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REVIEW

Pathophysiology of obesity and its associated diseases

Xin Jin[a,d,e], Tingting Qiu[a], Li Li[a], Rilei Yu[a], Xiguang Chen[d], Changgui Li[b,*], Christopher G. Proud[c,*], Tao Jiang[a,*]

[a]*School of Medicine and Pharmacy, Ocean University of China and Laboratory for Marine Drugs and Bioproducts, Qingdao National Laboratory for Marine Science and Technology, Qingdao 266100, China*
[b]*Shandong Provincial Key Laboratory of Metabolic Diseases, Qingdao Key Laboratory of Gout, Affiliated Hospital of Qingdao University Medical College, Qingdao University, Qingdao 266100, China*
[c]*Lifelong Health Theme, South Australian Health and Medical Research Institute, North Terrace, Adelaide SA 5000, Australia*
[d]*College of Marine Life Sciences, Ocean University of China, Qingdao 266100, China*
[e]*Shandong Laboratory of Yantai Drug Discovery, Bohai Rim Advanced Research Institute for Drug Discovery, Yantai 264117, China*

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Abstract The occurrence of obesity has increased across the whole world. Many epidemiological studies have indicated that obesity strongly contributes to the development of cancer, cardiovascular diseases, type 2 diabetes, liver diseases and other disorders, accounting for a heavy burden on the public and on health-care systems every year. Excess energy uptake induces adipocyte hypertrophy, hyperplasia and formation of visceral fat in other non-adipose tissues to evoke cardiovascular disease, liver diseases. Adipose tissue can also secrete adipokines and inflammatory cytokines to affect the local microenvironment, induce insulin resistance, hyperglycemia, and activate associated inflammatory signaling pathways. This further exacerbates the development and progression of obesity-associated diseases. Although some progress in the treatment of obesity has been achieved in preclinical and clinical studies, the progression and pathogenesis of obesity-induced diseases are complex and unclear. We still need to understand their links to better guide the treatment of obesity and associated diseases. In this review, we review the links between obesity and other diseases, with a view to improve the future management and treatment of obesity and its co-morbidities.

*Corresponding authors.
E-mail addresses: lichanggui@medmail.com.cn (Changgui Li), Christopher.Proud@sahmri.com (Christopher G. Proud), jiangtao@ouc.edu.cn (Tao Jiang).

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1. Introduction

Obesity is defined as abnormal or excessive fat accumulation (World Health Organization, WHO) and has been described as a 'global pandemic'[1–3]. Being overweight or obese are defined by measures of body mass index (BMI)[4]. A BMI of obesity is over 30 kg/m^2 while a BMI of 25−29.9 kg/m^2 is defined as overweight[5,6]. The standard for obesity and overweight are different in certain populations[7]. For example, for Chinese people, the standard is different from that of WHO. According to the recommended criteria for Chinese people, the categories are defined as follows: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5−23.9 kg/m^2), overweight (BMI 24.0−27.9 kg/m^2), and obese (BMI ≥28 kg/m^2)[8,9]. According to a WHO report published in 2021, more than 1 billion people were obese, including 650 million adults, 340 million adolescents and 39 million children based on data gathered in 2016. The global prevalence of being overweight or obese has increased by 27% in adulthood and 47% in childhood during 1980−2013[10]. This number is still increasing, and the WHO estimates that it will increase by approximately 167 million people by 2025 (www.who.int). Obesity is a risk factor for various diseases[11,12], notably type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), cardiovascular disease (CVD) and some kinds of cancer[13] (Fig. 1). SARS-CoV-2, also called COVID-19, has infected over 598 million people and killed over 6.2 million people worldwide. People with obesity who contracted COVID-19 showed higher levels of hospitalization, ICU admission, and death[14–17]. Obesity and related diseases impose a heavy burden on individuals, society, and on the economy, through greater public health costs, morbidity and mortality.

