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Endoplasmic reticulum stress and development of insulin resistance in adipose, skeletal, liver, and foetoplacental tissue in diabesity

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ABSTRACT

Diabesity is an abnormal metabolic condition shown by patients with obesity that develop type 2 diabetes mellitus. Patients with diabesity present with insulin resistance, reduced vascular response to insulin, and vascular endothelial dysfunction. Along with the several well-described mechanisms of insulin resistance, a state of endoplasmic reticulum (ER) stress, where the primary human targets are the adipose tissue, liver, skeletal muscle, and the foetoplacental vasculature, is apparent. ER stress characterises by the activation of the unfolded protein response via three canonical ER stress sensors, i.e., the protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1α (IRE1α), and activating transcription factor 6. Slightly different cell signalling mechanisms preferentially enable in diabesity in the ER stress-associated insulin resistance for adipose tissue (IRE1α/X-box binding protein 1 mRNA splicing/c-jun N-terminal kinase 1 activation), skeletal muscle (tribbles-like protein 3 (TRB3)/proinflammatory cytokines activation), and liver (PERK/activating transcription factor 4/TRB3 activation). There is no information in human subjects with diabesity in the foetoplacental vasculature. However, the available literature shows that pregnant women with pre-pregnancy obesity or overweight that develop gestational diabetes mellitus (GDM) and their newborn show insulin resistance. ER stress is recently reported to be triggered in endothelial cells from the human umbilical vein from mothers with pre-pregnancy obesity. However, whether a different metabolic alteration to obesity in pregnancy or GDM is present in women with pre-pregnancy obesity that develop GDM, is unknown. In this review, we summarised the findings on diabesity-associated mechanisms of insulin resistance with emphasis in the primary targets adipose, skeletal muscle, liver, and foetoplacental tissues. We also give evidence on the possibility of a new GDM-associated metabolic condition triggered in pregnancy by maternal obesity, i.e. gestational diabesity, leading to ER stress-associated insulin resistance in the human foetoplacental vasculature.

1. Introduction

Insulin is a hormone that is synthesised and released by the pancreatic β-cells in response to a variety of stimuli (Fu et al., 2013). The cells respond to insulin following activation of insulin receptors expressed at the plasma cell membrane, which leads to modifications of intracellular cell signalling ending in activation of cell metabolism. When a defective insulin signalling is seen, cells are metabolically disturbed and the normal physiological response to this hormone is altered, including disruption of the classical phosphatidylinositol 3 kinase (PI3K)-protein kinase B/Akt (Akt) and mitogen-activated protein kinases (MAPK) signalling pathways (Villalobos-Labra et al., 2017).

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Reduced insulin signalling is referred as insulin resistance, a condition seen in subjects affected with metabolic diseases such as obesity or type 2 diabetes mellitus (T2DM).

Obesity is a metabolic disease whose prevalence is increasing worldwide (WHO, 2018). Obese subjects show a high risk of developing hypertension, coronary heart disease, cardiovascular disease, T2DM, and insulin resistance. Also, maternal obesity in pregnancy results in different alterations in the normal physiology of the placenta leading to altered foetal development and growth (Desoye, 2018; Van De Maele et al., 2018). Thus, obesity is a disease with deleterious consequences from the gestational life through the whole lifespan period. Obesity-associated organs and cells dysfunction results from a condition where the endoplasmic reticulum (ER) homeostasis is disrupted. These alterations lead to a state of ER stress which characterises by an increase in the unfolded protein response (UPR) in most cells, including adipocytes and vascular endothelium (Van De Maele et al., 2018; Villalobos-Labra et al., 2017, 2018).

A large fraction of obese patients results in developing T2DM and are considered a group of subjects with an unhealthy condition referred to as 'diabesity' (Kalra, 2013; Ziv and Shafir, 1995). Patients with T2DM account for 90–95% of all diabetes and show a progressive loss of β-cell insulin secretion with abnormal insulin sensitivity due to defective cell signalling after activation of insulin receptors in the target tissues (ADA, 2018). Subjects at higher risk of developing this disease show previous maternal history of diabetes or gestational diabetes mellitus (GDM) during their gestational period, family history of T2DM, belong to certain racial/ethnic subgroup such as Native American, African American, Latino, and Asian American, or show signs of insulin resistance or conditions associated such as hypertension, dyslipidaemia, polycystic ovary syndrome, or being small-for-gestational age at birth.

Obesity management is the main line of action aiming to reduce the prevalence or incidence of T2DM (ADA, 2018). Therefore, a direct relationship concerning metabolic alterations between these two diseases is seen. One of these common links between T2DM and obesity is ER stress (Van De Maele et al., 2018) (Fig. 1). Patients with T2DM show with inflammation, a common condition between patients with obesity and T2DM (Esser et al., 2014), where a multi-organ dysfunction is seen including the liver, skeletal muscle, adipose tissue, brain, pancreas, and placenta. ER stress in T2DM also results in glucotoxicity, lipids associated toxicity, or apoptosis in an organ or cell-specific manner.

ER stress being an alteration in the function of organs and cells in the human body in obesity or T2DM, results in a potential target for treating or even preventing these disease-associated alterations in insulin resistance in different insulin target organs. However, it is unclear whether patients with diabesity (i.e., obese patients that develop T2DM) (Kalra, 2013; Ziv and Shafir, 1995) show abnormal tissue and ER homeostasis. In this review, the potential role of ER stress in insulin resistance and the involvement of these alterations in the abnormal organ and cell function seen in diabesity is summarised.

2. Diabesity

Diabesity is the term used to define the result of a combination of several factors determining metabolic disorders with a state of insulin resistance (Kalra, 2013; Potenza et al., 2017; Ziv and Shafir, 1995). It was originally described that patients that were obese and as a consequence of this metabolic pathology develop T2DM are considered as affected by diabesity (Kalra, 2013; Ziv and Shafir, 1995). It is unclear whether patients that are overweight and develop T2DM must be considered as patients affected by diabesity or a different clinical figure. The increased incidence of T2DM and obesity worldwide shows a pattern of metabolic alterations that are not exclusive for obesity or T2DM, but a mix of clinical parameters, thus making every time more difficult to separate patients with obesity from those with T2DM only. Patients showing diabesity present with common characteristics that have been described for obesity or T2DM including endothelial and vascular, as well as skeletal muscle, adipose tissue, and liver dysfunction in response to vasoactive endogenous molecules such as insulin, adenosine, or endothelin-1 (Campia et al., 2014; Pardo et al., 2017; Silva et al., 2017).

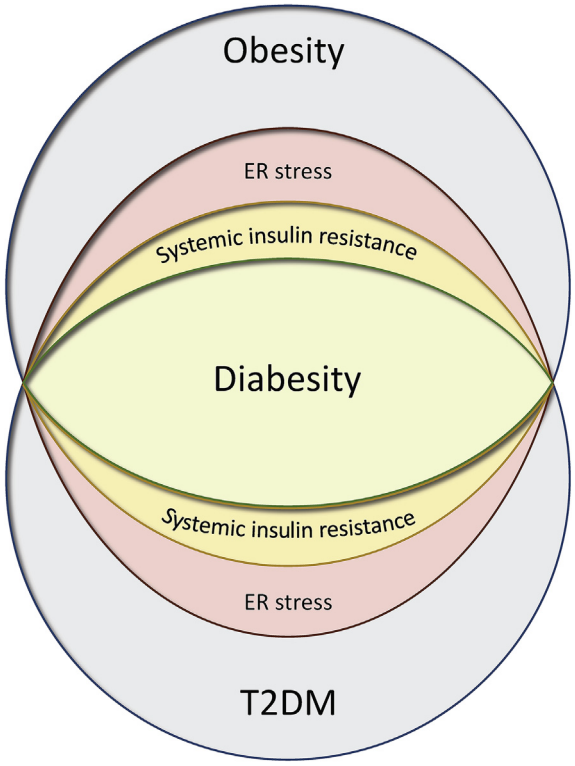

Fig. 1. Diabesity and endoplasmic reticulum stress. Obesity is a pathology associated with severe metabolic alterations which, in most cases, end in subjects developing type 2 diabetes mellitus (T2DM). Several specific mechanisms are reported to associate with these diseases among which the endoplasmic reticulum stress (ER stress) is one of these alterations that seems to be a common factor. ER stress results in abnormal cell signalling in response to insulin leading to systemic insulin resistance in these individuals that are nowadays referred as affected by diabesity. The metabolic condition of diabesity results from the congregate of the cell signalling alterations seen individually in patients with obesity and T2DM.

