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Review

Adipose tissue and insulin resistance in obese

Bulbul Ahmed [a,*], Rifat Sultana [b], Michael W. Greene [a]

[a] Department of Nutrition, Auburn University, Auburn, AL, 36849, United States
[b] Department of Biology and Microbiology, South Dakota State University, Brookings, SD, 57007, United States

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ABSTRACT

Currently, obesity has become a global health issue and is referred to as an epidemic. Dysfunctional obese adipose tissue plays a pivotal role in the development of insulin resistance. However, the mechanism of how dysfunctional obese-adipose tissue develops insulin-resistant circumstances remains poorly understood. Therefore, this review attempts to highlight the potential mechanisms behind obesity-associated insulin resistance. Multiple risk factors are directly or indirectly associated with the increased risk of obesity; among them, environmental factors, genetics, aging, gut microbiota, and diets are prominent. Once an individual becomes obese, adipocytes increase in their size; therefore, adipose tissues become larger and dysfunctional, recruit macrophages, and then these polarize to pro-inflammatory states. Enlarged adipose tissues release excess free fatty acids (FFAs), reactive oxygen species (ROS), and pro-inflammatory cytokines. Excess systemic FFAs and dietary lipids enter inside the cells of non-adipose organs such as the liver, muscle, and pancreas, and are deposited as ectopic fat, generating lipotoxicity. Toxic lipids dysregulate cellular organelles, e.g., mitochondria, endoplasmic reticulum, and lysosomes. Dysregulated organelles release excess ROS and pro-inflammation, resulting in systemic inflammation. Long term low-grade systemic inflammation prevents insulin from its action in the insulin signaling pathway, disrupts glucose homeostasis, and results in systemic dysregulation. Overall, long-term obesity and overnutrition develop into insulin resistance and chronic low-grade systemic inflammation through lipotoxicity, creating the circumstances to develop clinical conditions. This review also shows that the liver is the most sensitive organ undergoing insulin impairment faster than other organs, and thus, hepatic

Abbreviations: FFA, free fatty acid; ROS, reactive oxygen species; T2DM, type 2 diabetes mellitus; HDL, high-density lipoprotein; BMI, body mass index; DNA, deoxyribonucleic acid; LPS, lipopolysaccharides; GLUT4, glucose transporter type 4; TLR4, toll-like receptor 4; NF-κB, nuclear factor NF-kappa-B; MAPK, mitogen-activated protein kinase; MTD88, myeloid differentiation primary response 88; TRIF, TIR-domain-containing adapter-inducing interferon-β; ER, endoplasmic reticulum; MCP-1, monocyte chemotactic protein-1; TNF-α, tumor necrosis factor-α; IL-1β, interleukin 1 beta; IL, interleukin; CCR, C-C hemokine receptor type; ATM, adipose tissue macrophage; CLS, crown-like structure; IKK, IκB kinase; JNK, C-jun n-terminal kinases JNK; PKC, protein kinase C; PTP1B, protein tyrosine phosphatase 1B; STAT, signal transducer and activator of transcription protein; SOCS, suppressor of cytokine signaling; CD8T, cluster of differentiation 8T lymphocyte; Th1, T helper type 1 cell; iNKT, natural killer T cell; Treg, regulatory T cell; DAG, diacylglycerol; NALP3, NLR family pyrin domain containing 3; NOX, NADPH oxidase; CD36, cluster of differentiation 36; PP2A, protein phosphatase 2; Akt/PKB, protein kinase B; NO, nitric oxide; Cers, ceramide synthase; ATP, adenosine triphosphate; VLDL, very low density lipoprotein; Acetyl-CoA, acetyl coenzyme A; TCA, cycle tricarboxylic acid cycle; NADPH, nicotinamide adenine dinucleotide phosphate; FADH2, flavin adenine dinucleotide 2; DAMP, damaged-associated molecular patterns; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1; IRF, interferon regulatory factor; IFN, interferon; H_2O_2, hydrogen peroxide; $^{\cdot}O^{2-}$, superoxide; $^{\cdot}OH$, hydroxyl radical; PTP1B, protein-tyrosine phosphatase 1B; SOD, superoxide dismutase; GPX, glutathione peroxidase; MEK, MAP kinse-ERK kinase; ERK, extracellular regulated MAP kinase; SOS, son-of sevenless; Grb2, growth factor receptor-bound protein 2; SHC, SHC-adaptor protein; IRS, insulin receptor substrate; PI3K, phosphoinositide 3-kinase; PIP3, phosphatidylinositol (3, 4, 5)-trisphosphate; pAKT, phospho-akt; FOXO1, forkhead box protein 01; mTORc1, mammalian target of rapamycin complex 1; P70S6K, ribosomal protein S6 kinase beta-1 (S6K1)/ P70S6K kinase; GSK3β, glycogen synthase kinase 3 beta; PDE, phosphodiesterase; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; HSL, hormone sensitive lipase; AS160, Akt substrate of 160 kDa; TXNIP, thioredoxin interacting protein; PC, phosphatidylcholine; PE, phosphatidylethanolamine; SERCA, ER calcium ATPase; PERK, PKR like ER kinase; IRE1, inositol requiring enzyme 1; ATF-6, activating transcription factor 6; eIF2α, eukaryotic Initiation Factor 2; IκB, IkappaB; XBP1, X-box binding protein 1; mTOR, mammalian target of rapamycin; ULK1, Unc-51 like autophagy activating kinase; GSNOR, *S*-nitrosoglutathione reductase; Atg, autophagy related; AMPK, AMP-dependent protein kinase; UPR, unfolded protein response; JAK, janus kinase; ZNF423, zinc finger protein; PPAR-α, peroxisome proliferator-activated receptor alpha; CEBP-α, CCAAT/enhancer-binding protein alpha; Mfn, mitofusin; DRP1, dynamin related protein.

* Corresponding author.
E-mail address: bza0017@auburn.edu (B. Ahmed).

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insulin resistance is the primary event that leads to the subsequent development of peripheral tissue insulin resistance.

1. Introduction

Obesity has become an epidemic worldwide and is a significant public health concern. In the US, obesity becomes the second most preventable cause of death [7]. Obesity has nearly tripled since 1975, and it is estimated that 51 % of the population will be obese by 2030 [9]. During obesity and overnutrition, the excess nutrients are stored as lipids in adipose tissues, causing obesity. In prolonged overnutrition, the excess free fatty acids (FFAs) are stored in different organs as ectopic fat and produce excess reactive oxygen species (ROS) and pro-inflammation [3]. Obesity-induced chronic pro-inflammation contributes to a pivotal role in the development of insulin resistance.

Insulin is a hormone secreted by pancreatic β-cells based on the availability of circulating blood glucose and fatty acids [11]. The metabolic function of insulin is to maintain the homeostasis of glucose and lipids. When we take a meal, the blood glucose level rises in circulation; pancreatic β-cells sense and release insulin depending on the glucose level. Insulin binds to the cell receptors primarily on skeletal muscle, adipose tissue, and liver [12]. Insulin allows glucose to enter the cells for energy metabolism, fatty acid synthesis, and protein synthesis. When cells do not respond to insulin appropriately and cannot use glucose for energy metabolism, the blood glucose level goes up, and the pancreatic β-cells produce more insulin to compensate for the high circulating blood glucose level, which is the initial insulin-resistant circumstance. As insulin-resistant environments develop, β-cells fight back by producing more insulin in response to impaired glucose supply [13]. If the insulin-resistant condition stays steady over months and years, the β-cells work hard continuously to produce excess insulin to compensate for the glucose overload. Because of continuous overload, β-cells get worn out, causing an increase in glucose in circulation.