Obesity mainly develops as an imbalance between caloric intake and energy expenditure[18]. When energy intake is more than needed, it will be stored as fat and glycogen in subcutaneous adipose tissue (SAT) and organs[19,20]. Adipose tissue (AT) consists of functionally distinct depots[21]. White adipose tissue (WAT) is an active endocrine and a major and safe lipid storage organ, whereas brown adipose tissue (BAT) produces heat upon β-adrenergic stimulation or cold exposure, a process known as adaptive thermogenesis[22]. In humans, WAT can be classified in two main depots: visceral WAT (VAT) and SAT, which have been widely studied for their association with the development of related diseases[23]. BAT represents merely 1%−2% of fat, but it is vital in maintaining homeostasis and shows beneficial effects on blood glucose[24].

People who are overweight or obese has been linked with a low-grade, chronic inflammatory state, which is associated with

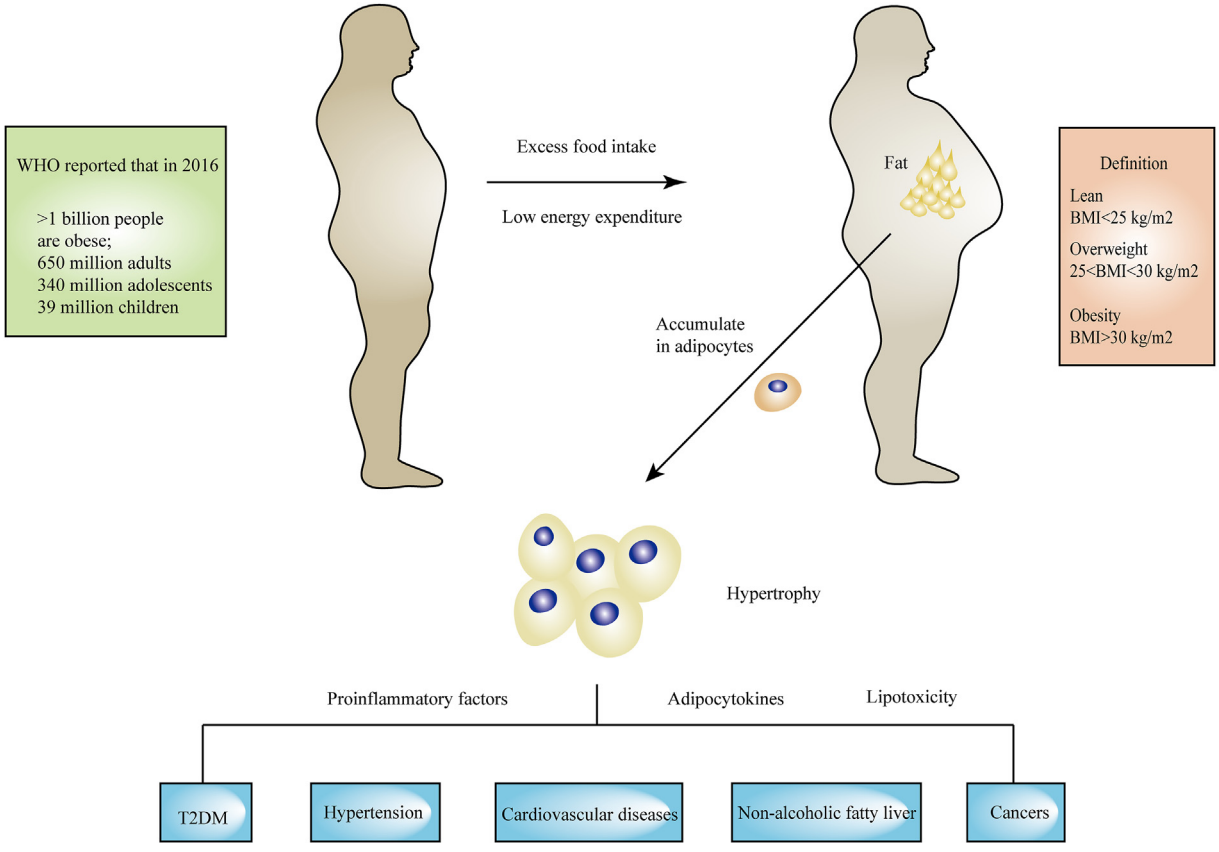

Figure 1 Overview of the obesity epidemic, obesity definition and obesity-associated diseases.