3. Endoplasmic reticulum stress

The homeostasis of the endoplasmic reticulum (ER), an organelle in charge of the synthesis and processing for secretory and membrane proteins, Ca^{2+} storage, and lipid biosynthesis (Cnop et al., 2012; Flamment et al., 2012), is maintained by a variety of modulatory mechanisms securing cell survival, proliferation, growth, among others. A disturbance of this state results in an altered metabolism and ER stress (Ghemrawi et al., 2018; Hetz et al., 2015; Mukherjee et al., 2015) as reported in patients with obesity, T2DM, GDM, or diabesity (Van De Maele et al., 2018; Villalobos-Labra et al., 2017, 2018).

ER stress results in accumulation of misfolding proteins and activation of UPR in most cells (Ghemrawi et al., 2018; Mukherjee et al., 2015; Van De Maele et al., 2018), including the human adult (Kaplon et al., 2013) and foetal endothelium (Villalobos-Labra et al., 2018). The UPR activation is intended to restore the defective homeostasis of the endoplasmic reticulum and characterises by the activation of three canonical ER stress sensors, i.e., the protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1α (IRE1α), and activating transcription factor 6 (ATF6) (Ghemrawi et al., 2018; Hetz et al., 2015; Mukherjee et al., 2015; Villalobos-Labra et al., 2018).

PERK phosphorylates the eukaryotic translation initiator factor 2

(eIF2), which attenuates the general protein translation but increases the translation of some proteins (Komar and Hatzoglou, 2011) including the activating transcription factor 4 (ATF4), a key transcription factor for PERK-modulated gene expression. IRE1α shows kinase and endoribonuclease activity catalysing the processing of X-box binding protein 1 (XBP1) mRNA, cleaving a 26-nucleotide intron, and shifting the reading frame to translate the transcription factor XBP1 spliced (XBP1s). The cytosolic domain of IRE1α binds to tumour necrosis factor receptor-associated factor 2 (TRAF2), activating the IκB kinase β (IKKβ) and c-jun N-terminal kinase 1 (JNK1) pathways through IRE1α kinase domain. ATF6 translocates to the Golgi where it is cleaved. The cleaved-off cytoplasmic domain acts as a transcriptional activator for several genes. Through the expression of chaperones, such as binding immunoglobulin protein, calnexin, or calreticulin, foldases (e.g. protein disulfide isomerase A3), and genes involved in redox metabolism, antioxidant proteins, autophagy, and apoptosis (e.g. CCAAT-enhancer-binding protein homologous protein (CHOP)) among others, UPR is aimed to reduce the unfolded protein load and to increase the size and the folding capacity of ER to restore its homeostasis (Cnop et al., 2012; Dufey et al., 2014; Hetz et al., 2015).

4. Diabesity and ER stress-induced insulin resistance

ER stress is a key phenomenon in the obesity- and T2DM-associated adverse metabolic outcomes, including insulin resistance in key metabolic organs (Table 1) (Cnop et al., 2012; Flamment et al., 2012). The causes leading to ER stress are still not well defined; however, one of the proposed causes is the increase in the circulating proinflammatory cytokines seen in these metabolic conditions (Esser et al., 2014). Cytokines, such as tumour necrosis factor α (TNFα) or interleukin 6 (IL-6) induce ER stress in different cell types (Denis et al., 2010; Hardy et al., 2012; Hu et al., 2006; McArdle et al., 2013; Xue et al., 2005). Also, the major concentration of free fatty acids (FFAs) in blood seen in obesity and T2DM (Boden, 2009; Mandal et al., 2017) contributes to the generation of ER stress in different cell types (Alhusaini et al., 2010; Jiao et al., 2011; Kim et al., 2015). Hyperglycaemia and hyperinsulinemia, common characteristics in the metabolic syndrome-associated diseases, are also shown to induce ER stress in human tissues (Boden et al., 2014b) (Fig. 2). However, studies in diabesity patients are necessary to define clearly the potential factors involved in this particular metabolic abnormality.

Several mechanisms linking ER stress with insulin resistance through the direct disruption of the insulin signalling pathway are described, but currently, the most supported by literature are two mechanisms proposed in the contexts of obesity and T2DM. The first one is an IRE1α-dependent activation of JNK1, which results in insulin receptor substrate 1 (IRS1) inhibitory serine phosphorylation in obesity associated-systemic insulin resistance (Flamment et al., 2012; Hirosumi et al., 2002; Ozcan et al., 2004). The second mechanism involves activation of PERK/eIF2/ATF4 signalling leading to increased expression of tribbles-like protein 3 (TRB3) (Ohoka et al., 2005), a pseudokinase that inhibits Akt activity promoting insulin resistance (Du et al., 2003; Flamment et al., 2012; Ozcan et al., 2013). As shown below, JNK1 activation and TRB3 expression are increased in different organs from patients with obesity or T2DM. Thus, JNK1 and TRB3 are suggested as links involved in diabesity-induced insulin resistance. Here we summarise the available information of the main metabolic organs associated to diabesity-associated metabolic alterations.

4.1. Adipose tissue

Adipose tissue is considered a master regulator of systemic energy homeostasis by being involved in energy expenditure by thermogenesis, energy storage, and in the regulation of key metabolic organs, such as liver, skeletal muscle, and pancreas (Kusminski et al., 2016). Adipose tissue is of two types: brown adipose tissue, involved in thermogenesis, and white adipose tissue (WAT), as the major adipose depot in the body contributing to the control of systemic metabolic homeostasis (McArdle et al., 2013). WAT is sub-grouped depending on its anatomical location, i.e., the subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). WAT plays a key role in the regulation of insulin sensitivity in target tissues, such as skeletal muscle and liver, two of the main organs involved in D-glucose homeostasis control (Bjørndal et al., 2011; Hardy et al., 2012; Wilcox, 2005). Thus, dysfunction of the adipose tissue is a condition tightly related to the development of insulin resistance contributing to the development of obesity-associated T2DM or diabesity (Kohlgruber and Lynch, 2015; Kusminski et al., 2016).

Although the whole WAT is involved in insulin resistance, an increase in only the VAT volume in obesity was associated with higher risk to develop insulin resistance and T2DM (Bjørndal et al., 2011; Hardy et al., 2012). The regulation of insulin sensitivity by WAT is mainly given by its function as an endocrine organ through the release of adipokines (adipocytes-derived hormones). Leptin and adiponectin increase but TNFα, IL-6 or interleukin 1 (IL-1) decrease the insulin sensitivity in targets organs (Hardy et al., 2012; McArdle et al., 2013). On the other hand, the increase of VAT volume in obesity and the insulin resistance itself result in a higher release of FFAs into the circulation leading to the accumulation of these molecules in target tissues, including the skeletal muscle and liver. This phenomenon induces toxicity and promotes insulin resistance in these tissues (Kahn and Flier, 2000; McArdle et al., 2013). Thus, a better understanding of the mechanisms that regulate WAT function in diabesity may be relevant in the control of systemic insulin resistance in patients with this abnormal metabolic condition.

ER stress is also seen in association with adipose tissue dysfunction. ER stress is detected in SAT (Alhusaini et al., 2010; Boden et al., 2008; Díaz-Ruiz et al., 2015; Vendrell et al., 2010) and VAT (Alhusaini et al., 2010; Liong and Lappas, 2015; Vendrell et al., 2010) from patients that are overweight or obese (Table 1). Interestingly, loss of weight reduces ER stress in WAT as seen after bariatric surgery (Gregor et al., 2009). Thus, WAT from patients with obesity also presents ER stress. On the other hand, T2DM has also been related with ER stress in the adipose tissue, particularly in SAT (Boden et al., 2014a) and VAT (Li et al., 2014). Currently, there are no studies addressing ER stress in subjects with diabesity; however, some reports refer to patients with T2DM that were also with overweight or obesity, even when they do not refer to these subjects as having diabesity (Boden et al., 2014a; Vendrell et al., 2010). These studies show that diabetes in obese patients does not change the ER stress seen in VAT and SAT from subjects only with obesity. In addition to the studies in obese subjects, and again not specifically mentioned by the authors, pregnant women affected by only with obesity and pregnant women with obesity that developed GDM showed a similar increase of ER stress markers in VAT (Liong and Lappas, 2015). Thus, GDM does not increase ER stress over that induced by obesity. These findings suggest that diabetes *per se* would not increase the ER stress present in obesity, but diabetes alone also causes ER stress. Thus, although more studies are still needed in patients with diabesity, the occurrence of ER stress in adipose tissues from this condition is likely.