In humans, increased blood glucose level, reduced insulin sensitivity, and increased insulin secretion are observed 13 years before type 2 diabetes mellitus (T2DM) is fully diagnosed [14]. The total duration from the beginning of insulin resistance circumstances to T2DM can be divided into three stages. The first stage is the long compensatory period when insulin resistance develops, raises blood glucose level, and increases β-cell mass. The second stage is the adaptation period when β-cells are no longer fully compensating for increasing insulin resistance. The first two stages occur before the prediabetes phase is achieved. The third stage is the development of prediabetes to T2DM; at this stage, the β-cells become dysfunctional and are unable to compensate for the insulin resistance, which in turn, raise blood glucose levels rapidly [14]. Approximately 25–70 % of subjects develop prediabetes to T2DM within 3–5 years in their lifetime, and 80 % of them develop the non-alcoholic fatty liver disease [15,16]. Insulin resistance also increases the risk of heart failure, fuels tumor growth, and declines memory functions that increase the risk of Alzheimer disease [17–19].

Several risk factors are involved in insulin resistance, such as obesity, impaired glucose tolerance, alcoholism, smoking, hypercholesterolemia, hypertriglyceridemia, low HDL, hyperuricemia, and hypertension [20–22]. Obese individuals develop insulin resistance at specific points in their lifetime in more than 80 % of cases [23,24]. Therefore, this review has primarily focused on the potential mechanisms of obesity-associated insulin resistance.

2. Definition of obesity

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse health effect. Obesity is defined by the National Institute of Health based on the body mass index (BMI), calculated as the person's weight in kilograms divided by the square of height in meters. If the BMI is above 30, the individual is considered to be obese [25]. The enlargement of fat mass characterizes obesity through adipocyte cell size enlargement (hypertrophy) and proliferation (hyperplasia) [26]. The excess accumulation of body fat is usually caused by more nutrients than the body requires. These excess nutrients are stored as triglycerides, commonly known as fat, and the adipocytes where triglycerides are stored, are known as fat cells. The primary composition of the adipose tissue is adipocytes. Adipose tissue is a large and dynamic endocrine organ responsible for energy storage, making up between 2–70 % of body weight in humans [27]. When adipocytes cannot uptake excess triglycerides, the body synthesizes new adipocytes; the process is termed adipogenesis (Fig. 1), which creates enormous space for fat storage [28]. Adipose tissues (mainly white adipose tissues) are distributed in several depots, which can be divided into two types, the subcutaneous depots and the visceral depots; some of the subcutaneous depots are gluteal, femoral, and subcutaneous abdominal; and some of the visceral depots are omental, mesenteric, and perirenal [29]. During the consumption of excess nutrients, the fat tends to accumulate in the visceral and subcutaneous depots, making these depots bigger by hypertrophy and hyperplasia [30], and become unhealthy.

Evidence has shown that unhealthy obesity, which has dysfunctional adipose tissue, restricts the hyperplastic remolding, leading to adipocyte hypertrophy and systemic metabolic dysfunction [31]. Unhealthy hypertrophic obesity is associated with abdominal obesity, which is more deleterious to metabolic health, recruits macrophages, and other immune cells, promotes systemic inflammation and upholds ectopic fat

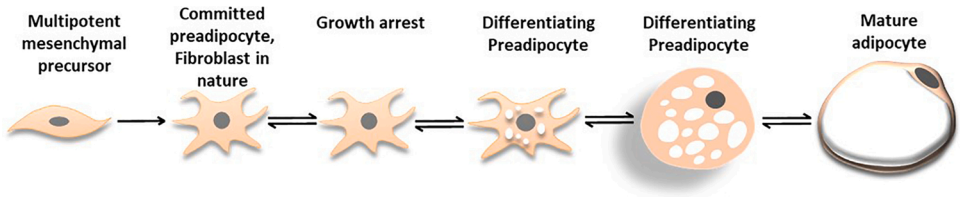

Fig. 1. Adipogenesis: Bone marrow-derived mesenchymal stem cells are recruited to adipose tissue and get committed to preadipocyte development, restrict their growth to adipogenic lineage, and accumulate triglyceride from nutrients. Bone morphogenic protein regulates the fate of mesenchymal stem cells committed to adipocyte lineage. The committed preadipocytes express the transcription factor ZNF423 and arrest their growth. Sequentially preadipocytes are induced by the master regulator PPAR-α and CEBP-α, which enhances lipid accumulation and becomes mature adipocytes. In some instances, mature adipocytes able to return to fibroblast-like preadipocytes precursor in a de-differentiation process on specific occasions, e.g., wound healing [1–4].

accumulation [32,33]. Human study has shown that omental adipocyte size positively correlates with insulin resistance [34]. Even a modest increase in inflammation in the subcutaneous adipose tissue of moderately obese women is associated with insulin resistance [35].

Approximately 10–25 % of obese individuals are metabolically healthy [23] because their insulin is still sensitive, and they are not prone to develop any associated diseases. However, a recent study has shown that metabolically healthy obesity is not a harmless condition at all, though it remains free of metabolic diseases for decades faces an increased risk of cardiovascular events [36]. The rest of the metabolically unhealthy obese individuals are characterized by bigger visceral fat mass and lower subcutaneous fat mass. The impaired fat storage capacity of the adipose tissue results in ectopic fat deposition and contributes to the development of insulin resistance [37]. Unhealthy obesity is associated with several chronic conditions, such as kidney diseases, osteoarthritis, cancer, diabetes, sleep apnea, non-alcoholic fatty liver disease, hypertension, and cardiovascular diseases [38].

3. Prevalence and incidence of obesity

Obesity rates are increasing frighteningly worldwide; since 1975, obesity has nearly tripled. The prevalence of obesity increased from 3.2 to 10.8% among men and 6.4–14.9% among women of adult age from 1975 to 2014. If the trend continues, 57.8 % of the world population will be overweight or obese by 2030 [39]. In 2016, a total of 1.9 billion adults aged 18 and over were overweight, and 650 million were obese, which was about 13 % of the total population [40].

More specifically, in 1990, obese adults made up less than 15 % of the population in most states in the US [41]. In contrast, currently, nationwide, approximately two out of three US adults are overweight, and one out of three (about 40 %) are obese [42]. Obesity is also rising among children and adolescents alarmingly; one out of 5 children and adolescents ages 2–19 are obese [42]. The estimated total annual health care cost of obesity was 147 billion dollars per year by 2008, and the medical cost for people who had obesity was $1,429 higher than those of healthy weight [43].

4. Risk factors of obesity

There are many risk factors for obesity, some of which are dependent on the environment and lifestyle, and others are independent. Regardless of the environment, independent risk factors are modifiable and may change themselves. Here are some detailed explanations of independent and dependent risk factors directly or indirectly associated with obesity.

4.1. Environmental factors

Environmental factors increase the risk of becoming overweight and obese. Nowadays, the communities are structured in a way that it may pose a risk contributing to obesity. High energy condensed foods are very accessible and cheap in the community and are being sold in places like gas stations and office supply stores. These processed and high energy condensed unhealthy food products are intensively advertised on televisions and radios. The people of lower socioeconomic status have frequent access to these unhealthy and cheap foods.

Recreation facilities in the neighborhood are associated with increased physical activity and a healthy food environment, whereas limited access to physical activity or recreational activities is associated with increased obesity [44]. A landmark study on the spread of obesity for a 32-years prospective data found that an individual's chances of becoming obese increased by 57 % if he or she had a friend who became obese in a given 4-year interval [45]. Furthermore, same-sex individuals have a relatively more significant influence on each other than those of the opposite sex [45].