increased infiltration into AT from the circulation by macrophages of the M1 or 'classically activated' phenotype[25]. These macrophages can be recruited to AT where they secrete inflammatory cytokines (TNF-α, IL-6, IL-8, etc.)[26]. Along with pro-inflammatory cytokines, anti-inflammatory cytokines (such as IL-4, IL-10, IL-13, IL-19) are secreted from adipocytes; however, their abundance and secretion appear to decrease with weight gain since obesity definitively induces the balance to increase production of more pro-inflammatory adipokines[27,28]. AT also secretes adipokines (leptin, adiponectin, visfatin and resistin, etc.) and constituents of the extracellular matrix (ECM) to regulate related pathways[29,30]. Excess accumulation of fat leads to adipose tissue hyperplasia and hypertrophy, which changes the secretome and metabolites released and influences the surrounding microenvironment[31,32].

Leptin, one of the most abundant adipokines with proinflammatory properties, increases along with other factors, such as hepatocyte growth factor (HGF)[33], plasminogen activator inhibitor-1 (PAI-1), resistin[34], TNF-α, IL-1β, IL-6, and monocyte-chemoattractant protein-1 (MCP-1)[35,36], while the production of adiponectin is decreased. The inflammatory cytokines released by AT contribute to the progression of the metabolic syndrome (it is well known as a metabolic disorder resulting from obesity which involves glucose intolerance, insulin resistance, central obesity, dyslipidaemia, hypertension and all risk factors for CVD)[37] and increased risk for several cancers. Increased free fatty acids (FFAs) in the serum of obese individuals promote the expression of vascular endothelial growth factor-A (VEGF-A) and vimentin by upregulating PPARγ, which is implicated in tumor growth and tumor initiation through cell intrinsic and extrinsic mechanisms[38], resulting in insulin resistance[39,40] and steatosis in the liver[40]. Overexpression of TNF-α and leptin can inhibit insulin receptor activation and induce insulin resistance in muscle, liver, islet α-cells and AT, eventually lead to T2DM[41]. Furthermore, obesity can cause lipid accumulation in non-adipose tissue, such as liver, muscle, pancreas, epicardial and perivascular tissue, among which, the build-up of lipid in epicardial adipose tissue (EAT) and perivascular adipose tissue (PVAT) cause hypoxia and dysfunction of tissue and macrophage infiltration, leading to increases in inflammatory factors associated with CVD[42,43].

This review will provide a global overview of the main obesity-associated diseases and associated mechanisms. There is an urgent need to develop advanced approaches to treat these conditions which in turn requires detailed understanding of the molecular mechanisms involved.

2. Obesity and cancer

Obesity is known to be associated with 13 types of cancer[44–47], including breast, uterine, ovarian, esophagal, stomach, colon/rectal, liver, gallbladder, pancreatic, renal, thyroid, and meningeal cancers, as well as multiple myeloma, according to the International Agency for Research on Cancer (IARC) Working Group[5,48,49]. A 204 meta-analyses revealed that the increased risk of developing cancer for every 5 kg/m^2 increase in BMI ranged from 9% for rectal cancer among men to 56% for biliary tract system cancer[50]. A systematic review and meta-analysis conducted by the World Cancer Research Fund & the American Institute for Cancer Research assessed a cohort of over 9 million men, including 191,000 men with prostate cancer[51]. They concluded that there was a strong level of evidence indicating an 8%−11% increased risk of advanced prostate cancer and prostate cancer-specific mortality in obese men and found a 6% increased risk of advanced disease per 5% kg/m^2 increase in BMI[51,52]. Additionally, a meta-analysis of 56 observational studies involving more than 7 million individuals and 93,812 colorectal cancer (CRC) cases confirmed that a higher BMI was associated with a higher CRC risk; for every 5% kg/m^2 increase in BMI, CRC risk increased by 18%[53]. There is growing observational evidence that obesity is associated with worse cancer outcomes among individuals with cancer[51,54]. A meta-analysis of 82 studies involving 213,075 women with breast cancer found a 41% relative increase in all-cause mortality for women with obesity *vs* those of normal weight[55]. Similarly, adverse associations of obesity with survival have been reported for endometrial, prostatic, pancreatic[56,57], colorectal and ovarian cancers, as well as some hematologic malignancies[58]. However, being overweight or obese does not always show a positive relationship with cancer, and is actually associated with better outcomes in lung, esophageal and kidney cancer[10,59,60].