ER stress is associated with the development of insulin resistance in adipose tissue. Induction of ER stress by tunicamycin (ER stress inducer) in human preadipocytes-visceral cells reduced IRS1 and Akt phosphorylation in response to insulin, which was caused through the activation of an IRE1α/JNK1 signalling pathway (Li et al., 2014). This mechanism has been fully described in mice adipocytes and in other cell types (Ozcan et al., 2004; Xu et al., 2010). IRE1α activation, XBP1 splicing, and JNK1 activation are reported to be increased in adipose tissue of patients with obesity and in patients with T2DM (Boden et al., 2008; Li et al., 2014). Despite there are reports on the actual measurement of these proteins in patients with diabesity, the described findings strongly suggest that this could be one mechanism of ER stress-induced insulin resistance in adipose tissue from this type of patients

Table 1
Induced endoplasmic reticulum stress in human tissues in pathologies associated with obesity.

Pathology	Tissue/cell	Effect	Protein abundance	mRNA level	Reference
Diabesity[a]	Skeletal muscle	Increase	–	TRB3	Liu et al. (2010)
Obesity	SAT	Increase	PDI CRT CNX P ~ JNK1	XBP1s	Boden et al. (2008)
Obesity	OAT	Increase	IRE1α BiP	XBP1s	Liong and Lappas (2015)
Obesity	Adipose tissue	Increase	P ~ eIF2	XBP1s ATF6	Sharma et al., 2008
Obesity	Abdominal SAT	Decrease	P ~ eIF2 BiP P ~ JNK1	XBP1s	Gregor et al. (2009)
Obesity	Abdominal SAT	Increase	IRE1α BiP	ATF6	Alhusaini et al. (2010)
Obesity[b]	SAT	Increase	CHOP P ~ JNK1	–	Díaz-Ruiz et al. (2015)
Obesity	Skeletal muscle	Increase	IRE1α BiP	XBP1s	Liong and Lappas (2016)
Obesity	Placenta	Increase	P ~ eIF2	XBP1s	Yung et al. (2016)
Obesity	HUVECs	Increase	P ~ PERK IRE1α ATF6[c] P ~ eIF2 CHOP TRB3 P ~ JNK1	CHOP TRB3 BiP – – – –	Villalobos-Labra et al. (2018)
Severe obesity[d]	VAT, SAT	Increase	BiP	XBP1s	Vendrell et al. (2010)
T2DM	Visceral preadipocytes from OAT	Increase	P ~ PERK P ~ eIF2 P ~ JNK1 P ~ IRE1α	ATF6 XBP1s – –	Li et al. (2014)
GDM	OAT	Increase	IRE1α BiP	XBP1s	Liong and Lappas (2015)
GDM	Skeletal muscle	Increase	IRE1α BiP	XBP1s	Liong and Lappas (2016)
GDM	Placenta	Increase	P ~ eIF2	XBP1s	Yung et al. (2016)
GDM	HUVECs	Increase	CHOP	–	Farías et al. (2010)
Gestational diabesity[e]	OAT	Increase	IRE1α BiP	XBP1s	Liong and Lappas (2015)
Gestational diabesity[e]	Skeletal muscle	Increase	IRE1α BiP	XBP1s	Liong and Lappas (2016)

T2DM, type 2 diabetes mellitus; HUVECs, human umbilical vein endothelial cells; SAT, subcutaneous adipose tissue; OAT, omental adipose tissue; VAT, visceral adipose tissue; P ~ PERK, phosphorylated protein kinase RNA-like endoplasmic reticulum kinase; TRB3, tribbles-like protein 3; PDI, protein disulfide isomerase A3; CRT, calreticulin; CNX, calnexin; P ~ JNK1, phosphorylated c-jun N-terminal kinase 1 phosphorylated; XBP1s, spliced X-box binding protein 1 mRNA; IRE1α, inositol-requiring enzyme 1α; BiP, binding immunoglobulin protein; P ~ eIF2, phosphorylated eukaryotic translation initiator factor 2; ATF6, activating transcription factor 6; CHOP, CCAAT-enhancer-binding protein homologous protein. –, not reported.

[a] Obese subjects with T2DM.
[b] Comparison between obese subjects with insulin resistance versus obese subjects without insulin resistance.
[c] Protein translocation to the nucleus.
[d] Severe obesity refers to BMI ≥ 40 kg/m^2.
[e] Pregnancies where the mother was obese and developed gestational diabetes mellitus (GDM).

(Fig. 2).

TRB3 is another potential link between ER stress and insulin resistance in adipose tissue from diabesity. This protein has been associated with the development of insulin resistance in the metabolic syndrome (Marinho et al., 2015). That relationship is made by a direct disruption on the insulin signalling pathway through the inhibition of Akt (Du et al., 2003), a mechanism that is also described in adipocytes (Du and Ding, 2009). A recent study in rats induced to have diabesity showed that TRB3 is increased in the adipose tissue and that TRB3 silencing increased insulin response in this tissue and the systemic insulin sensitivity (Sun et al., 2017). Since TRB3 protein level is reported to be increased in the blood of patients with obesity (Nourbakhsh et al., 2017), this protein involvement in adipose tissue insulin resistance is likely. However, it is still needed to run studies in adipose tissue from subjects with diabesity.

ER stress in adipocytes not only causes insulin resistance in adipose tissue, but it is involved in the promotion of insulin desensitisation in other organs. ER stress associated with reduced adiponectin secretion, whose plasma level is reduced in patients with obesity and with T2DM (Blüher, 2014; Yamamoto et al., 2014). Induction of ER stress in human adipocytes *in vitro* reduces adiponectin expression (Mondal et al., 2012; Xu et al., 2010). That is further supported by findings showing that a high-fat diet-induced ER stress in VAT and SAT of mice reduced the release of adiponectin, and that reduction of ER stress increases extracellular adiponectin levels (Torre-Villalvazo et al., 2018). Thus, ER stress present in the adipose tissue of patients with diabesity could result in reducing the adiponectin level in the plasma of these subjects.

Studies *in vitro* and in animal models showed that ER stress promotes the secretion of proinflammatory cytokines by the adipocytes (Kawasaki et al., 2012; Xu et al., 2010). Thus, ER stress may be involved in the higher secretion of proinflammatory cytokines by the adipose tissue reported in obesity and T2DM, including TNFα, IL-6, and IL-1 (Boden et al., 2014a, 2008; Li et al., 2014). Also, the mentioned cytokines contribute to inducing ER stress and insulin desensitisation in other organs (Hardy et al., 2012; Kohlgruber and Lynch, 2015; McArdle et al., 2013). Additionally, insulin desensitisation and ER stress itself

