[5] Ogden CL CM, Fryar CD, Flegal KM. Prevalence of childhood obesity in the united states, 2011-2014 [Internet]. Atlanta, USA: Centers for Disease Control and Prevention 2015; Available from: https://www.cdc.gov/obesity/data/childhood.html, accessed on 23/04/2018.

[6] Yan Y, Cheng H, Zhao X, Liu J, Hou D, Su Z, Huang G, Ding W, Liu Q and Mi J. Change in the prevalence of obesity phenotypes and cardiometabolic disorders among children aged 6-17 in Beijing during 2004-2013. Zhonghua Yu Fang Yi Xue Za Zhi 2016; 50: 34-39.

[7] Deshmukh-Taskar P, Nicklas TA, Morales M, Yang SJ, Zakeri I and Berenson GS. Tracking of overweight status from childhood to young adulthood: the bogalusa heart study. Eur J Clin Nutr 2006; 60: 48-57.

[8] Togashi K, Masuda H, Rankinen T, Tanaka S, Bouchard C and Kamiya H. A 12-year follow-up study of treated obese children in Japan. Int J Obes Relat Metab Disord 2002; 26: 770-777.

[9] Umer A, Kelley GA, Cottrell LE, Giacobbi P Jr, Innes KE and Lilly CL. Childhood obesity and adult cardiovascular disease risk factors: a systematic review with meta-analysis. BMC Public Health 2017; 17: 683.

[10] O'Connor EA, Evans CV, Burda BU, Walsh ES, Eder M and Lozano P. Screening for obesity and intervention for weight management in children and adolescents: evidence report and systematic review for the US preventive services task force. JAMA 2017; 317: 2427-2444.

[11] Ouchi N. Adipocytokines in cardiovascular and metabolic diseases. J Atheroscler Thromb 2016; 23: 645-654.

[12] Boden G and Merali S. Measurement of the increase in endoplasmic reticulum stress-related proteins and genes in adipose tissue of obese, insulin-resistant individuals. Methods Enzymol 2011; 489: 67-82.

[13] Boden G, Duan X, Homko C, Molina EJ, Song W, Perez O, Cheung P and Merali S. Increase in endoplasmic reticulum stress-related proteins and genes in adipose tissue of obese, insulin-resistant individuals. Diabetes 2008; 57: 2438-2444.

[14] DeFronzo RA, Ferrannini E, Zimmet P and KGMM A. International textbook of diabetes mellitus. Chichester: John Wiley & Sons, Ltd; 2015.

[15] Krishnan S, Coogan PF, Boggs DA, Rosenberg L and Palmer JR. Consumption of restaurant foods and incidence of type 2 diabetes in African American women. Am J Clin Nutr 2010; 91: 465-471.

[16] Jefferies C, Carter P, Reed PW, Cutfield W, Mouat F, Hofman PL and Gunn AJ. The incidence, clinical features, and treatment of type 2 diabetes in children <15 yr in a population-based cohort from Auckland, New Zealand, 1995-2007. Pediatr Diabetes 2012; 13: 294-300.

[17] Amed S, Dean HJ, Panagiotopoulos C, Sellers EA, Hadjiyannakis S, Laubscher TA, Dannen-