Environmental temperature is also a concern for obesity. Energy expenditure increases or decreases with the increase or decrease of ambient temperature to maintain body homeostasis [46]. Humans have an optimal body temperature, which is higher than the temperature of the environment. At lower temperatures, the human body adjusts its temperature by increasing metabolic rates. The metabolic rates also increase when the ambient temperature rises. With the widespread control of climate by heating and air conditioning in cars, homes, and workplaces, humans enjoy comfortable temperatures where energy demands are minimized, and because of spending more time in thermo-neutral zone, humans are at risk for obesity [46].

4.2. Genetics

Genetics is also a strong risk factor for obesity. Genes may affect the amount of body fat storage and distribution. Genes also affect how efficiently the body uses food for energy. Diet and lifestyle, including famine exposure, parental obesity, smoking and exposure to other chemicals, endocrine-disruption, weight gain during gestation, and gestational diabetes influence to modify or methylate genes that have been implicated in subsequent offspring, which increases the risk for obesity [47]. Genetic modification also depends on food habits during pregnancy, which can change the baby's DNA by methylation, and subsequently affect the child's fat deposition in the future [48]. Obese fathers also have DNA methylation in the imprinted genes in human sperm that may pass on to their children [49]. Many genes may contribute to obesity; however, only 32 of the most common genes are thought to be responsible for the overall variation in obesity [50].

4.3. Aging

Aging is associated with changes in body composition. The total fat mass rearranges in the aging process, such as an increase in the chance of ectopic fat depositions in the liver and skeletal muscle and visceral fat deposition in the abdomen. Several studies have supported that decreasing energy expenditure plays a critical role in increasing fat deposition in the aging process. After 20, the resting energy expenditure rate decreases by 2–3 % per decade, and skeletal muscle mass reduces 40 % by ages between 20–70 years [51]. Additionally, physical activity declines, and people become sedentary, which reduces half of the total energy expenditure in old age [51].

Interestingly, the body weight and body fat mass tend to be a maximum at the age of 65 for men, while for women, the bodyweight increases to its maximum ten years later than the men, in the following years, both for men and women, body fat mass, muscle mass, and FFAs tend to decrease [52,53]. Remarkably, though the body fat mass percentage decreases in old age, the ratio of body fat mass to muscle mass becomes higher in elderly persons compared to young adults [54].

4.4. Gut microbiota

The human gut contains trillions of microbes; the numbers are more than ten times the total numbers of human body cells [55]. An individual's gut microbiota composition is influenced by diet, age, birth delivery, breastfeeding, antibiotic use, ethnicity, host genetics, and medications [56]. The variability starts at the birth of a baby as soon as amniotic fluid disappears; in the case of standard delivery, gut microbiota resembles the vaginal microbiota composition; and in the case of cesarean section, gut microbiota resembles the skin microbiota composition [57].

Diet and sedentary lifestyles are the most significant modulator of gut microbiota [58,59]. Plant-based fiber-containing low-calorie diets increase gut microbiota diversities with low microbial gene richness [60], whereas high-calorie diets increase diversities. In obese animals, the gut microbiota is more active than in lean animals. Obese humans have a higher amount of small chain fatty acids and a reduced amount of caloric content in fecal materials [61]. Therefore, it is assumed that

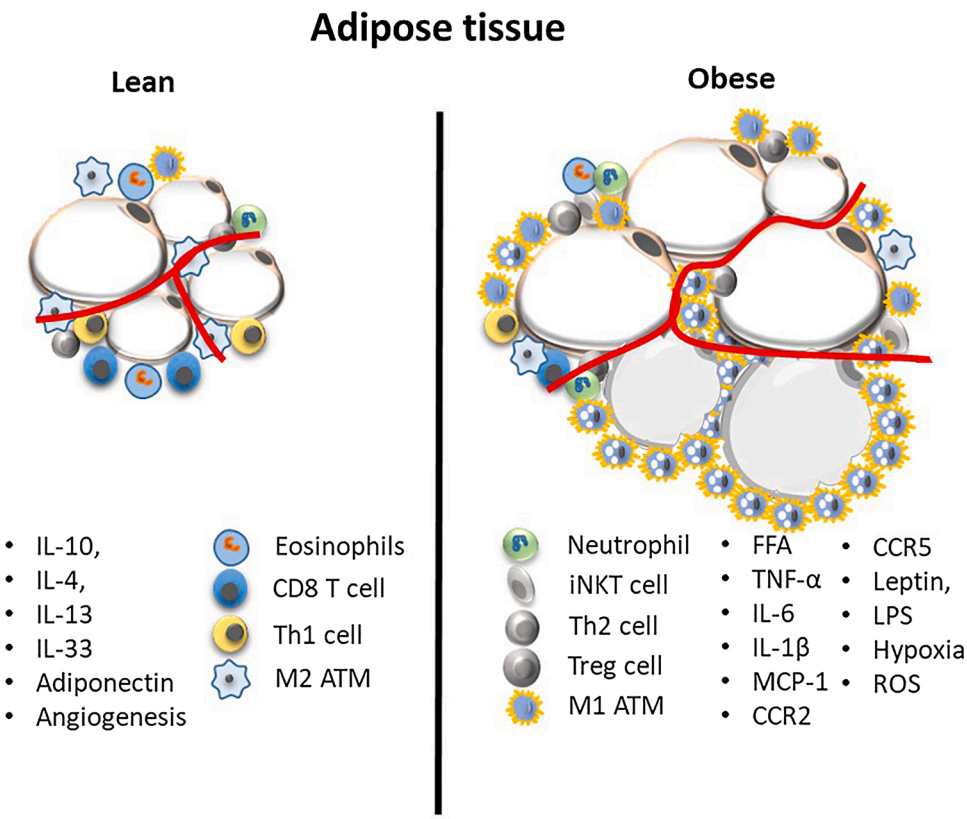

Fig. 2. Lean vs. obese adipose tissue: During chronic overnutrition, the frequency of adipocyte hyperplasia and hypertrophy increases. Studies demonstrated that hypertrophy is a more prominent mechanism during obesity, which increases the size of adipocytes and adipose tissues, creates hypoxic conditions, and increases adipocyte cell death. Hypertrophic adipocytes, hypoxia, and dead adipocytes generate potent environmental factors to recruit macrophages to solve the impairment. Most of the recruited macrophages present near the perilipin negative dead adipocytes form CLSs. Macrophages clear the dead adipocytes through lysosomal exocytosis and, because the macrophages are smaller than adipocytes, large amounts of lipids enter into macrophages and slow down exocytosis, which may be a reason behind polarization of anti-inflammatory M2 macrophages to pro-inflammatory M1 phenotype. Besides macrophages, some other immune cells, like neutrophil, iNKT, Th2, and Treg, also increase in obese adipose tissues, but their role in adipose tissue dysfunction is unidentified. Dysfunctional adipocytes and M1 macrophages induce several factors, e.g., FFAs, TNF-α, IL-6, IL-1β, MCP-1, CCR2, CCR5, Leptin, and LPS, which create complex systemic environments [4–6].

obese people consume more high-calorie foods than lean people, and during high-calorie diet adaptation, the adapted gut microbiota composition becomes more active for energy biosynthesis. A study has shown that transplanting gut microbiota from western diet mice to low-fat plant polysaccharide-rich diet mice increases the total body fat by 43 % after two weeks of colonization despite mice consuming the same foods [62]. A similar result has been observed when obese human fecal microbiota is transferred to mice that have contributed to fat mass regulation [63,64]. Similarly, three weeks of high-intensity interval training has not affected the overall bacterial diversity or community structure in human obese [65]; and also low bacterial gene count has been persisted one year after bariatric surgery [66]. Therefore, it is assumed that gut microbiota takes a long-time to adjust to new circumstances, and because of microbiotal persistence, it may require long-term maintenance of healthy food and quality exercises to reduce body weight. In an obese individual, a common bacterium in phylum *Firmicutes* is highly increased in gut microbiota [67]. *Firmicutes* are responsible for metabolizing bile acids into active secondary bile acids (deoxycholic or lithocholic acid), which are highly responsible for lipid emulsification and ceramide synthesis in the gut and subsequent transfer to the liver [56,68,69]. Diet-rich saturated fat also causes microbiota dysfunction and releases endotoxin, e.g., lipopolysaccharides (LPS), leading to systemic lipotoxicity [70].