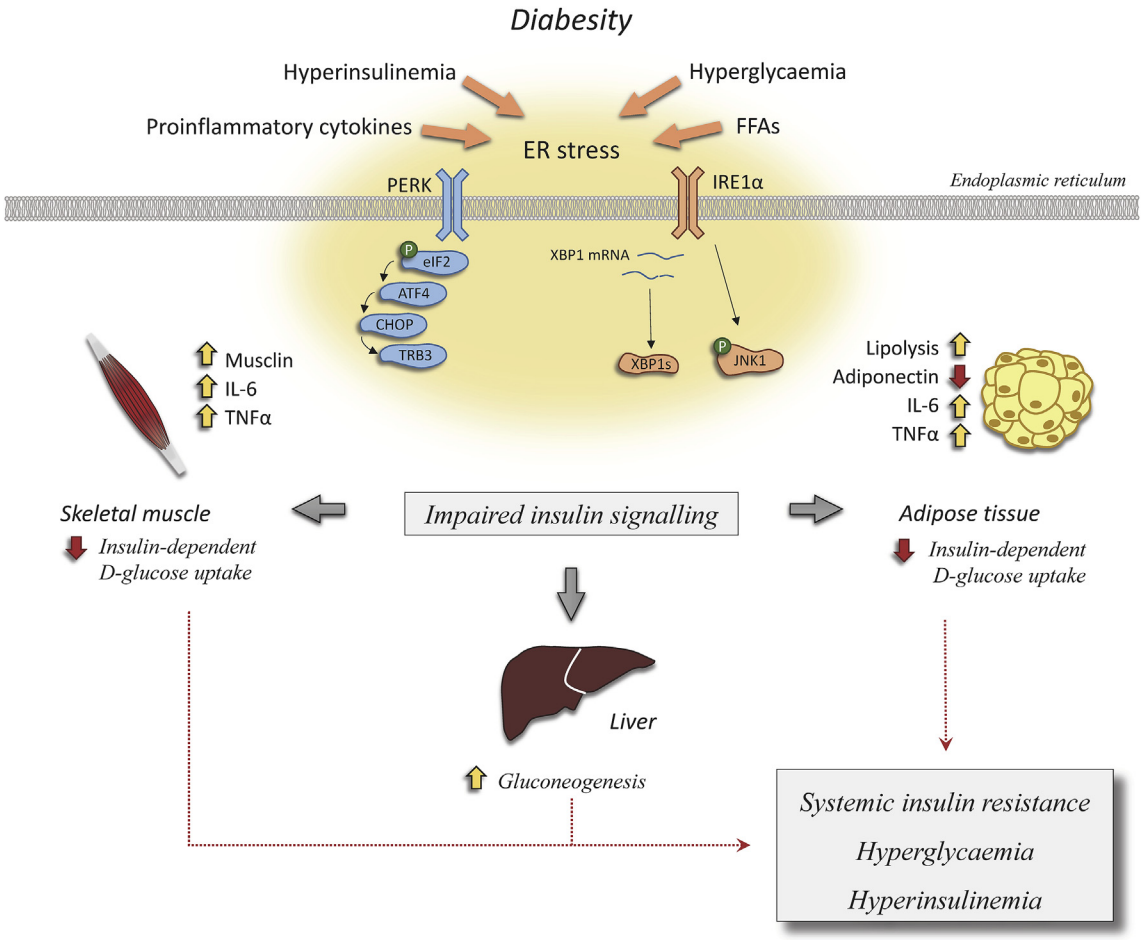

Fig. 2. Target organs of endoplasmic reticulum stress in diabesity. Severe metabolic alterations seen in patients affected by obesity and type 2 diabetes mellitus are referred as a state of diabesity. Patients with diabesity show hyperglycaemia and hyperinsulinemia, as well as higher circulating levels of proinflammatory cytokines and free fatty acids (FFAs). These factors all together induce a state of endoplasmic reticulum stress (ER stress). ER stress is characterised by an increase in the unfolded-protein response resulting in the activation of canonical ER stress sensors including the protein kinase RNA-like endoplasmic reticulum kinase (PERK) and the inositol-requiring enzyme 1α (IRE1α). PERK signalling is mediated by the sequential activation by phosphorylation of the eukaryotic translation initiator factor 2 (P ~ eIF2), transcription factor 4 (ATF4), CCAAT-enhancer-binding protein homologous protein (CHOP), and tribbles-like protein 3 (TRB3) (see text for details). IRE1α signalling includes the cleavage of the X-box binding protein 1 (XBP1) mRNA to translate the transcription factor XBP1 spliced (XBP1s). Increased IRE1α signalling also includes activation by phosphorylation of the c-jun N-terminal kinase 1 (P ~ JNK1). The alterations resulting from ER stress result in impaired insulin signalling ending in increased (⇧) expression and activity of several molecules in the skeletal muscle, adipose tissue, and liver. Instead, adiponectin release from the adipose tissue instead is reduced (⇩) in this condition. ER stress-impaired insulin signalling leads to reduced insulin-dependent D-glucose uptake in the skeletal muscle and adipose tissue, and increased gluconeogenesis in the liver. The resulting effect of diabesity on the metabolic modifications in these organs specialised in the modulation of the glycaemia includes systemic insulin resistance, hyperglycaemia and hyperinsulinemia.

result in increased lipolysis and consequent release of FFAs (Deng et al., 2012; Xu et al., 2010; Zhou et al., 2009), which in turn increase ER stress and insulin resistance in adipose tissue and other tissues (Guilherme et al., 2008; Jiao et al., 2011).

4.2. Skeletal muscle

Skeletal muscle is the main site of insulin-mediated D-glucose uptake in the postprandial state, reaching up to 60–70% of the circulating D-glucose (Wilcox, 2005). Thus, the metabolic alteration of skeletal muscle strongly affects the D-glucose homeostasis and the systemic insulin sensitivity, a phenomenon that plays a key role in metabolic syndrome-associated diseases (DeFronzo and Tripathy, 2009; Wu and Ballantyne, 2017). Insulin increases the uptake of D-glucose and promotes its metabolization (glycogen synthesis and glycolysis) in this organ by activating the Akt-associated metabolic signalling pathway leading to increased translocation of the D-glucose transporter type 4 from the internal compartments towards the plasma membrane (Sakamoto and Holman, 2008). In a state of insulin resistance these mechanisms of signalling are disrupted ending in a reduced capacity of the skeletal muscle to take up the extracellular D-glucose in response to insulin and thus contributing to the overdemand at pancreas β-cells, D-glucose intolerance, and to the development of T2DM (DeFronzo and Tripathy, 2009). The skeletal muscle from D-glucose tolerant obese patients (Adams et al., 2004) and patients with T2DM (Reeds et al., 2006) present insulin resistance in the skeletal muscle tissue. Thus, insulin resistance in the skeletal muscle tissue in diabesity is highly probable and could contribute to the systemic insulin resistance.

The development of insulin resistance in skeletal muscle cells involves ER stress (Table 1). An increase of ER stress is reported in skeletal muscle from patients with diabesity (these patients were catalogued as having only T2DM in the original report), compared with non-diabetic lean patients (Koh et al., 2013). Also, pregnant women with obesity or obesity plus GDM presented signs of ER stress in the skeletal muscle (Liong and Lappas, 2016). Additionally, higher level of ceramide in obese patients have been reported (Adams et al., 2004), a molecule known to induce ER stress and insulin resistance (Choi et al., 2018; Flamment et al., 2012; Liu et al., 2014), supporting the existence

of ER stress in this tissue. Other studies show induction of ER stress-associated impaired insulin signalling in human skeletal muscle cells (Hage Hassan et al., 2012), the mouse myoblast (C2C12 cells) and rat skeletal myoblast (L6 cells) cell lines (Hage Hassan et al., 2012; Hwang et al., 2013; Ijuin et al., 2016; Koh et al., 2013). Similar to what is described in adipose tissue or liver, TRB3 plays a key role in the impaired insulin signalling. An increase of TRB3 protein abundance in skeletal muscle from obese and diabesity patients (referred by the authors as only showing T2DM) was reported (Koh et al., 2013; Liu et al., 2010). Overexpression of TRB3 in C2C12 and L6 cells prevented the insulin-induced D-glucose uptake by inactivation of Akt (Koh et al., 2013; Liu et al., 2010). Also, the ER stress-induced TRB3 expression impaired insulin response in mice skeletal muscles, an effect blocked in C2C12 cells and mice skeletal muscle knockdown for TRB3 (Koh et al., 2013). Furthermore, TRB3 knocking out prevented the high fat diet (HFD)-induced insulin resistance in mice skeletal muscle (Koh et al., 2013). Thus, TRB3 is proposed as a potential protein linking ER stress with diabesity-induced insulin resistance in the human skeletal muscle.