baum D, Shah BR, Booth GL and Hamilton JK. Type 2 diabetes, medication-induced diabetes, and monogenic diabetes in Canadian children: a prospective national surveillance study. Diabetes Care 2010; 33: 786-791.
[18] l'Allemand-Jander D. Clinical diagnosis of metabolic and cardiovascular risks in overweight children: early development of chronic diseases in the obese child. Int J Obes (Lond) 2010; 34 Suppl 2: S32-36.
[19] Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, Imperatore G, Linder B, Marcovina S, Pettitt DJ, Pihoker C, Saydah S and Wagenknecht L; SEARCH for Diabetes in Youth Study. Incidence trends of type 1 and type 2 diabetes among youths, 2002-2012. N Engl J Med 2017; 376: 1419-1429.
[20] Fu JF, Liang L, Gong CX, Xiong F, Luo FH, Liu GL, Li P, Liu L, Xin Y, Yao H, Cui LW, Shi X, Yang Y, Chen LQ and Wei HY. Status and trends of diabetes in Chinese children: analysis of data from 14 medical centers. World J Pediatr 2013; 9: 127-134.
[21] Khullar M, Cheema BS and Raut SK. Emerging evidence of epigenetic modifications in vascular complication of diabetes. Front Endocrinol (Lausanne) 2017; 8: 237.
[22] Dabelea D, Stafford JM, Mayer-Davis EJ, D'Agostino R Jr, Dolan L, Imperatore G, Linder B, Lawrence JM, Marcovina SM, Mottl AK, Black MH, Pop-Busui R, Saydah S, Hamman RF and Pihoker C. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. JAMA 2017; 317: 825-835.
[23] Viner R, White B and Christie D. Type 2 diabetes in adolescents: a severe phenotype posing major clinical challenges and public health burden. Lancet 2017; 389: 2252-2260.
[24] Thota P, Perez-Lopez FR, Benites-Zapata VA, Pasupuleti V and Hernandez AV. Obesity-related insulin resistance in adolescents: a systematic review and meta-analysis of observational studies. Gynecol Endocrinol 2017; 33: 179-184.
[25] Li L, Perez A, Wu LT, Ranjit N, Brown HS and Kelder SH. Cardiometabolic risk factors among severely obese children and adolescents in the united states, 1999-2012. Child Obes 2016; 12: 12-19.
[26] Skinner AC, Perrin EM, Moss LA and Skelton JA. Cardiometabolic risks and severity of obesity in children and young adults. N Engl J Med 2015; 373: 1307-1317.
[27] Jayawardene WP, Lohrmann D, Dickinson S, Talagala S and Torabi M. Clinical measures of obesity and cumulative cardiometabolic risk in adolescents. Clin Obes 2017; 7: 11-21.
[28] World Health Organization. Cardiovascular diseases (CVDs) [Internet]. Geneva, Switzerland: World Health Organization 2015. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/, accessed on 23/04/2018.
[29] Chen WW, Gao RL, Liu LS, Zhu ML, Wang W, Wang YJ, Wu ZS, Li HJ, Gu DF, Yang YJ, Zheng Z, Jiang LX and Hu SS. Outline of the report on cardiovascular disease in china, 2015. Chinese Circulation Journal 2016; 31: 521-528.
[30] Oliveira FL, Patin RV and Escrivao MA. Atherosclerosis prevention and treatment in children and adolescents. Expert Rev Cardiovasc Ther 2010; 8: 513-528.
[31] Yan Y, Hou D, Liu J, Zhao X, Cheng H, Yang P, Shan X and Mi J. Effect of childhood adiposity on long-term risks of carotid atherosclerosis and arterial stiffness in adulthood. Zhonghua Yu Fang Yi Xue Za Zhi 2016; 50: 28-33.
[32] Ford ES; National Health and Nutrition Examination Survey. C-reactive protein concentration and cardiovascular disease risk factors in children: findings from the national health and nutrition examination survey 1999-2000. Circulation 2003; 108: 1053-1058.
[33] Davis PH, Dawson JD, Riley WA and Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: the muscatine study. Circulation 2001; 104: 2815-2819.
[34] Daniels SR and Greer FR. Lipid screening and cardiovascular health in childhood. Pediatrics 2008; 122: 198-208.
[35] Magnussen CG, Venn A, Thomson R, Juonala M, Srinivasan SR, Viikari JS, Berenson GS, Dwyer T and Raitakari OT. The association of pediatric low- and high-density lipoprotein cholesterol dyslipidemia classifications and change in dyslipidemia status with carotid intima-media thickness in adulthood evidence from the cardiovascular risk in young finns study, the bogalusa heart study, and the CDAH (childhood determinants of adult health) study. J Am Coll Cardiol 2009; 53: 860-869.
[36] Ding W, Cheng H, Yan Y, Zhao X, Chen F, Huang G, Hou D and Mi J. 10-year trends in serum lipid levels and dyslipidemia among children and adolescents from several schools in Beijing, China. J Epidemiol 2016; 26: 637-645.
[37] Webber LS, Srinivasan SR, Wattigney WA and Berenson GS. Tracking of serum lipids and lipoproteins from childhood to adulthood. The bogalusa heart study. Am J Epidemiol 1991; 133: 884-899.
[38] Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM and Berenson GS. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the bogalusa heart Study. JAMA 2003; 290: 2271-2276.