The association of obesity with cancer is biologically complex[61]. Many studies have indicated that obesity-related effects on DNA damage and/or repair pathways may be involved in obesity-induced genetic instability due to the formation of reactive oxygen species (ROS)[62]. Oxidative stress (OS) could be induced by the formation of ROS, and OS promotes the structure modification of carbohydrates, proteins, phospholipids and nucleic acids by the process of oxidation[63]. Oxidation modification of DNA induces the formation of 8-oxo-dG, which increases genetic instability due to its mutagenic potential[64–66]. In obese individuals, excessive accumulation of TG in adipocytes results in enhanced mitochondrial β-oxidation of FFA and increased mitochondrial ROS generation[67–69], which drives the accumulation of genomic damage, reduces the efficacy of DNA repair, and/or enhances the competitiveness of tumor cells by regulating intracellular molecular networks such as the NF-κB, JAK2/STAT3 or PI3K/AKT pathway[70]. The circulating pro-inflammatory cytokines (TNF-α, IL-1, IL-6 and others) are known to induce the production of ROS[71], and this may accelerate the mutational rate of cells and/or interfere with DNA repair mechanisms leading to an increase and accumulation of genetic events[63]. Furthermore, adipocyte hypertrophy in tissue leads to ischemia and hypoxia, which can cause a greater state of OS and release of ROS to induce mitochondrial dysfunction and damage DNA[72]. The obesity-associated conditions of hyperglycemia, hyperlipidemia and hyperinsulinemia lead to increased OS and ROS, exacerbating the inflammatory process in obesity.

Moreover, the cellular lipid remodeling induced by obesity impacts multiple facets of physiology relevant to carcinogenesis[73]. The lipids from neighboring adipocytes stores can be transferred into cancer cells to be used as energy source and promote tumor growth[74], which led to the direct transfer of lipids from the adipocytes to the cancer cells and induce lipolysis in the adipocytes and β-oxidation in the cancer cells[75]. Obesity may drive cancer development through converting fatty acids into protumorigenic signaling lipids (*e.g.*, lysophosphatidic acid, prostaglandins, sphingolipids, phosphatidylinositols) that can then activate cancer cells through paracrine or autocrine interactions to trigger oncogenic responses, including proliferation, tumor growth, immunological responses, motility, invasiveness, and metastasis[76]. The low-grade inflammation of AT leads to chronic activation of the innate immune system, which speeds the progression of cancer[77,78].

Obesity promotes insulin production and creates a hyperinsulinemic state *in vivo*, which activates the PI3K/AKT/mTOR and RAS/MAPK signaling pathways, involving in cell proliferation and protein synthesis in cancer cells[79,80] (Fig. 2). Specifically, high level of insulin raises the level of insulin-like growth factor (IGF), which is associated with inflammation and impairs the immune system[81,82]. Increased secretion of IGF-1 promotes mitogenesis and angiogenesis and inhibits apoptosis, facilitating cancer progression[83,84]. High levels of insulin or hyperinsulinemia are associated with low sex hormone-binding globulin levels and high estrogen bioavailability[85], which facilitates the development of hormone-related cancers[86,87], such as in breast cancer after menopause[88]. Estrogen biosynthesis after menopause is induced largely in obese adipose tissue, where it involves the conversion of adrenal androgens into estrogens by aromatase that is increased through the activation of NF-κB pathway and the upregulation of proinflammation cytokines[89,90]. Further, increased aromatase activity in obese individuals converts testosterone to estradiol resulting in increased concentrations of estradiol[91], which may promote prostate cancer growth[51].