The involvement of extracellular signal-regulated kinases activation in the ER stress-induced impairment of insulin signalling pathway, which finally resulted in reduced insulin-induced D-glucose uptake by L6 cells, is reported (Hwang et al., 2013). Moreover, in addition to ER stress induction, obesity increased the PIP3 phosphatase skeletal muscle and kidney-enriched inositol polyphosphate 5-phosphatase (SKIP) in the skeletal muscle from diet induced obesity (DIO) and db/db mice (Ijuin and Takenawa, 2003). This phosphatase negatively regulates the insulin signalling pathway, an effect that seems to be mediated by SKIP expression through ATF6 and XBP1 dependent mechanisms in C2C12 cells (Ijuin et al., 2016). Altogether, these data show that diabesity-induced ER stress could be a key step in the development of insulin resistance in skeletal muscle.

As well as adipose tissue or liver, FFAs are shown to induce ER stress in the skeletal muscle. This fact takes more importance since skeletal muscle from obese and diabetic patients has increased ectopic accumulation of FFAs. Palmitate induces ER stress in human skeletal cells (Hage Hassan et al., 2012; Peter et al., 2009) as well as in human skeletal muscle, C2C12 myotubes, and L6 cells (Peng et al., 2011; Perry et al., 2018; Peter et al., 2009; Rieusset et al., 2012; Salvadó et al., 2013). Palmitate also caused insulin resistance (Hage Hassan et al., 2012; Peng et al., 2011; Rieusset et al., 2012). However, a reduction of ER stress by chemical chaperones did not improve the palmitate-induced insulin resistance (Hage Hassan et al., 2012; Rieusset et al., 2012). Thus, even when palmitate induces ER stress in skeletal muscle cells, ER stress seems not to be the main mechanism in the palmitate-induced insulin resistance in skeletal muscle. Also, it is worth noting that other FFAs, such as oleate, block the palmitate-induced insulin resistance and ER stress in skeletal muscle cells (Peng et al., 2011; Salvadó et al., 2013). The latter suggests that a change in fat diet towards a more enriched in unsaturated-FFAs could be beneficial by improving insulin sensitisation in skeletal muscle from patients with diabesity.

Skeletal muscle also acts as an endocrine organ regulating the systemic insulin sensitivity through the secretion of hormones known as myokines, such as musclin, IL-6 or TNFα (Wu and Ballantyne, 2017) (Fig. 2). These myokines also act in an autocrine or paracrine way and contribute to insulin desensitisation in most if not all the tissues, including the skeletal muscle. It is reported that subjects with obesity or T2DM present with higher expression of these myokines. The participation of ER stress in this increase is also possible. Musclin is increased in obesity and has a strong correlation with insulin resistance (Chen et al., 2017). This myokine induces the inhibition of insulin-triggered Akt activation in rat skeletal muscle (Liu et al., 2008) and ER stress in C2C12 cells (Chen et al., 2017). Additionally, palmitate increases the expression of musclin in C2C12 cells through the activation of PERK-associated signalling, suggesting the involvement of ER stress in the increased secretion of musclin in obesity.

Other studies report that the human skeletal muscle shows increased expression and release of IL-6 in patients with diabesity (Ciaraldi et al., 2016; Reyna et al., 2008), as well as in insulin-resistant obese subjects (Corpeleijn et al., 2005; Reyna et al., 2008). Additionally, TNFα expression is increased in skeletal muscle from patients with diabesity (Plomgaard et al., 2007; Saghizadeh et al., 1996), even more than in patients with only obesity (Plomgaard et al., 2007). Thus, the skeletal muscle is one of the sources for the increased circulating levels of IL-6 and TNFα seen in diabesity (Goyal et al., 2012). Since these cytokines also induce ER stress and insulin resistance in skeletal muscle and other tissues (Borst, 2004; Denis et al., 2010; Kohlgruber and Lynch, 2015; Liong and Lappas, 2016; Plomgaard et al., 2005), this could be another way on how the skeletal muscle influences or is involved in the development of systemic insulin resistance. The relation between UPR and diabesity-induced IL-6 or TNFα expression in skeletal muscle cells is not well understood. It is reported that ER stress is involved in the expression of cytokines by the human skeletal muscle (Liong and Lappas, 2016). However, and as described above, ER stress seems involved in the expression and release of IL-6 and TNFα in other cell types (Hosoi et al., 2013; Hu et al., 2006; Kim et al., 2015; Li et al., 2014). Thus, since ER stress is present in the skeletal muscle from diabesity patients, ER stress could be involved in the increased expression and release of cytokines seen in this tissue from these subjects. Altogether the above-mentioned findings strongly suggest the involvement of ER stress and UPR signalling in the skeletal muscle effect on the systemic insulin resistance in diabesity by dysregulation of myokines secretion from this tissue.

4.3. Liver

The liver is a central organ in the control of D-glucose homeostasis and therefore is key in systemic insulin resistance. Despite that D-glucose uptake is not insulin-dependent in the liver, this organ is responsible for ~30% of whole body insulin-mediated D-glucose disposal through insulin-regulated metabolic processes, such as glycogenesis, inhibition of gluconeogenesis, and release of D-glucose (Wilcox, 2005). In a state of hepatic insulin resistance all these functions are altered, resulting in an excessive release of D-glucose by liver, which is considered as one of the major causes of insulin resistance and hyperglycaemia in patients with obesity-induced T2DM (Pajvani and Accili, 2015) (Fig. 2). The insulin effect on hepatocytes is mediated by Akt activation, which leads to inhibition of the expression of gluconeogenesis enzymes, among other effects. When hepatic insulin signalling is impaired, the resulting inefficient gluconeogenesis inhibition leads to abnormally higher levels of postprandial and fasting glycaemia (Marinho et al., 2015).

There are no studies addressing ER stress in the liver from subjects with obesity or diabesity. However, there is strong evidence showing ER stress in the liver from obese and diabesity mice models (Lisbona et al., 2009; Ning et al., 2011; Ozcan et al., 2004; Wang et al., 2009). Considering this latter finding and since the adipose tissue or skeletal muscle from subjects with diabesity present with ER stress, it is strongly suggested that patients with diabesity will show ER stress in the liver. Interestingly, most of the mechanisms linking obesity-associated ER stress with insulin resistance have been described in hepatocytes. It is reported the activation of the three canonical pathways of UPR in mice liver (Kammoun et al., 2009; Ozcan et al., 2004) an also an association between ER stress and impaired insulin response in this organ (Kammoun et al., 2009; Ozcan et al., 2004). Based on results available in animal models, different mechanisms have been proposed to be involved in the UPR-associated insulin resistance in the liver in diabesity which could be present in humans with this metabolic alteration.

PERK signalling branch has been linked to ER stress-induced insulin signalling impairment in the liver. It is reported that eIF2 is required for the gluconeogenesis mechanism by hepatocytes. The liver-specific overexpression of a constitutively active form of growth arrest and DNA

damage-inducible protein GADD34, a specific phosphatase of eIF2, prevented the obesity-induced insulin resistance and D-glucose intolerance in a model of diet-induced obesity and induced hypoglycaemia in lean mice (Oyadomari et al., 2008). Moreover, mice expressing an eIF2 protein unable to be phosphorylated showed severe hypoglycaemia (Scheuner et al., 2001). Thus, eIF2 seems crucial for gluconeogenesis by the liver. The evidence in animal models support findings showing a positive correlation between eIF2 phosphorylation and insulin resistance in the liver from obese subjects, suggesting the involvement of PERK branch in liver insulin resistance from these patients (Kumashiro et al., 2011).

The mechanisms inducing impaired insulin signalling in the liver by PERK branch involves TRB3. ER stress causes an increase in TRB3 protein level in human hepatocellular carcinoma cells (HepG2) involving ATF4 and CHOP activity (Ohoka et al., 2005). Genetic mice models of obesity (ob/ob), diabesity (db/db) (Belke and Severson, 2012), and DIO showed increased expression of TRB3 in the liver (Du et al., 2003; Lima et al., 2009). Also, TRB3 knockdown resulted in increased insulin-induction of Akt activity in HepG2 cells, and TRB3 overexpression reduced the insulin-decreased D-glucose release by Fao rat hepatoma cells (Fao cells). This phenomenon was supported by findings showing that specific overexpression of TRB3 in the liver of mice generated hyperglycaemia and an impaired D-glucose tolerance. Besides, in mice with normal expression of TRB3 in their liver showed increased TRB3 protein levels in the fasting period, potentially contributing to physiological gluconeogenesis by inhibiting the insulin-induced effect on hepatocytes (Du et al., 2003).