4.5. Diets

The foods and beverages we consume every day have an essential role in our overall health. In the optimal diet, adequate nutrients and energy are required for healthy tissue maintenance and growth. The human body in good health needs to acquire the essential nutrients: proteins, carbohydrates, fats, vitamins, and minerals from various foods. Due to urbanization and high income, diets with high sugar, fat, and animal meat replaced traditional diets high in carbohydrates and fats [71,72]. Ethnic and unique traditional healthy food habits are increasingly being replaced by western high sugar-containing soft drinks, energy-dense fast food, and animal products [72]. The increasing westernization and mechanical life in the most developed countries are associated with diet changes toward high fat, sugar-sweetened beverages, and a sedentary lifestyle [71]. Westernization is also influencing middle and low-income countries; therefore, obesity and nutritional deficiency are also increasing in low-income countries. Regardless of dietary patterns, evidence from clinical trials has shown that only caloric restriction is associated with weight balance [73].

Overeating sugar and saturated fat and frequently have an impact on obesity. The overconsumption of added sugar is one of the most important factors that directly affects the long-term development of obesity. Here, added sugar is the extra sugar added on top of natural sugar content in the foods, such as glucose, sucrose, maltose, dextrose, and fructose. Studies have shown that 5.5 mM fructose down-regulates GLUT4 30–50 % (GLUT4 is a glucose importer in cells) in differentiated adipocytes, and excess fructose intake significantly increases hepatic triglyceride content, impairing insulin sensitivity [74,75]. High glucose directly impairs insulin sensitivity in hepatocytes [76] and generates glucotoxicity; if the glucotoxicity persists, it may lead to numerous clinical conditions [77]. A study showed that there was a 1.63–5.24 lb change in weight within every 4 years in the three cohorts through the middle age group who were used to consuming sugar-sweetened beverages, potato chips, and processed and unprocessed red meats, compared to the group who were used to taking vegetables, fruits, whole grains, nuts, and yogurts [78]. Lack of breastfeeding, high early energy intake, and high intake of sugar-sweetened beverages are also significant contributors to childhood obesity [79]. Consumption of saturated fat was linked to a higher risk of obesity. Eating a meal with high saturated fat impacts on insulin sensitivity and increases postprandial blood sugar and inflammation, contributing to obesity. Dietary fat is much more energy-dense than protein and carbohydrates, but it has less potential to inhibit food intake and evoke insulin secretion [80]; therefore, it is assumed that surplus dietary fats are positively associated with

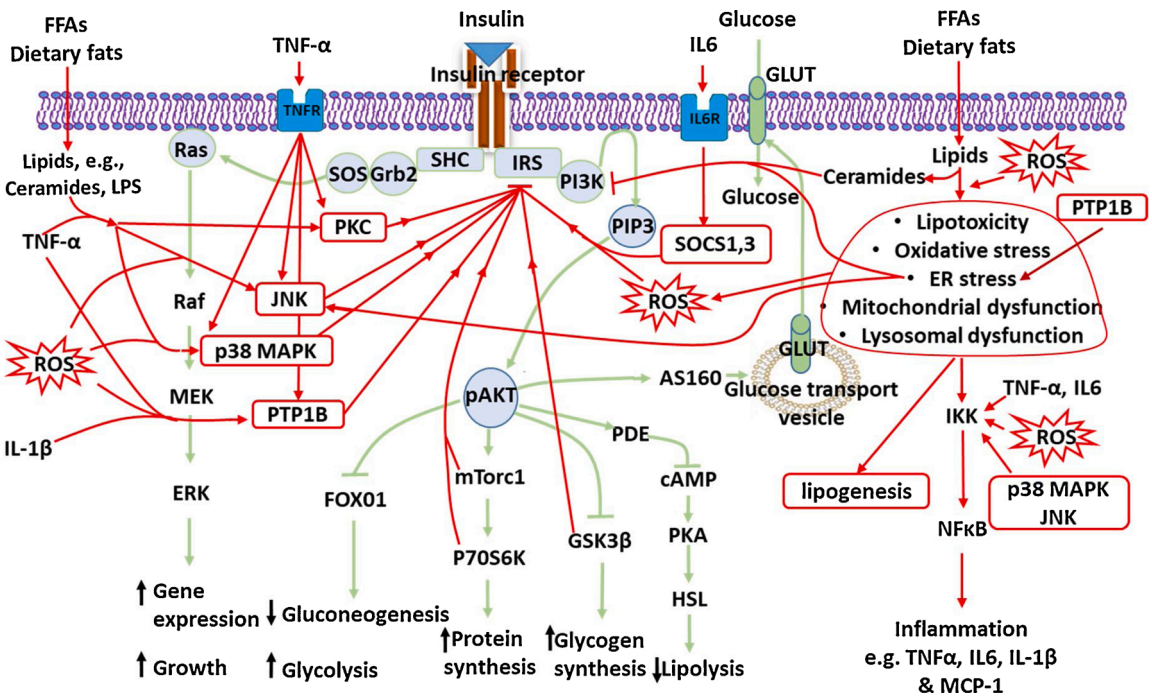

Fig. 3. Potential cellular mechanisms of obesity-induced insulin resistance: Insulin has possible effects on glucose homeostasis, energy metabolism, energy storage, and growth. Chronic overnutrition and obesity intercept insulin's action in cellular metabolism, which increases systemic insulin, FFAs, inflammation, and glucose levels. This figure illustrates how elevated lipids (e.g., FFAs, LPS, ceramides), pro-inflammation, and ROS interrupt the insulin signaling pathway targeting IRS kinases, e.g., p38 MAPK, p70S6K, PKC, IKKβ, GSK-3β, PTP1B, SOCS, and JNK. In obesity, these kinases negatively regulate IRS proteins upon prolonged insulin stimulation or activate unrelated pathways to inhibit insulin action by serine residue phosphorylation [8]. The red color indicates the molecular mechanism of the obesity-associated insulin resistance. The light green color indicates the modified insulin signaling pathway [10].

increased obesity.

5. Cellular dysfunctions associated with obesity-induced insulin resistance

Obesity is rapidly increasing worldwide; long-term obesity induces low-grade systemic inflammation and insulin resistance. This section will provide details and in-depth knowledge of how the dysfunctional obese adipose tissues generate complications, associated with insulin-resistant circumstances.

5.1. Inflammation

Numerous mechanisms take place during the progression of obesity. The size of adipocytes is increased with weight gain, which elevates adipocyte death because of an inadequate supply of oxygen in the face of expanding adipose tissue [81,82]. The enlarged adipocytes and adipose tissues then release FFAs, reactive oxygen species (ROS), and pro-inflammatory cytokines. The possible mechanism is that fatty acids activate NF-κB and P38 MAPK signaling through the MyD88 and TRIF-mediated downstream pathways following activation of TLR4 (Toll-like receptor 4) expression in resident adipocytes and macrophages, enhance ER stress and produce ROS, and promote the secretion of pro-inflammatory cytokines [83].