Additionally, more than 15 adipokines (such as adiponectin, leptin, adipsin, apelin) secreted by AT stimulate cancer cell growth, invasion, angiogenesis, and metastasis[54,92].

Leptin plays an important role in the development of obesity and cancer[93]. It is produced primarily by AT and controls food intake and energy expenditure *via* a feedback mechanism in the brain[94]. Leptin has growth-promoting, mitogenic, and anti-apoptotic properties in many cancer cells and increases the expression of TNF-α, IL-6 and angiogenic factors[95]. When leptin circulates in plasma, it binds to its receptors (OB-Rs) and activates Notch signaling to control downstream effector molecules or signaling events; leptin signaling regulates intracellular pathways such as the PI3K/AKT/mTOR, JAK2/STAT3 and ERK/MAPK pathways involved in the control of cell proliferation, differentiation, survival, migration, and invasion[96,97]. Leptin also has been found to induce phospholipase C γ (PLC-γ), PKC, p38 and nitric oxide (NO), which can activate several genes involved in cell proliferation, including *C-FOS*, *C-JUN*, *JUNB*, *EGR-1* and *SOCS3*, and upregulate the expression angiogenic factors, such as VEGF[98,99]. Leptin increases estrogen levels through the activation of the aromatase gene expression and aromatase activity to contribute to tumor growth and the development of antiestrogen resistance in obese breast cancer patients[100], and enhances the stability of the estrogen receptor alpha (ERα), leading to the maintenance of ERα-dependent transcription in breast cancer cells in the presence of antiestrogens. Several *in vitro* studies have demonstrated leptin-induced cell invasion and migration in different cancer cells[101], for example, leptin stimulated the expression of acetyl-CoA acetyltransferase 2 (ACAT2) through the PI3K/AKT/SREBP2 signaling pathway to enhance the proliferation, migration and invasion of breast cancer cells[102] and induce IL-18 expression both in tumor-associated macrophages (TAMs) *via* NF-κB/NF-κB1 signaling and in breast cancer *via* PI3K−AKT/ATF-2 signaling to promote the invasion and metastasis of breast cancer cells[103]. Conversely, leptin also showed a good action in some conditions[104]. Leptin increased Th1 and suppressed Th2 cytokine production and has been shown to reverse the immunosuppressive effects of acute starvation in mice[105]; another study found that leptin showed antitumoral functions in human pancreatic cancer cell lines[106].

Adiponectin (APN) is also an important adipokine secreted by adipose tissue and is involved in the etiology of some cancers[107,108]. Obesity is associated with a decreased level of APN in plasma, which activates the insulin pathway and decreases levels of the adipose-derived cytokines IL-6, IL-8 and TNF-α[108]. Research on the role of APN in tumor growth has provided evidence for both positive and negative influences. In several human studies, adiponectin has been found to be associated with a number of cancer types: its levels are decreased in breast and endometrial cancer but increase in non-small cell lung cancer, prostate, gastric, liver, pancreatic, and hematological cancers, colon cancer, and renal cell carcinoma[109−113]. APN shows antitumor effects by affecting some key mechanisms that regulate cell growth[114,115], such as inducing the expression of p53 and p21[116] and inhibiting the mTOR and PI3K/AKT signaling pathways[116,117]. Additionally, APN can increase insulin sensitivity[118], and the complex synergistic interaction between APN and the IGF system or other various obesity-related biomarkers is believed to induce tumorigenesis and development[119]. Adiponectin also potently stimulates ceramidase activity by binding with AdipoR1 and AdipoR2, and enhance pro-apoptotic ceramide catabolism leading to formation of its downstream anti-apoptotic metabolite sphingosine-1-phosphate (S1P) independently of AMPK[120]. However, adiponectin deficiency limited tumor vascularization and significantly reduced tumor growth and angiogenesis in a MMTV polyoma middle T antigen (PyMT) mouse model[121]. Thus, the role of adiponectin in tumor angiogenesis remains flexible.