Other studies show that overexpression of TRB3 in the liver induced systemic D-glucose intolerance and insulin resistance in this organ (Matsushima et al., 2006). Also, TRB3 coimmunoprecipitate with Akt in liver from DIO and ob/ob mice, suggesting regulation of Akt by TRB3 *in vivo* (Lima et al., 2009). Additionally, it has been shown that calcium/calmodulin dependent-protein kinase II (CaMKII) is increased in the liver from obese mice and contributes to insulin signalling impairment through a mechanism involving PERK/ATF4-mediated TRB3 increase in primary hepatocytes (Ozcan et al., 2013). Furthermore, potential involvement of TRB3 in the liver from subjects with diabesity is supported by the findings showing that this protein expression in patients with obesity increases in parallel with the development of systemic insulin resistance (Oberkofler et al., 2010). Altogether these findings suggest that PERK activation could be participating in ER stress-induced hepatic insulin resistance through the expression of TRB3 in diabesity.

IRE1α kinase and endonuclease activity have also been found increased in liver from obese mice (Bailly-Maitre et al., 2010; Ning et al., 2011; Ozcan et al., 2004). It is shown that activated JNK1 was increased in liver from ob/ob and DIO mice models. ER stress-induced inactivation of IRS1 through the IRE1α-induced activation of JNK1 in Fao cells (Ozcan et al., 2004). Additionally, ER stress induction increased the expression and activity of the glucose-6 phosphatase, the release of D-glucose, and blunted the gluconeogenesis inhibition induced by insulin in primary rat hepatocytes, an effect that was partially mediated by JNK1 (Wang et al., 2006). Thus, JNK1 is proposed as one of the links in the ER stress-induced insulin resistance in the liver in obesity. Also, FFAs, lipopolysaccharides, and other proteins, such as double-stranded RNA-dependent protein kinase (PKR), have been associated to JNK1 activation and induction of insulin resistance (Flamment et al., 2012). Thus, ER stress could not be the unique inductor of insulin resistance through JNK1 activation in the liver.

Other studies show that XBP1 splicing and nuclear localisation is higher in the liver from DIO mice (Ning et al., 2011). A protective effect of XBP1 on ER stress-induced insulin resistance in the liver of mice was seen. Mice with a null mutation in one XBP-1 allele fed with DIO showed enhanced obesity-induced insulin resistance in the liver and the systemic insulin resistance and D-glucose intolerance compared with IRE1α$^{+/+}$ mice (Ozcan et al., 2004). However, studies modifying XBP1 expression specifically in the liver showed the opposite results. It was found that in obese and diabetic mice models (ob/ob, db/db, and DIO), obesity-induced IRE1α-XBP1 activation was associated with lower expression of the Bax-inhibitor 1 (BI-1), an ER membrane protein that inhibits IRE1α endonuclease activity (Lisbona et al., 2009). The restoration of liver BI-1 expression by adenovirus in db/db and DIO mice blunted the obesity-induced IRE1α-XBP1 endonuclease activity, improved insulin response in the liver, and protected from obesity-induced systemic insulin resistance and D-glucose intolerance (Bailly-Maitre et al., 2010). A conditional hepatic XBP1 depletion in mice caused lower fructose-induced insulin resistance in the liver and D-glucose intolerance even when hepatic ER stress and JNK1 activity in this organ were higher than in wild-type mice (Jurczak et al., 2012). Thus, JNK1 could not be the unique mechanism involved in the ER stress-induced insulin resistance in the liver from subjects with diabesity. The apparent discrepancy of XBP1 effects on insulin sensitivity and D-glucose homeostasis could be due to the differences in the molecular tools used to evaluate XBP1 involvement. Since XBP1 was shown to be deleterious for the effect of insulin in animals with genetic modifications in their liver, it is likely that hepatic XBP1 may be involved in the ER stress-associated systemic insulin resistance in subjects with diabesity.

A lower expression of ATF6 is reported in the liver from obese subjects with insulin resistance compared with non-insulin resistant subjects (Kumashiro et al., 2011) as well as in db/db mice (Wang et al., 2009). It is reported that ATF6 acts as a regulator of PERK and IRE1α resulting in a protective effect against ER stress (Wu et al., 2007). Overexpression of ATF6, particularly the ATF6α isoform, in the liver of db/db and DIO mice protected from obesity-induced hyperglycaemia and expression of various enzymes involved in the liver gluconeogenesis process. Conversely, ATF6α knockdown induced hyperglycaemia and increased the expression of gluconeogenesis enzymes in the liver from lean mice (Wang et al., 2009). Thus, ATF6 expression and activity in the liver protects against hyperglycaemia.

It has been reported that improvement of insulin sensitivity in hepatocytes is also caused by inhibition of CaMKII via a mechanism that required ATF6 activation (Yan et al., 2002). Activation of ATF6 resulted in higher expression and activity of p58IPK, which inhibits PERK-mediated signalling resulting in lower TRB3 expression activation (Yan et al., 2002) and subsequent increase in the insulin response in hepatocytes (Ozcan et al., 2013). In fact, CaMKII reduces ATF6 expression in the liver of obese mice, and ATF6 overexpression inhibited PERK/TRB3 branch in the liver, protecting from the obesity-induced insulin resistance in this organ and improving insulin sensitivity and D-glucose tolerance in DIO mice (Ozcan et al., 2016). Despite there is scarce information about ATF6 involvement in the liver of patients with diabesity or animal models of this metabolic alteration, it is suggested that ATF6 will play a protecting role in obesity-induced D-glucose metabolism alterations in the liver, a mechanism that could be key in the altered D-glucose metabolism in subjects with diabesity.

Other proteins have also been associated with the ER stress-induced insulin resistance in the liver. Reduction of ER stress by overexpression of the endogenous chaperone BiP protected from obesity-induced systemic insulin resistance in ob/ob mice (Kammoun et al., 2009). Also, the transcription factor Kruppel-like factor 15 (KLF15) is shown to play a key role in ER stress-induced insulin resistance in the liver. DIO KLF15$^{-/-}$ mice and DIO mice with liver-specific KLF15 knockdown were protected from ER stress-induced liver and systemic insulin resistance. An association was found for an increase in ER stress, cytokines expression, and JNK1 activation, supporting the role of ER stress in DIO-induced insulin resistance in the mice liver (Jung et al., 2013). Unfortunately, the mechanisms of KLF15 activity on the insulin signalling pathway and UPR proteins is still unknown.

4.4. Foetoplacental tissue

Children born to mothers with obesity or GDM are prone to develop

metabolic disorders in adulthood (Gaillard et al., 2014; Pirkola et al., 2010; Sobrevia et al., 2014; Stuebe et al., 2012, 2009). Indeed, newborns from insulin-resistant obese mothers have already increased insulin resistance at birth (Catalano et al., 2009; Desoye, 2018). Equally, newborns and the mothers in GDM pregnancies show increased the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) (Guzmán-Gutiérrez et al., 2016; Subiabre et al., 2017; Westermeier et al., 2015). Recent reports show that newborns and women with GDM treated only with diet or under an insulin therapy protocol still show insulin resistance at birth suggesting that these therapeutic approaches may resolve the maternal and newborn glycaemia to values within the required ranges but did not resolve the reduced response of the vasculature to insulin (Subiabre et al., 2018, 2017).