Several types of pro-inflammatory adipokines are secreted by obese adipose tissues, such as monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor α (TNF-α), Interleukin 1 beta (IL-1β), and interleukin 6 (IL-6). Secreted MCP-1 recruits monocytes in the chemotaxis process by drawing C-C motif chemokine receptor 2 (CCR2) to obese adipose tissues [84–86]. Once the monocytes join with adipose tissues on the inflammation site, monocytes differentiate into macrophages [81, 87]. The phenotypes of resident obese adipose tissue macrophages (ATMs) polarize from an anti-inflammatory M2 to a pro-inflammatory M1 phenotype [88] (**detail in** Fig. 2). Resident pro-inflammatory M1 macrophages release cytokines, including MCP1, IL-1β, and IL6, which can recruit more monocytes, depending on the adipocyte size and conditions [89–92]. Macrophages and adipocytes interact in a paracrine manner. The macrophages surrounding the dead adipocytes make a crown-like structure (CLS) to scavenge the dead adipocytes; thus, lipids from dead adipocytes are taken up by macrophages, which dysregulate the regular activity of macrophages; the prevalence of CLS is highly interconnected with the metabolic disorder and inflammation [93–95] (Fig. 2). In obese adipose tissues, the M1 macrophages and adipocytes release excess pro-inflammatory cytokines, recruiting more monocytes; the percentage of macrophages can reach over 50 % [96]. Eventually, dysfunctional adipose tissues in chronic overnutrition and obesity induce FFAs, ROS, and pro-inflammation in the systemic environment, eliciting the initial step of low-grade systemic inflammation.

Increasing systemic TNF-α in obesity promotes the activity of IKK, p38 MAPK, JNK, and PKC proteins, which directly target serine residues of the insulin receptor substrate (IRS) protein and impair tyrosine phosphorylation, leading to insulin resistance in adipose tissues, muscles, and liver [97,98] (Fig. 3). The TNF-α also promotes PTP1B, which impairs insulin signaling by dephosphorylation of the phospho-tyrosine residues in the insulin receptor and IRS protein [97]. Increasing IL6 can induce the JAK-STAT signaling pathways and increase the expression of SOCS1 (suppressor of cytokine signaling 1) and SOCS3 proteins, which can downregulate the insulin receptor function by sterically blocking its interaction with the IRS proteins or by modifying kinase activity [99–102]. The IL-6 can also induce TLR-4 gene expression through activation of STAT3; and together with IL-1β enhance STAT3 and NF-κB in hepatocytes, causing inflammation [103,104]. The IL-1β activates p38 MAPK via the IL-1 β receptor and prevents insulin signaling by serine phosphorylation on IRS1/2 [105]. The TNF-α may impair β-Cell insulin sensitivity mediated by nitric oxide [106]; however, there is no substantial evidence that pro-inflammation dysregulates β-Cells.

5.2. Lipotoxicity

The chronic overproduction of FFAs and the dietary lipid deposition in obesity and overnutrition lead to lipotoxicity in the cells of muscle, heart, liver, pancreas, and other organs. One study has claimed that insulin resistance is not only induced by fat accumulation itself in adipose tissues but also by the pro-inflammation caused by ectopic fat deposition [107]. Ectopic fat produces toxic lipids, e.g., ceramides, diacyl-glycerides (DAG), alters the PI3K pathway, activates PKC, JNK, and IKK complex, generates ROS, promotes the development of stress in the endoplasmic reticulum (ER) and membrane stiffening, induces inflammation, and activates apoptosis [108]. However, several studies have demonstrated that there are no significant associations between total DAG and insulin resistance [109,110].

Dietary fats also activate the downstream intracellular signaling pathways of MAPK and NFκB, and upregulate the expression of NALP3 and systemic pro-inflammation [111,112]. Increasing dietary fat and chylomicron production has been closely connected to raising plasma LPS levels and absorption in the liver, which is involved in decreasing hepatic intracellular lipid/LPS metabolism and leads to hepatic inflammation [113]. Like FFAs, LPS also induce inflammation via stimulation of the cell-surface receptor TLR4 and subsequently lead to the activations of NF-κB, P38 MAPK, and JNK pathways [114]. The LPS also induce inflammation in human peripheral blood mononuclear cells mediated by NOX4 [115]. The LPS directly interact with mouse caspase-11 or human caspase-4/5 and causes stimulation of inflammasomes, leading to the production of IL-1β [116].

However, a study has shown that LPS may be converted into ceramides in murine macrophage cell lines [117]. Another study has demonstrated that TLR4 requires saturated fatty acid-induced ceramide biosynthesis to induce insulin resistance, where IKKβ is essential for TLR4-mediated pro-inflammation and ceramide synthesis in muscles [118]. Absorbed and esterified fatty acids in obese mice in different organs initiate the production and activation of ceramides [119–122]. Ceramide content increase in obese skeletal muscles and serum of T2DM patients, while exercise reduces the ceramide levels in obese and T2DM patients and improves insulin sensitivity [123–126]. Ceramides stimulate Protein kinase C zeta (PKCζ), which phosphorylates the PH domain of PKB)/Akt on Thr, thereby suppressing the binding of PIP3 to this site and severely limiting its activation in the response of insulin [127] (Fig. 3). The activation of PKCζ further induces CD36-mediated fatty acid uptake in the liver [128]. Ceramides can activate PP2A and block the translocation of PKB/Akt to the plasma membrane while simultaneously promote Akt/PKB dephosphorylation in differentiated adipocytes [129]. Excess FFAs cause ceramide level elevation, leading to the generation of nitric oxide (NO) in β-cells [130]. Two studies demonstrated that *Cers6* and *CerS1* (genes associated with ceramide modulations) are absent in obese mice and protected from diet-induced insulin resistance and increased lipid unitization independently in the liver [131,132]. Most importantly, insulin resistance drives hepatic de novo lipogenesis in humans [133], enhancing further ceramide and lipid deposition in the liver and worsening insulin sensitivity.

5.3. Mitochondrial dysfunction

The mitochondrion is an essential organelle that generates energy as adenosine triphosphate (ATP) in a catalytic pathway to maintain normal physiological function. It has dynamic processes to adapt systemically in metabolic environments such as mitophagy, apoptosis, fusion, and fission. The dysfunction of the mitochondrial dynamics causes loss of integrity and functions, impairs energy production, and causes several metabolic alterations and damages, such as continuous fusion of mitochondria, abnormal elongation, and loss of functionality. Therefore, the fission process activates to prevent abnormality by mitochondria splitting into two, transforming mitochondrial fragments into small spherical organelles and reducing their energy generation capacity [134]. These dysfunctional processes damage mitochondrial DNA, which can halt energy production, generate ROS, and induce oxidative stress and apoptosis [134]. Mitochondrial dysfunctions increase mitophagy, the process that removes dysfunctional mitochondria by fusing with lysosomes [135,136]. Mitophagy can decrease the number of mitochondria, indicating reduced energy expenditure, which can enhance more lipid accumulation in excess overnutrition, induce lipotoxicity, and mitochondria-mediated cell apoptosis.

Obesity and excess consumption of nutrients are associated with mitochondrial dysfunctions [137]. Mitochondria can be dysfunctional in several organs; however, in obesity, most mitochondrial dysfunctions are assumed to take place in adipose tissues, muscles, and liver because these organs are involved in high energy processes with an excessive overload of nutrition and lipids. In obese adipose tissues of the high-fat diet mice, the fusion markers mitofusin 1 and 2 (Mfn1 and Mfn2) expressions have significantly reduced compared to that of standard diet, whereas fission related protein Drp1 has increased [138]; however, in human obese adipose tissues, Mfn2 significantly reduces although they have not reported about Mfn1 in the human study [138]. Overall, Mitochondrial dysfunctions in obese adipose tissues dramatically increase biogenesis, alter metabolism, increase respiration, and promote fatty acid oxidation, leading to excessive acetyl-co-A production [139, 140]. In skeletal muscles of mice, fission protein Drp1 level was increased upon high fed diet or induction of obesity, although there was no change in Mfn1 and Mfn2 levels [141]. However, Mfn2 mRNA expression was reduced in obese type 2 diabetic patients [142,143]. Additionally, excess FFAs uptake in the skeletal muscle causes an increase in the rate of β-oxidation [75]. Overall, in obese, mitochondria in skeletal muscles become smaller and shorter because of increasing mitochondrial fission that reduces mitochondrial function and mass associated with mitochondrial dysfunctions and insulin resistance [144–146].