Obesity has been shown to increase risk of 'obesity-related cancers'[122]. Worsening obesity tends to increase serum concentrations of glucose, insulin, IGF-1, lipids, leptin, estrogen, resistin, and inflammatory cytokines and reduces IGF binding protein and adiponectin levels, each of which has been suggested to contribute to cancer pathogenesis[86]. Interestingly, recent epidemiological data showed that obesity may be a protective factor for certain cancer types regarding their incidence and mortality, *e.g.*, non-small cell lung cancer (NSCLC) and head and neck cancers[59]. Potential explanations of the 'obesity paradox' (it occurs where the risk of outcome, typically mortality, is significantly reduced for BMI values above this referent, where an increased risk is expected) in cancer patients may include the use of BMI as a measure of general adiposity; study limitations including inadequate adjustment for confounding, selection, stratification and detection biases; confounders such as age, smoking, physical activity, etc.[123]. We should avoid the misinterpretation that being obese might be 'good' or 'protective' for cancer patients[60].

3. Obesity and cardiovascular diseases

Clinical trials and epidemiological studies have shown that obesity can increase the risk of CVDs[124−127], including coronary artery disease (CAD), heart failure (HF) and atherosclerosis (AS)[128]. Furthermore, obesity has a strong relationship with other CVD risk factors, such as hypertension (HTN), insulin resistance, and dyslipidemia[129]. Obesity leads to adipose tissue hypertrophy, dysfunction and inflammation, which ultimately change the structure and function of the cardiovascular system[130], including left ventricular (LV) remodeling, greater left ventricular mass, left atrial enlargement, and increased stroke volume[131,132], increased total and central blood volume, decreased systemic vascular resistance, cardiac output, LV filling pressure and pulmonary arterial pressure[128].

Ectopic deposition of AT in other organs leads to abnormal fat accumulation around the heart, which has been consistently