[39] Steinberger J, Daniels SR, Eckel RH, Hayman L, Lustig RH, McCrindle B, Mietus-Snyder ML; American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism. Progress and challenges in metabolic syndrome in children and adolescents: a scientific statement from the American heart association atherosclerosis, hypertension, and obesity in the young committee of the council on cardiovascular disease in the young; council on cardiovascular nursing; and council on nutrition, physical activity, and metabolism. Circulation 2009; 119: 628-647.

[40] Kannel WB and McGee DL. Diabetes and cardiovascular disease. The framingham study. JAMA 1979; 241: 2035-2038.

[41] Rhodes ET, Prosser LA, Hoerger TJ, Lieu T, Ludwig DS and Laffel LM. Estimated morbidity and mortality in adolescents and young adults diagnosed with type 2 diabetes mellitus. Diabet Med 2012; 29: 453-463.

[42] Fonseca V, Desouza C, Asnani S and Jialal I. Nontraditional risk factors for cardiovascular disease in diabetes. Endocr Rev 2004; 25: 153-175.

[43] Renard CB, Kramer F, Johansson F, Lamharzi N, Tannock LR, von Herrath MG, Chait A and Bornfeldt KE. Diabetes and diabetes-associated lipid abnormalities have distinct effects on initiation and progression of atherosclerotic lesions. J Clin Invest 2004; 114: 659-668.

[44] Lamharzi N, Renard CB, Kramer F, Pennathur S, Heinecke JW, Chait A and Bornfeldt KE. Hyperlipidemia in concert with hyperglycemia stimulates the proliferation of macrophages in atherosclerotic lesions: potential role of glucose-oxidized LDL. Diabetes 2004; 53: 3217-3225.

[45] Morel O, Jesel L, Abbas M and Morel N. Prothrombotic changes in diabetes mellitus. Semin Thromb Hemost 2013; 39: 477-488.

[46] Parathath S, Grauer L, Huang LS, Sanson M, Distel E, Goldberg IJ and Fisher EA. Diabetes adversely affects macrophages during atherosclerotic plaque regression in mice. Diabetes 2011; 60: 1759-1769.

[47] Kahn SE, Hull RL and Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006; 444: 840-846.

[48] Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, Knowler WC, Bennett PH and Bogardus C. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of pima Indians. N Engl J Med 1993; 329: 1988-1992.

[49] Misra A. Risk factors for atherosclerosis in young individuals. J Cardiovasc Risk 2000; 7: 215-229.

[50] Bourgeois F, Alexiu A and Lemonnier D. Dietary-induced obesity: effect of dietary fats on adipose tissue cellularity in mice. Br J Nutr 1983; 49: 17-26.

[51] Thomas A, Belaidi E, Aron-Wisnewsky J, van der Zon GC, Levy P, Clement K, Pepin JL, Godin-Ribuot D and Guigas B. Hypoxia-inducible factor prolyl hydroxylase 1 (PHD1) deficiency promotes hepatic steatosis and liver-specific insulin resistance in mice. Sci Rep 2016; 6: 24618.

[52] Ka SO, Song MY, Bae EJ and Park BH. Myeloid SIRT1 regulates macrophage infiltration and insulin sensitivity in mice fed a high-fat diet. J Endocrinol 2015; 224: 109-118.

[53] Kawasaki N, Asada R, Saito A, Kanemoto S and Imaizumi K. Obesity-induced endoplasmic reticulum stress causes chronic inflammation in adipose tissue. Sci Rep 2012; 2: 799.

[54] Ozcan U, Cao Q, Yilmaz E, Lee AH, Iwakoshi NN, Ozdelen E, Tuncman G, Gorgun C, Glimcher LH and Hotamisligil GS. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science 2004; 306: 457-461.

[55] Ozcan U, Yilmaz E, Ozcan L, Furuhashi M, Vaillancourt E, Smith RO, Gorgun CZ and Hotamisligil GS. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. Science 2006; 313: 1137-1140.

[56] Alhusaini S, McGee K, Schisano B, Harte A, McTernan P, Kumar S and Tripathi G. Lipopolysaccharide, high glucose and saturated fatty acids induce endoplasmic reticulum stress in cultured primary human adipocytes: salicylate alleviates this stress. Biochem Biophys Res Commun 2010; 397: 472-478.

[57] Kamiya T, Hara H and Adachi T. Effect of endoplasmic reticulum (ER) stress inducer thapsigargin on the expression of extracellular-superoxide dismutase in mouse 3T3-L1 adipocytes. J Clin Biochem Nutr 2013; 52: 101-105.