Enhanced mitochondrial fission was also observed in the liver of a mouse model similar to adipose tissues and skeletal muscles of obese and insulin resistance, whereas the opposite was true for mitochondrial fusion (Mfn2) [147]. Acute exposure to high glucose in cultured hepatocytes and myocytes also causes an increase in mitochondrial fragmentation and overproduction of ROS production by inhibiting Drp-1, whereas promoting mitochondrial fusion prevents high glucose-induced ROS increase [148]. Hepatic lipid accumulation in the liver is counteracted by increased lipid expenditure by the β-oxidation and enhanced VLDL secretion [75]; therefore, mitochondrial fission increased in diet-induced obesity decreases the mitochondrial respiratory capacity and protein expression [144]. Obese hepatocytes also increase the transportation of Ca^{2+} from the ER to mitochondria through mitochondria-associated ER membrane, leading to Ca^{2+} overload, mitochondrial dysfunction, and activation of ER stress signaling [149].

The characteristics of mitochondria in obese individuals are different compared to that in lean individuals. In obese individuals, mitochondrial morphology is altered, mitochondrial biogenesis is impaired, mitochondrial lipid peroxides are increased, and incomplete fatty acid oxidation produces DAG, acetyl CoA molecules, and ceramides [75]. Rising levels of acetyl-CoA directly or via the TCA cycle produces NADH and FADH2. Therefore, the excess supply of electrons in the mitochondrial electron transport chain leaks from the system and directly reacts with O_2, generating superoxide radicals, which then convert to hydrogen peroxide spontaneously or enzymatically [139]. In obesity, hydrogen peroxide may undergo the Fenton reaction to produce hydroxyl radicals, which are highly reactive ROS [150–153]. Because of lipid and glucose overload, mitochondria produce more than the required amounts of ROS. In healthy mitochondria, less than 5% of collected oxygen produces ROS; in the case of obesity, mitochondria produce an uncontrollable amount of ROS, which damage the DNA, lipid membranes, protein, and enzymes in the mitochondrial respiratory chain [154]. Obesity and comorbidities caused by excessive ROS production overwhelm the antioxidant defense systems, leading to

oxidative stress [155]. Mitochondrial dysfunction and oxidative stress lead to an accumulation of intracellular oxidized components, including lipids, proteins, nuclear and mitochondrial DNA, which are then released as damage-associated molecular patterns (DAMPs), and trigger pro-inflammation. Picca et al. propose that DAMPs can activate inflammatory responses via three distinct signaling pathways, as following 1) DAMPs→TLR-9→Neutrophil→NF-κB pathway, 2) DAMPs→cGAS/STRING/TBK1 →IRF-1→IFNβ, IFNλ1 pathway, and 3) DAMPs-NLRP3→Caspase-1→IL-1β pathway [156]. The IFN-γ signaling leads to the phosphorylation of STAT1 and STAT3; STAT1 activates immune cells, and STAT3 induces inflammatory inflammation. The best-known pathway of IFN-β is the stimulation of NFκB signaling [157,158].

5.4. Reactive oxygen species

Storing excess fat generates lipotoxicity, which produces different lethal ROS, such as superoxide (O^{-}_{2}), hydrogen peroxide (H_2O_2), hydroxyl radical (O˙H), and NO. Obesity enhances ROS production and induces lipid peroxidation in adipocytes, liver, and skeletal muscles of humans [159–161]. In the previous section, the possible mechanism whereby obesity-associated mitochondrial dysfunction induces excessive ROS has been discussed. Another possible mechanism is that the NADPH oxidases (NOX) present in the plasma membrane can potentially generate excess ROS. There are several isoforms of NOX, e.g., NOX1, NOX2, NOX3, and NOX4. The NOX maintain a healthy body by defending microbial attack; NOX generate superoxide radicals in phagosomes that help destroy microbial organisms [162]. In healthy adipocytes, insulin stimulated NOX4 mediates H_2O_2 production, which promotes insulin signaling through inhibition of PTP1b, and drives adipocyte differentiation [163,164]. However, excess superoxide formation by NOX generates excess ROS, which inactivates critical metabolic enzymes, degrades cellular molecules, and initiates lipid peroxidation in obesity [165].

High glucose and FFAs increase intracellular ROS generation from NOX4, and inhibition of NOX4 reduces ROS production and MCP-1 expression in differentiated adipocytes [166,167]. It has been shown that adipocyte-specific deficiency of NOX4 delays the onset of adipose inflammation and insulin resistance [168]. Overexpression of NOX4 in excess overnutrition significantly reversed the inhibition of PTP1B, contributing to insulin resistance in adipocytes [163]. In contrast, expression and activation of antioxidant enzymes such as catalase, SOD1, and GPX decreased in adipose tissues of obese individuals [169].

Interestingly, a study has claimed that in obese mice, the mRNA expression of NOX subunits is only increased in adipose tissues, not in the liver or muscles, and it impairs the antioxidant defense system [167]. The NOX are expressed in both human and mouse pancreatic islets and correlate with increased oxidative stress in the T2DM animal model [170]. However, DeVallance et al. have mentioned that hyperglycemia and hyperlipidemia enhance ROS production through NOX in obesity, contributing to skeletal muscle insulin resistance by potentially reducing Akt [171]. The NOX2 is also induced for macrophage chemotaxis and polarization toward pro-inflammation in adipose tissue of obese mice [172,173]. Like obese adipocytes, the infiltrated macrophages also show induced ROS production through NOX2 in the presence of excess fatty acids and glucose [174,175]. Excess FFAs stimulate NOX production through the PKC dependent pathway in vascular cells within 72 h treatment *in vitro* [176]. Therefore, the lipid accumulation and excess lipids promoting ROS through the dysfunctions of NOX and mitochondria in the obese adipose tissues can be the spur of metabolic dysfunction, besides pro-inflammatory protein secretion.

Excess ROS make oxidative stress and activates numerous transcription factors, including NF-κB, which elevates systemic pro-inflammatory cytokines, promoting an insulin-resistant environment [177]. Production of ROS by fructose metabolism induces the accumulation of citrate in the TCA and increases the availability of substrates for de novo lipogenesis [178], enhancing further lipid accumulation and ROS production. The ROS dysregulate multiple biochemical mechanisms such as oxidative phosphorylation, superoxide generation from NOX, glyceraldehyde auto-oxidation, chronic inflammation, PKC activation, and hyper-leptinemia [179]. The ROS activate potential serine/threonine kinase cascades, which interact with several targets in the insulin signaling pathways. One of the most important targets of ROS is the insulin receptor and the family of IRS proteins. The ROS activate serine kinases, resulting in hyper serine/threonine phosphorylation, which inhibits the tyrosine phosphorylation of IRS-1 and IRS-2, and diminish the catalytic activity of insulin signaling [180] (Fig. 3). They also activate the serine/threonine cascade of IKKβ, JNK, and P38 MAPK kinases; IKKβ is also an important mediator of pro-inflammation in the NF-κB pathway [180], leading to insulin resistance.