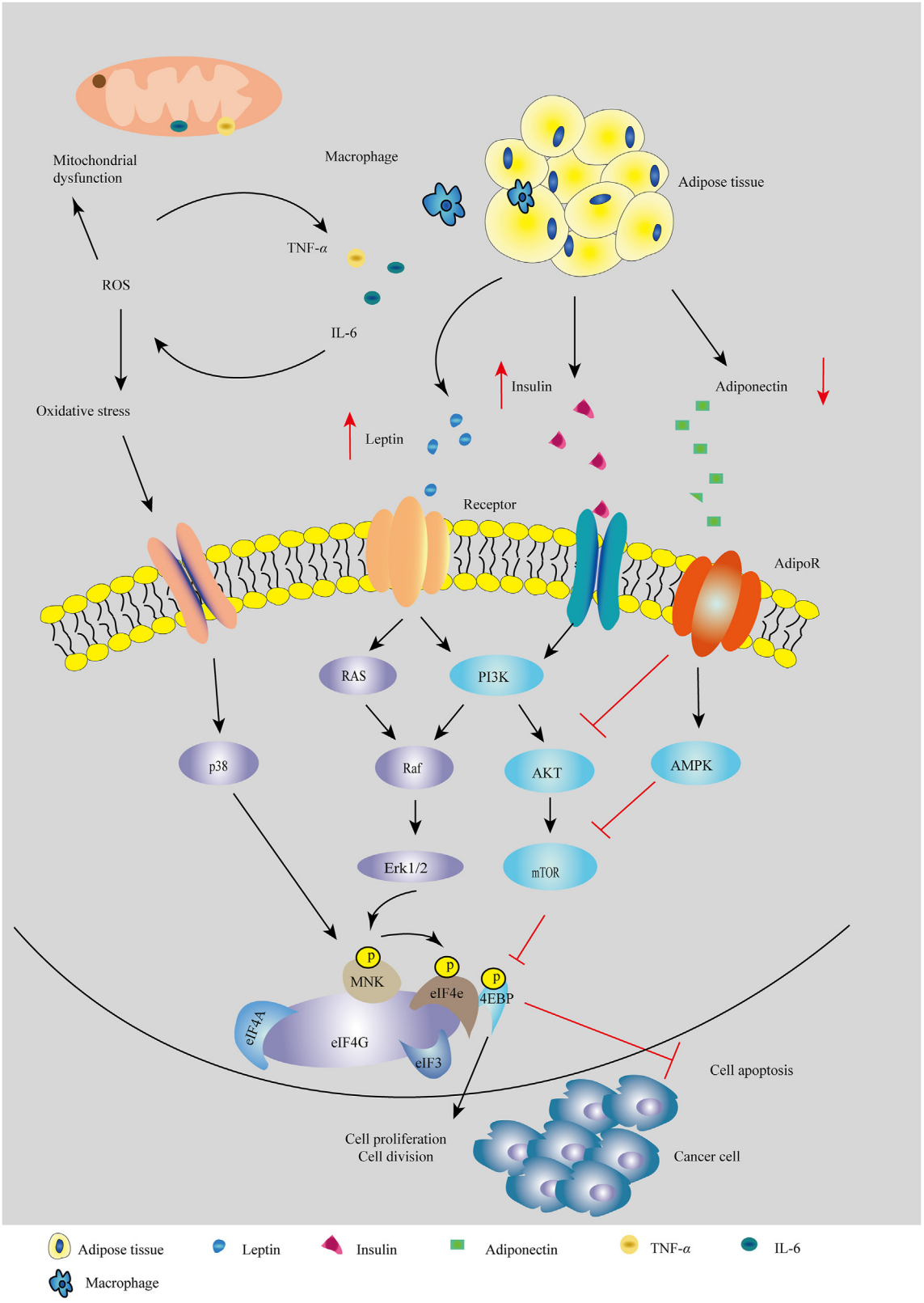

Figure 2 Cellular mechanisms linking obesity and cancer. Adipose tissue is enlarged by excess fat and secretes adipokines, such as leptin and insulin that activate the RAS/Erk and PI3K/AKT/mTOR signaling pathways. Adipose tissue also produces proinflammatory cytokines which induce oxidative stress and mitochondrial dysfunction, triggering the p38/MAPK signaling pathway. All these changes promote cancer cell proliferation and cell division and inhibit cell apoptosis.

related to CVD risk[133]. For example, in healthy individuals, cardiomyocytes generate ATP primarily in mitochondria which is associated with ROS production. In patients with obesity and IR, excess FFAs accumulate in cardiomyocytes, which results in increased ROS *via* fatty acid oxidation and eventually leading to mitochondrial dysfunction[134,135]. Furthermore, increased myocardial lipid deposition would induce cardiomyopathy owing to cardiac lipotoxicity[136]. Cardiomyocyte lipid accumulation leads to cell apoptosis and cardiac dysfunction by increasing the synthesis of the pro-apoptotic sphingolipid ceramide, which activates inducible NO synthase[137]. AT surrounding the major conduit coronary arteries is termed PVAT and has emerged as a major contributor to CVD risk[42]. Build-up of VAT and PVAT impairs angiogenesis and promotes localized hypoxia and ischemic necrosis, leading to adipocyte death that may stimulate infiltration by activated macrophages thereby causing inflammation in tissues[42,138,139].