Metabolic disorders derived from obesity and GDM may be transferred from the mother to their offspring (Sobrevia et al., 2014). Several reports show that this transference occurs during pregnancy (Longtine and Nelson, 2011; Sobrevia et al., 2014). This possibility is supported by findings showing that after the weight loss following a bariatric surgery, children born from these mothers presented a reduced incidence of obesity and insulin resistance (Guenard et al., 2013; Kral et al., 2006; Smith et al., 2009) compared to their siblings born before the intervention. Foetoplacental tissues play a key role in this transference, since they are the structural and functional connection of the foetus with the mother (Griffiths and Campbell, 2015). The placenta is an organ specialised in vital processes including gas exchange, transport of ions, nutrients and waste products between the maternal and foetal plasma, and it is active in the synthesis and secretion of hormones and extracellular vesicles, including nanovesicles (also referred as exosomes) (Chiarello et al., 2018; Jayabalan et al., 2017; Pardo et al., 2018; Sáez et al., 2018a), reaching the maternal and foetal circulation (Chiarello et al., 2018; Sáez et al., 2018a,b). Maternal substances are transferred from the maternal blood through the chorionic villous into the foetal capillaries, then blood flows through chorionic veins and reaches the umbilical vein returning the freshly oxygenated blood to the foetal circulation (Griffiths and Campbell, 2015). Even when the foetoplacental tissues are a transient organ, foetoplacental tissue dysfunction is shown to be crucial in the foetal outcome and altered function in this tissue remains for the lifetime of the offspring (Longtine and Nelson, 2011; Sáez et al., 2018a,b; Sobrevia et al., 2014).

Insulin resistance in mothers with obesity is associated with higher placental weight, an effect not further increased by the co-existence of GDM (Tanaka et al., 2018). Thus, the mechanisms associated with insulin resistance in pregnant women with obesity and those with GDM may not be due to similar signalling mechanisms. In a study of the transcriptome of trophoblast cells from the first trimester of pregnancy in mothers with obesity, the insulin-induced gene expression was found to be lower compared with cells from normal pregnancies (Lassance et al., 2015). These findings suggest lower insulin sensitivity in these cells from obese mothers. Another set of studies reported that the foetoplacental vasculature from mothers with obesity also shows signs of insulin resistance since an insulin resistance genetic profile in umbilical cords from obese mothers was found (Thakali et al., 2014).

Vascular insulin resistance is tightly associated with endothelial dysfunction (Muniyappa and Sowers, 2013; Silva et al., 2017; Sobrevia et al., 2016; Subiabre et al., 2018; Villalobos-Labra et al., 2017), which is considered a key step in the beginning of cardiovascular disease (Versari et al., 2009) and characterises by a lower endothelial-dependent vasodilation (Deanfield et al., 2005; Guzmán-Gutiérrez et al., 2016; Silva et al., 2017; Sobrevia et al., 2016). Increased resistance of the umbilical arteries from pregnancies where the mothers were obese is reported, where the umbilical artery endothelial dysfunction was suggested as the responsible mechanism of this vascular dysfunction (Sarno et al., 2015). Furthermore, HUVECs from mothers with pre-pregnancy maternal obesity (Villalobos-Labra et al., 2018) or mother with normal weight before pregnancy but with supraphysiological total gestational weight gain (sptGWG) (Pardo et al., 2015) also presented metabolic alterations. Altogether these findings suggest that foetoplacental vascular tissues from mothers with obesity or sptGWG are dysfunctional.

Since already three decades the GDM was shown to associate with alterations in the human placenta and foetoplacental vasculature (Sobrevia et al., 1994, 1995, 1996). HUVECs from GDM pregnancies showed a lower response to insulin and other endothelial-dependent vasodilators (Sáez et al., 2018a; Sobrevia et al., 1996; Subiabre et al., 2017), a phenomenon proposed to be due to insulin desensitisation and endothelial dysfunction since L-arginine transport and NO synthesis were increased compared with normal pregnancies.

Based on the above-described studies it is now clearer that foetoplacental tissues are altered in pregnancies where the mother was with obesity, sptGWG, or GDM. However, it is still necessary to reach to a state where a better-defined selection of pregnant women with pre-pregnancy obesity or sptGWG developing GDM, i.e., gestational diabesity, as recently proposed (Pardo and Sobrevia, 2018), are different from those that do not develop GDM (i.e., true pre-pregnancy obesity or obesity in pregnancy). These metabolic conditions are different for women with obesity, GDM, or pregnancy diabesity with different consequences to the foetus growth and development.

ER stress shows a strong relationship with insulin resistance and endothelial dysfunction in metabolic syndrome-associated diseases (Battson et al., 2017; Cnop et al., 2012). It is reported that placentas from mothers with obesity that develop GDM present higher phosphorylation of eIF2 and processed XBP1 levels than control, lean not-GDM mothers, a finding that correlates positively with glycated haemoglobin A1c level, evidencing a potential influence of hyperglycaemia with the induction of ER stress in this tissue (Yung et al., 2016) (Table 1). Interestingly, the control referred to in the latter study, as almost in all of the studies with a similar approach and study group selections, corresponded to women with a normal weight that did not course with GDM. Thus, a proper comparison to define the potential effect of a gestational diabesity state in the reported parameters is unclear.

Placentas from mothers with obesity or with GDM, showed higher expression of phosphorylated JNK1 (Saben et al., 2013; Yung et al., 2016), suggesting this molecule as a potential candidate to obesity-induced, ER stress-associated insulin resistance in foetoplacental tissues (Fig. 3). Besides, placentas from mothers with GDM (Coughlan et al., 2004; Desoye and Hauguel-De Mouzon, 2007; Zhu et al., 2015) or obesity (Bar et al., 2012; Ferretti et al., 2014; Saben et al., 2014) presented higher levels of inflammatory and oxidative markers, which are tightly associated with ER stress (Flamment et al., 2012). Studies in HUVECs from GDM pregnancies show higher expression and activity of CHOP (Farías et al., 2010). The latter phenomenon is related with abnormal function of HUVECs since repression of *SLC29A1* coding for the human equilibrative nucleoside transporter 1 (Farías et al., 2010) and overexpression of *SLC7A1* coding for the human cationic amino acid transporter 1 (Guzmán-Gutiérrez, 2014) associated with increased CHOP activity. In a recent study, it was reported that HUVECs from women with pre-pregnancy obesity show activation of PERK, IRE1α, ATF6, and their downstream proteins, including TRB3 and JNK1 (Villalobos-Labra et al., 2018), suggesting that these cells from this maternal metabolic condition showed with ER stress. Since maternal pre-pregnancy obesity associated with higher expression of TRB3 and activated JNK1, it is suggested that these proteins may play a role acting as links between obesity-induced ER stress and human foetoplacental endothelial dysfunction (Villalobos-Labra et al., 2018). Although studies in foetoplacental tissues are still necessary, the reported findings suggest ER stress in the human placenta and foetoplacental vasculature in gestational diabesity.

5. Gender-associated insulin resistance predisposition

Substantial evidence shows that cardiovascular risk tightly

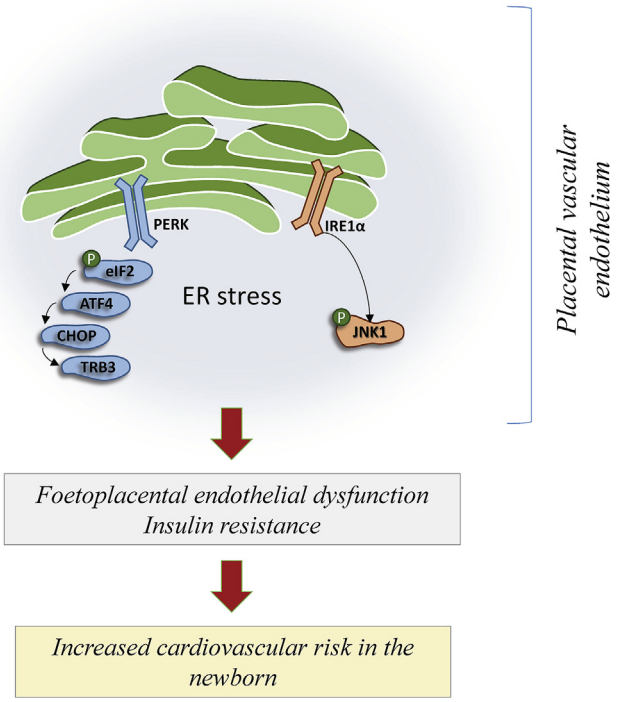

Fig. 3. Endoplasmic reticulum stress in the foetoplacental endothelium in diabesity. Pregnant women with obesity and type 2 diabetes mellitus classify as patients with diabesity. This metabolic condition alters the endothelial cells from the placenta circulation (*Placenta vascular endothelium*) due to endoplasmic reticulum stress (ER stress). ER stress characterises by an increase in the unfolded-protein response (UPR) leading to activation of the protein kinase RNA-like endoplasmic reticulum kinase (PERK) and the inositol-requiring enzyme 1α (IRE1α), canonical ER stress sensors. PERK triggers the sequential activation by phosphorylation of the eukaryotic translation initiator factor 2 (P ~ eIF2), transcription factor 4 (ATF4), CCAAT-enhancer-binding protein homologous protein (CHOP), and tribbles-like protein 3 (TRB3) (see text for details). On the other hand, IRE1α triggers the activation by phosphorylation of the c-jun N-terminal kinase 1 (P ~ JNK1). Activation of the PERK and IRE1α signalling cascades result in a deficient response of the foetoplacental endothelium to insulin (*Insulin resistance*) due or leading to a dysfunctional macrovascular (and likely microvascular) endothelium (*Foetoplacental endothelial dysfunction*). The newborn outcome of the ER stress in the foetoplacental vasculature in pregnant women with diabesity is an increase in the risk of developing cardiovascular diseases (*Increased cardiovascular risk in the newborn*). Whether these metabolic alterations are seen in the foetoplacental vasculature from women with pre-pregnancy obesity or showing supraphysiological total gestational weight gain that develop gestational diabetes mellitus (i.e. gestational diabesity) is still unknown.