5.5. ER stress

The ER is another crucial organelle in a eukaryotic cell. The primary functions of ER are synthesis, folding, and transportation of proteins; ER also maintains Ca^{2+} homeostasis and lipid synthesis, including biosynthesis of cholesterol, phospholipids, and ceramides [181–184]. Recently, ER stress was designed as the key player in the development of obesity-associated metabolic dysfunction. During obesity and over-nutrition, the high load of lipids and unfolded/ misfolded proteins are accumulated in the ER, thus resulting in ER stress and chronic inflammation of mice adipose tissue and liver [185,186]. Like unsaturated fatty acids, LPS, high glucose, and saturated fatty acids also induce ER stress in differentiated primary human adipocytes [187,188]. Exercise ameliorates ER stress and insulin resistance in adipose and hepatic tissues in obese rats [189]. A human study has shown that ER stress is reduced in adipose and hepatic tissues of obese subjects after weight loss by gastric bypass surgery. The study has also demonstrated that human obesity is associated with insulin resistance and ER stress in adipose tissue and the liver; additionally, weight loss is associated with decreased ER stress [190]. The saturated fatty acid and hyperglycemia also activate ER stress in hepatocytes and enhance lipid accumulation through the mTORC1 pathway; conversely, AMPK activation prevents excess nutrient-induced hepatic lipid accumulation by inhibiting mTORC1 signaling and ER stress response [191].

Direct exposure of human and murine myotubes to palmitic acid and β-cells induce ER stress; however, oleic acid prevents palmitic acid from inducing ER stress and insulin resistance [130,192,193], but Hassan et al. has claimed that insulin resistance induced by palmitic acid is not related to ER stress in muscle cells [194]. A study has demonstrated that a full-range of ER stress activation is required to induce PTP1B for mediating insulin resistance in the skeletal muscle in high-fat diet-induced mice [195]. Like FFAs, the elevated glucose level in obesity has detrimental effects on β-cell dysfunction and leads to glucotoxicity, which generates ER stress, and impairs insulin production, and irreversible β-cell loss by apoptosis through the TXNIP pathway [196,197].

Hotamisligil et al. have demonstrated that during chronic overnutrition and obesity, the liver increases lipogenesis and gluconeogenesis for energy storage, which creates excess lipid overload. Because of excess lipids, the ER suppresses protein synthesis and stimulates lipid biosynthesis. The synthesized lipid droplets in the ER by lipogenesis are preferred phosphatidylcholine (PC) for a phospholipid coat in obesity. Monounsaturated fatty acids synthesized in the liver are also incorporated into the PC, whereas phosphatidylethanolamine (PE), is another major membrane phospholipid, decreases compared to PC. The high PC/PE ratio impairs the ER function, resulting in stress and promoting the excretion of the excessive lipids from the liver into circulation, increasing hyperinsulinemia [198].

Another possible mechanism is that overloaded Ca^{2+} in the cytoplasm may trigger ER stress and apoptosis [199,200]. The normal function of the ER is to store Ca^{2+} and regulates Ca^{2+} signaling. The concentration of Ca^{2+} in the ER is very high and is regulated by the ER calcium ATPase (SERCA) pump. However, saturated fatty acids can

cause ER stress and JNK activation by increasing ER membrane rigidity; therefore, high saturated fatty acids reduce ER membrane fluidity resulting in inhibition of SERCA, subsequently elevates cytosolic Ca^{2+} [201]. Pahl et al. have stated that the efflux of Ca^{2+} from the ER because of SERCA inhibition and the subsequent generation of ROS are required for ER stress-mediated NF-κB activation [202]. In pancreatic β-cells, FFAs cause a rise in cytosolic Ca^{2+} and stimulate insulin release in healthy mice [203]. However, excess FFAs cause the Ca^{2+} depletion from ER in pancreatic β-cells and hepatocytes and help develop ER stress [203–205].

ER stress induces systemic pro-inflammation via several mechanisms. Eukaryotic cells have a system to alleviate ER stress, called the UPR (Unfolded protein response). The ultimate goal of UPR is to restore ER protein biosynthesis to maintain normal activity by removing unnecessary and overloaded lipids and misfolded proteins. There are three major transducer proteins of UPR that may be generated in the ER to alleviate stress: 1) PKR like ER kinase (PERK), 2) inositol requiring enzyme 1 (IRE1), and 3) activating transcription factor 6 (ATF-6) [206]. However, the chronic overload of nutrition and obesity generates excess UPR transducer, leading to the release of pro-inflammatory cytokines and causing cell apoptosis. In the PERK pathway, PERK-mediated phosphorylation of eIF2α suppresses the protein translation to relieve ER load; however, eIF2α phosphorylation inhibits the IκB protein, therefore, releasing the transcription factor NF-κB from the IKK complex, transferring it into the nucleus, and promoting the expression of pro-inflammatory proteins [207]. The PERK-eIF2α-ATF5 and IRE-1 pathways induce TXNIP-NLRP3 protein production, which is directly causing induces IL-1β secretion. Similarly, IRE-1 can also promote the synthesis of IKKβ, XBP1s, and JNK protein, and induce inflammation [207] (Fig. 3). Furthermore, the ATF-6 pathway also generates pro-inflammation through NF-κB and inhibits the anti-inflammatory PKB/AKT [208,209]. Therefore, the excess pro-inflammation release due to the fat deposition in the ER generates stress, leading to the development of insulin resistance.

5.6. Lysosomal dysfunction

The lysosome is another important organelle in a eukaryotic cell. The lysosome's functions are to degrade and recycle long-lived, unnecessary/dysfunctional proteins, lipids, and organelles; and generate ATP, new lipids, proteins, organelles, and excrete cell debris in the process called autophagy [210,211]. The process of autophagy is essential to attenuate stress, remove ROS, and maintain cellular homeostasis. During excess carbohydrate, fatty acid, and amino acid consumption, one of the central regulatory proteins, mTOR, is increased, which inhibits autophagy [212,213]. In contrast, during nutrient deprivation, AMPK mediates through mTOR inhibition and activates autophagy [214–216]. Several studies have suggested that mTOR is a major autophagy regulator [217,218]. During obesity and overnutrition, mTOR phosphorylates ULK1 protein on Ser637 and Ser757, and ULK1 complex protein Atg13 on Ser258; therefore, the regulation of the ULK1 complex halts autophagosome formation [219]. Besides the direct mTOR regulated pathway, autophagosome formation is also regulated mTOR independent pathways. Due to the elevation of cytosolic Ca^{2+} during obesity and lipotoxicity, the ER generates stress and weakens autophagic flux that may prevent the fusion between autophagosomes and lysosomes [220]. Moreover, lipotoxicity mediated inhibition of SERCA is likely to be involved in autophagy dysregulation [221].

In the liver, autophagy is necessary for maintaining lipid homeostasis [222,223]. Excessive lipid deposition increases the possibility of hepatocyte dysfunction and suppresses autophagy by impairing the function of autophagolysosomes, hydrolase activity, and lysosomal acidifications [224,225]. Importantly, liver-specific knockout of atg7 and TFEB genes (associated with autophagy) in diet-induced obese mice promotes steatosis, and overexpression of these genes prevents weight gain and metabolic abnormalities [226,227], indicating that autophagy in the liver might be important to suppress obesity. Conversely, obesity also promotes the S-nitrosylation of lysosomal proteins, thereby causing lysosomal dysfunction and defective autophagy [228]. The defective hepatic autophagy then increases the accumulation of misfolded/unfolded proteins and lipids, promoting ER stress and mitochondrial dysfunction, leading to chronic systemic inflammation and creating an insulin-resistant environment.

Interestingly, the opposite is true when autophagy is inhibited in adipocytes through adipose-specific deletion of atg7; the tissue content is decreased, the number of mitochondria are increased, and insulin sensitivity is improved [229–231]. Increased autophagy decreases mitochondrial number in differentiated adipocytes [232]; however, the precise mechanism is unknown. Mice with adipose-specific deletion of atg7 exhibit decreased leptin levels, reduced plasma concentrations of triglycerides and cholesterol, and are resistant to high-fat diet-induced obesity [233]. Additionally, autophagy is also upregulated in human subcutaneous adipose tissue of obese compared to lean subjects and positively correlated with systemic insulin resistance [234]. Furthermore, the autophagosome activities are increased in adipose tissue of obese compared to lean mice [234]. Possibly, obese adipose tissues induce lipophagy flux suppressing the lipid congestion and creating complexity, which generates ROS, impairs lipid oxidation, and upregulates β-oxidation.