[58] Schroder M and Kaufman RJ. ER stress and the unfolded protein response. Mutat Res 2005; 569: 29-63.

[59] Walter P and Ron D. The unfolded protein response: from stress pathway to homeostatic regulation. Science 2011; 334: 1081-1086.

[60] Lee J and Ozcan U. Unfolded protein response signaling and metabolic diseases. J Biol Chem 2014; 289: 1203-1211.

[61] Yorimitsu T, Nair U, Yang Z and Klionsky DJ. Endoplasmic reticulum stress triggers autophagy. J Biol Chem 2006; 281: 30299-30304.

[62] Gan L, Liu Z, Luo D, Ren Q, Wu H, Li C and Sun C. Reduced endoplasmic reticulum stress-mediated autophagy is required for leptin alleviating inflammation in adipose tissue. Front Immunol 2017; 8: 1507.
[63] Benbrook DM and Long A. Integration of autophagy, proteasomal degradation, unfolded protein response and apoptosis. Exp Oncol 2012; 34: 286-297.
[64] Chakrabarti A, Chen AW and Varner JD. A review of the mammalian unfolded protein response. Biotechnol Bioeng 2011; 108: 2777-2793.
[65] Chen X and Yin XM. Coordination of autophagy and the proteasome in resolving endoplasmic reticulum stress. Vet Pathol 2011; 48: 245-253.
[66] Brewer JW. Regulatory crosstalk within the mammalian unfolded protein response. Cell Mol Life Sci 2014; 71: 1067-1079.
[67] Tan SX, Fisher-Wellman KH, Fazakerley DJ, Ng Y, Pant H, Li J, Meoli CC, Coster AC, Stockli J and James DE. Selective insulin resistance in adipocytes. J Biol Chem 2015; 290: 11337-11348.
[68] Withers DJ and White M. Perspective: the insulin signaling system–a common link in the pathogenesis of type 2 diabetes. Endocrinology 2000; 141: 1917-1921.
[69] Gual P, Le Marchand-Brustel Y and Tanti JF. Positive and negative regulation of insulin signaling through IRS-1 phosphorylation. Biochimie 2005; 87: 99-109.
[70] Kim DS, Jeong SK, Kim HR, Kim DS, Chae SW and Chae HJ. Effects of triglyceride on ER stress and insulin resistance. Biochem Biophys Res Commun 2007; 363: 140-145.
[71] Zhou L, Zhang J, Fang Q, Liu M, Liu X, Jia W, Dong LQ and Liu F. Autophagy-mediated insulin receptor down-regulation contributes to endoplasmic reticulum stress-induced insulin resistance. Mol Pharmacol 2009; 76: 596-603.
[72] Guo Q, Xu L, Li H, Sun H, Liu J, Wu S and Zhou B. Progranulin causes adipose insulin resistance via increased autophagy resulting from activated oxidative stress and endoplasmic reticulum stress. Lipids Health Dis 2017; 16: 25.
[73] Xiao C, Giacca A and Lewis GF. Sodium phenylbutyrate, a drug with known capacity to reduce endoplasmic reticulum stress, partially alleviates lipid-induced insulin resistance and beta-cell dysfunction in humans. Diabetes 2011; 60: 918-924.
[74] Kars M, Yang L, Gregor MF, Mohammed BS, Pietka TA, Finck BN, Patterson BW, Horton JD, Mittendorfer B, Hotamisligil GS and Klein S. Tauroursodeoxycholic Acid may improve liver and muscle but not adipose tissue insulin sensitivity in obese men and women. Diabetes 2010; 59: 1899-1905.
[75] Myoishi M, Hao H, Minamino T, Watanabe K, Nishihira K, Hatakeyama K, Asada Y, Okada K, Ishibashi-Ueda H, Gabbiani G, Bochaton-Piallat ML, Mochizuki N and Kitakaze M. Increased endoplasmic reticulum stress in atherosclerotic plaques associated with acute coronary syndrome. Circulation 2007; 116: 1226-1233.
[76] Zhou J, Lhotak S, Hilditch BA and Austin RC. Activation of the unfolded protein response occurs at all stages of atherosclerotic lesion development in apolipoprotein E-deficient mice. Circulation 2005; 111: 1814-1821.
[77] Dickhout JG, Lhotak S, Hilditch BA, Basseri S, Colgan SM, Lynn EG, Carlisle RE, Zhou J, Sood SK, Ingram AJ and Austin RC. Induction of the unfolded protein response after monocyte to macrophage differentiation augments cell survival in early atherosclerotic lesions. FASEB J 2011; 25: 576-589.
[78] Seimon T and Tabas I. Mechanisms and consequences of macrophage apoptosis in atherosclerosis. J Lipid Res 2009; 50 Suppl: S382-387.
[79] Lohmann C, Schafer N, von Lukowicz T, Sokrates Stein MA, Boren J, Rutti S, Wahli W, Donath MY, Luscher TF and Matter CM. Atherosclerotic mice exhibit systemic inflammation in periadventitial and visceral adipose tissue, liver, and pancreatic islets. Atherosclerosis 2009; 207: 360-367.
[80] Cinti S, Mitchell G, Barbatelli G, Murano I, Ceresi E, Faloia E, Wang S, Fortier M, Greenberg AS and Obin MS. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. J Lipid Res 2005; 46: 2347-2355.
[81] Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL and Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003; 112: 1796-1808.
[82] Wellen KE and Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. J Clin Invest 2003; 112: 1785-1788.
[83] Lumeng CN, Bodzin JL and Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007; 117: 175-184.
[84] Olefsky JM and Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol 2010; 72: 219-246.
[85] Wang N, Guo J, Liu F, Wang M, Li C, Jia L, Zhai L, Wei W and Bai Y. Depot-specific inflammation with decreased expression of ATM2 in white adipose tissues induced by highmargarine/lard intake. PLoS One 2017; 12: e0188007.
[86] Mills CD. M1 and M2 macrophages: oracles of health and disease. Crit Rev Immunol 2012; 32: 463-488.