associated with gender. Interestingly, even when women show higher adiposity than men, women tend to accumulate fat at subcutaneous depots, but fat accumulation in men is preferentially at visceral depots (Geer and Shen, 2009). The gender-dependent fat distribution results in men showing higher metabolic risk than women. Thus, adolescent obese males exhibit a higher chance to develop insulin resistance and D-glucose intolerance (Aldhoon-Hainerová et al., 2014; Denzer et al., 2009). Also, these subjects show with fatty liver, have a lower level of plasma adiponectin, and store fat at visceral depots (Denzer et al., 2009), all factors that contribute to the development of systemic insulin resistance. Therefore, women show protection against the alterations mentioned above in the metabolism. One of the causes that are proposed to lead to this protection in women are the sexual hormones. Oestrogens have been shown to promote insulin sensitivity in metabolic tissues (Jelenik and Roden, 2013). Interestingly, since oestrogens reduced the ER stress in INS-1 cells, a rat insulinoma cell line and human umbilical vein endothelial cells (Kooptiwut et al., 2014; Su et al., 2017) a potential mechanism of action of oestrogens could involve protection against or amelioration of ER stress. However, a protective effect of oestrogens against the ER stress-associated insulin resistance in women with diabesity is a mechanism not yet described.

Foetus gender also associated with the metabolic state of the mother and placental tissues. Pregnant women with male foetuses have higher HOMA-IR compared with women with female foetuses, evidencing increased risk to develop insulin resistance (Walsh et al., 2015). Indeed, another study shows that the development of GDM associated with women carrying a boy compared with those taking a girl (Retnakaran and Shah, 2015). In addition to these findings, maternal obesity-induced oxidative stress in the placenta is under modulation by foetal gender (Evans and Myatt, 2017). The results suggest that the damage in the placentas from women with obesity where the foetus was male was higher compared with pregnancies where the foetus was female. Since oxidative stress associated with ER stress and insulin resistance, obesity-increased oxidative stress in the placenta may result in a higher occurrence of ER stress in this organ in women with diabesity with a male foetus which could explain the foetoplacental dysfunction seen in these women. Altogether, the available evidence, even when limited, suggests that the sexual dimorphism in fat accumulation, fatty liver, and systemic insulin resistance could associate with a higher occurrence of ER stress in men compared with women. Unfortunately, whether ER stress is also under modulation by gender is still not described (Sobrevia, 2018; Subiabre et al., 2018; Villalobos-Labra et al., 2017).

6. Concluding remarks

It is now accepted that obesity is pandemic and results in immediate alterations leading to an abnormal metabolic environment with a dysfunctional vasculature and in abnormal function in different targets including the adipose tissue, liver, and skeletal muscle. Also, pre-pregnancy maternal obesity and excessive weight gain in pregnancy result in a dysfunctional foetoplacental vasculature. In most cases, obese subjects progress to develop T2DM characterised by a defective uptake and metabolism of D-glucose in most cells as the major factor. These subjects are more recently referred to as having diabesity highlighting the appearance of T2DM in these subjects (Kalra, 2013; Potenza et al., 2017; Ziv and Shafir, 1995).

Patients with obesity, T2DM, or diabesity show with ER stress, with pronounced effects in adipose tissue (likely VAT), the liver, skeletal muscle, and the foetoplacental vascular endothelium. In these tissues the three canonical branches of ER stress, PERK, IRE1α, and ATF6, are activated leading to the UPR (Van De Maele et al., 2018), as a mechanism intending to restore the altered homeostasis of the endoplasmic reticulum seen in these (Ghemrawi et al., 2018; Hetz et al., 2015; Mukherjee et al., 2015; Villalobos-Labra et al., 2018). ER stress results in insulin resistance by mechanisms involving IRE1α/JNK1-mediated inhibition of IRS1-coupled insulin signalling. Alternatively, activation of PERK/eIF2/ATF4/TRB3 signalling leads to reduced Akt activity (Du et al., 2003; Flamment et al., 2012; Hirosumi et al., 2002; Ozcan et al., 2013, 2004) turning in a lower NO, endothelium-dependent vasodilatory effect of insulin (Villalobos-Labra et al., 2018, 2017).

Specific mechanisms of ER stress-associated insulin resistance in adipose tissue involve IRE1α activation, XBP1 splicing, and JNK1 activation (Boden et al., 2008; Li et al., 2014), as well as lower expression of the insulin sensitizer adiponectin (Mondal et al., 2012; Xu et al., 2010) and increased release of proinflammatory cytokines TNFα, IL-6, and IL-1 (Hardy et al., 2012; Kohlgruber and Lynch, 2015; McArdle et al., 2013). In the skeletal muscle, a role for TRB3 in insulin resistant is proposed. Additionally, increased release of IL-6 and TNFα in patients with diabesity (Goyal et al., 2012). The role of ER stress in the insulin resistance in the human liver is unknown. However, data reported in animal models suggest activation of the three canonical pathways of UPR, with a major role of PERK/ATF4/TRB3 signalling, and loss of insulin sensitivity in this organ (Kammoun et al., 2009;

Matsushima et al., 2006; Ozcan et al., 2016, 2013, 2004).

In the foetoplacental vasculature the role of ER stress in the insulin resistant state seen in obesity or GDM has been less studied (Villalobos-Labra et al., 2017). In fact, most of the studies that refers to GDM show groups of patients with a body mass index between 25 and 35 kg/m^2, i.e., including women with overweight and obesity (WHO, 2018). Therefore, not a clear conclusion is possible to reach from such studies regarding whether the reported effects, including maternal and newborn insulin resistance, were due to GDM, overweight, obesity, or a mix of these abnormal metabolic conditions. Whether the occurrence of GDM in women with pre-pregnancy obesity, which we refer as gestational diabesity, has a different aetiology and result in different metabolic consequences for the mother, the foetus, the newborn and their childhood and adulthood, compared with diabesity as currently known in the literature (obese patients that develop T2DM), is unknown.

Based on the specific modifications in the cell signalling mechanisms seen in the general context of ER stress-associated insulin resistance, it is likely that diabesity is an alteration that shows high cell, tissue, and organ specificity. The lack of studies in patients that are overweight and develop T2DM limit the possibility of a potential different or similar type of diabesity as referred up today (Desoye, 2018). Equally, since obesity in women in their reproductive age is increasing worldwide in the last decade (WHO, 2018) and GDM is increasing in parallel to obesity in the population (ADA, 2018), a different metabolic alteration to obesity in pregnancy or GDM, which we refer as gestational diabesity, is likely. Interestingly, ER stress and insulin resistance are adverse metabolic conditions in pregnant women that are obese with stronger harmful effects in the foetoplacental vascular function whether the foetus was men compared with female. Having a clearer picture of the mechanisms behind insulin resistance in subjects with diabesity, overweight + T2DM, or gestational diabesity will help to understand the clinical aspects of these patients favouring the design of specific or at least more differential protocols for the treatment of each of these metabolic alterations.

Conflicts of interest

The authors confirm that there are no conflicts of interest.

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