The knockout of β-cell-specific *Atg7* in mice reduced β-cell mass, developed mild ER stress and hyperglycemia, and lowered pancreatic insulin content. However, when β-cell-specific *Atg7* mice were crossed with leptin-deficient mice, they developed severe ER stress in β-cells and diabetes, indicating the critical role for autophagy in maintaining β-cell ER homeostasis [235]. Remarkably, studies have demonstrated that obesity and excess nutrition upregulate lysosomal autophagy in the adipose tissues and downregulate it in the liver and pancreas; interestingly, muscle tissues are unaffected [210,236]. However, Hasnain et al. have stated that the previous data are conflicting regarding autophagy and ER stress-induced β-cell apoptosis; the significance of β-cell apoptosis in T2DM remains a subject of debate [237]. It could be true for animal studies that β-cells can be dysfunctional through the ER stress, lysosomal dysfunction, and mitochondrial dysfunction within a few weeks of high-fat diets. However, obese human subjects are different; it may take more than a decade to develop dysfunctional β-cell after glucose impairment started and insulin resistance circumstances [238], indicating that the liver is the most sensitive organ to cave under insulin impairment than other organs in chronic obese environments through dysregulating mitochondria, ER and lysosome.

6. Conclusion

Several risk factors are linked with the increased risk of obesity and adipose tissue dysfunctions. Dysfunctional obese adipose tissues excessively release FFAs, ROS, and pro-inflammatory cytokines, which induce insulin-resistant circumstances at the early stage. Increased FFAs and dietary lipids enter into cells of different non-adipose organs, generate toxic lipids, e.g., ceramides. The toxic lipids then dysregulate several cellular organelles such as mitochondria, ER, and lysosomes. Chronic obesity and overnutrition push these organelles to enter a dysfunctional process; therefore, if one organelle is defective, others are affected and go through the impairment processes; the process can cause cellular impairment, systemic dysfunction, and cellular apoptosis. Because of cellular and systemic dysfunction, insulin sensitivity, and glucose homeostasis are disrupted, further increasing systemic FFAs and lipid deposition into non-obese organs. The process produces excess systemic pro-inflammation and ROS. Different immune cells accumulate in the inflamed areas to resolve the complications; sometimes, immune cells also produce inflammation from the affected site. The inflammation generated through ER stress and lysosomal dysfunction requires both overloaded Ca^{2+} and ROS as messengers, and the inflammatory status determines the onset of insulin resistance.

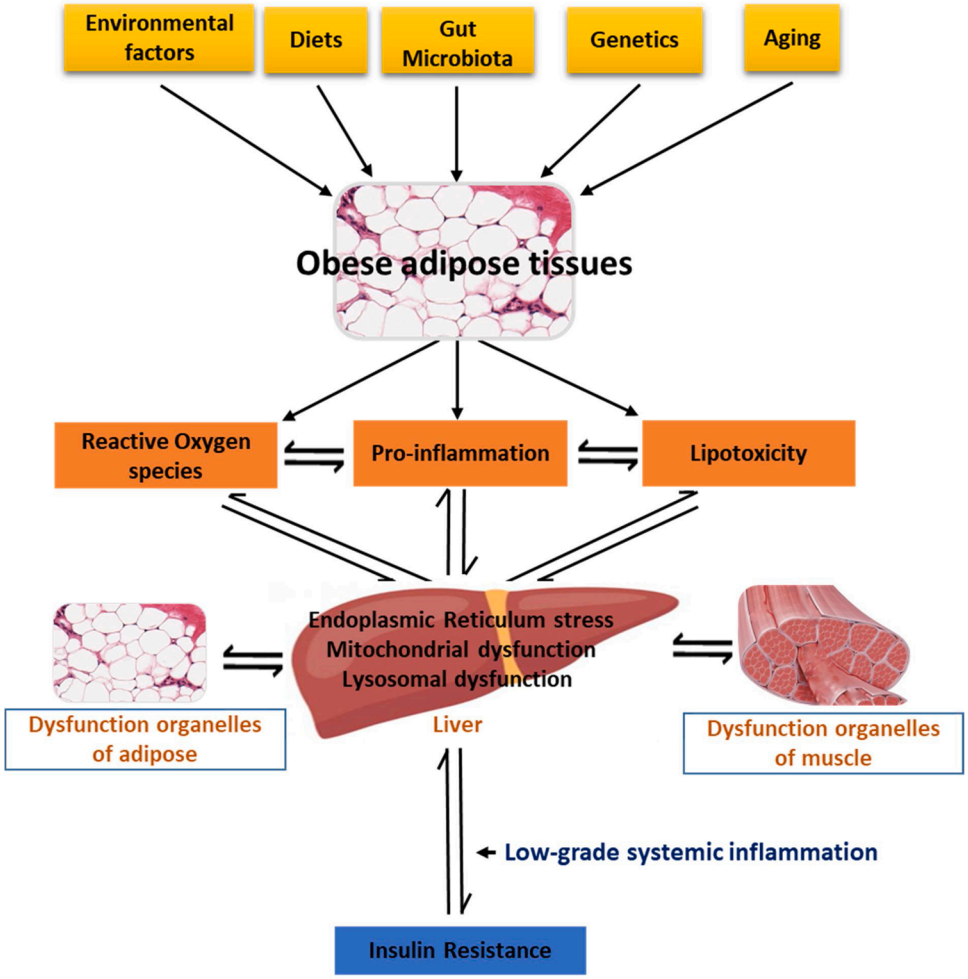

Fig. 4. Obesity-induced cellular dysfunction promotes insulin resistance: Multiple risk factors contribute to the development of obesity. Environmental factors, aging, diets, gut microbiota, and genetics are different factors that positively regulate obesity and adipose tissue dysfunction. Dysfunctional obese adipose tissues release FFAs, ROS, and pro-inflammation. Thus, excessive FFAs and other lipids, such as LPS, are deposited into cells of different organs, e.g., liver, muscle, and pancreas, create lipotoxicity, and dysregulate mitochondria, lysosomes, and ER. Dysregulated organelles then increase the release of the surplus of FFAs, pro-inflammation, and ROS. Eventually, chronic overnutrition and obesity create low-grade systemic inflammation, promoting the development of insulin-resistant circumstances.

Therefore, studies indicate that the lipodystrophic process is responsible for excess pro-inflammation to develop insulin resistance circumstances (Fig. 4). Thus, in the insulin resistance circumstances, insulin cannot properly handle glucose homeostasis; β-cells sense the increased glucose level in circulation and release more insulin to compensate. In a nutshell, long-term obesity induces chronic low-grade systemic inflammation, impairs insulin sensitivity raising the possibility of generating various chronic diseases, and causes healthcare burdens.

This study has shown that the liver is more prone to develop insulin resistance faster than other obese organs. Kahn's group has also demonstrated that muscle and adipose tissue-specific insulin receptor knockout mice have reduced glucose uptake (impaired insulin sensitivity), but the total-body glucose homeostasis has remained normal. However, the liver-specific insulin receptor knockout mice have both fasting and postprandial hyperglycemia and the subsequent development of peripheral (muscle) insulin resistance [239]. Therefore, evidence supports the view that muscle and adipose insulin resistance are the consequence of hepatic insulin resistance, and the adipose tissues are the primary initiator of insulin-resistant circumstances.

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Declaration of Competing Interest

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