[87] Williams H, Cassorla G, Pertsoulis N, Patel V, Vicaretti M, Marmash N, Hitos K, Fletcher JP and Medbury HJ. Human classical monocytes display unbalanced M1/M2 phenotype with increased atherosclerotic risk and presence of disease. Int Angiol 2017; 36: 145-155.

[88] McWhorter FY, Davis CT and Liu WF. Physical and mechanical regulation of macrophage phenotype and function. Cell Mol Life Sci 2015; 72: 1303-1316.

[89] Proenca AR, Sertie RA, Oliveira AC, Campana AB, Caminhotto RO, Chimin P and Lima FB. New concepts in white adipose tissue physiology. Braz J Med Biol Res 2014; 47: 192-205.

[90] Suganami T, Nishida J and Ogawa Y. A paracrine loop between adipocytes and macrophages aggravates inflammatory changes: role of free fatty acids and tumor necrosis factor alpha. Arterioscler Thromb Vasc Biol 2005; 25: 2062-2068.

[91] Sanada Y, Kumoto T, Suehiro H, Nishimura F, Kato N, Hata Y, Sorisky A and Yanaka N. RASSF6 expression in adipocytes is down-regulated by interaction with macrophages. PLoS One 2013; 8: e61931.

[92] Sanada Y, Kumoto T, Suehiro H, Yamamoto T, Nishimura F, Kato N and Yanaka N. IκB kinase epsilon expression in adipocytes is upregulated by interaction with macrophages. Biosci Biotechnol Biochem 2014; 78: 1357-1362.

[93] Hida K, Wada J, Eguchi J, Zhang H, Baba M, Seida A, Hashimoto I, Okada T, Yasuhara A, Nakatsuka A, Shikata K, Hourai S, Futami J, Watanabe E, Matsuki Y, Hiramatsu R, Akagi S, Makino H and Kanwar YS. Visceral adipose tissue-derived serine protease inhibitor: a unique insulin-sensitizing adipocytokine in obesity. Proc Natl Acad Sci U S A 2005; 102: 10610-10615.

[94] Youn BS, Kloting N, Kratzsch J, Lee N, Park JW, Song ES, Ruschke K, Oberbach A, Fasshauer M, Stumvoll M and Bluher M. Serum vaspin concentrations in human obesity and type 2 diabetes. Diabetes 2008; 57: 372-377.

[95] Lin Y, Zhuang J, Li H, Zhu G, Zhou S, Li W, Peng W and Xu Y. Vaspin attenuates the progression of atherosclerosis by inhibiting ER stress-induced macrophage apoptosis in apoE/mice. Mol Med Rep 2016; 13: 1509-1516.