WAT can be found around major organs and blood vessels in the abdominal cavity and subcutaneously, which is a key determinant of the relative risk for CVD. Brown adipose tissue (BAT) also plays important roles in regulating cardiovascular functions[140,141], through attenuating cardiac remodeling and suppressing inflammatory response[140]. The systemic activation of BAT can quickly induce the utilization of intracellular glycogen and lipid stores, increase uptake of glucose and lipoprotein derived NEFAs and drain remote nutrient stores in liver and WAT, which decreases the risk of CVD. BAT is enriched in mitochondria, and can significantly express uncoupling protein-1 (UCP-1), proliferator-activated receptor gamma coactivator-1α (PGC-1α), PR domain-containing protein 16 (PRDM16), β_3-adrenoceptor and other genes related to thermogenesis[140,142,143]. UCP-1, one of the most important proteins in BAT, uncouples oxidative phosphorylation from ATP production[144], ultimately resulting in the generation of heat[145,146]. Humans with obesity usually have lower BAT content[147], while decreased expression of UCP-1 in human EAT is associated with increased adipose tissue oxidative stress and dysfunction and can plausibly alter its communication with neighboring cells of the cardiovascular system[148]. Moreover, inflammation induced by obesity promote the production of inflammatory cytokines, which are thought to suppress UCP-1 expression in BAT[149,150]. BAT not only oxidizes fats but can also synthesize and release peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) to assist nitric oxide (NO) to complete vasodilation[140,151]. BAT also secrets cytokines, such as fibroblast growth factor 21 (FGF-21)[152], IL-6[153] and vascular endothelial growth factor A (VEGFA), which show protective effects on the cardiovascular system[154]. For example, FGF21 is shown to have an important protective effect on the cardiac hypertrophy by inducing the expression of PGC-1α and inhibiting the NF-κB pro-inflammatory pathway[152]; IL-6, whose levels are usually considered an indicator of inflammatory responses[155], has a positive function on regulating the glucose homeostasis and the insulin sensitivity of BAT, working together with FGF21[156,157]; VEGFA expression in BAT leads to increased vessel permeability, promotes TG clearance and provides a autocrine signal to maintain mitochondrial oxidative capacity[158]. Furthermore, experimental evidence from mice suggests that BAT has a vasoprotective action through an anticontractile effect. For example, protein expression of NADPH oxidase 4 (Nox4) was increased only in BAT, and Nox4-derived hydrogen peroxide from BAT, can induce cGMP-dependent protein kinase G type-1α (PKG-1α) activation, resulting in reduced vascular contractility[159]. There is some research showing that the activity of BAT declines in obesity[160], which results in the insufficient synthesis of PGC-1α and PGC-1α deficiency would impair vasodilation and induce vascular senescence[161]. This also leads to the elevation of blood pressure, left ventricular hypertrophy with an eccentric remodeling pattern and increased interstitial tissue[161]. One of the central modes of blood pressure regulation is *via* the renin-angiotensin aldosterone system (RAAS)[145]. Angiotensin II is produced from its precursor angiotensinogen by the activation of angiotensin-converting enzymes 1 and 2, and angiotensin-converting enzyme 2 can further induce angiotensin II to generate angiotensins 1−7, which has vasodilatory properties[162−164]. Additionally, activation of angiotensin receptor 2 or angiotensin II treatment can induce browning of subcutaneous WAT *in vivo* with increased UCP-1 expression and oxygen consumption and stimulation of brown precursor differentiation *in vitro* by increasing PPARγ expression *via* the ERK1/2, PI3K/AKT and AMPK signaling pathways[165,166]. Increased sympathetic nerve activation or increased conversion of angiotensin II to angiotensins 1−7 can enhance BAT thermogenesis and WAT lipolysis, which in turn has beneficial effects on blood pressure and attenuates development of CVD[166]. Moreover, PRDM16, the master regulator of thermogenic AT, interacts with MED1 at brown fat-specific genes to promote gene transcription and stimulates brown adipogenesis by binding to PPARγ[167], which is associated with hypertension in humans[168].

PVAT is now recognized as an important local regulator of vascular function and dysfunction given its ability to its proximity to the vascular wall and its ability to sense vascular paracrine signals. Signaling pathways in PVAT, such as those using APN, H_2S, GLP-1 or pro-inflammatory cytokines, facilitate a range of direct, paracrine effects[169,170]. Interestingly, PVAT is itself heterogeneous, with its anatomical localization[145,171]. PVAT surrounding the abdominal aorta and the mesenteric arteries appears to be similar to WAT phenotype in humans and mice, with large lipid droplets and low UCP-1 expressing thermogenic adipocytes. On the other hand, rodent PVAT surrounding the thoracic aorta has a BAT-like phenotype with multilocular adipocytes and similar UCP-1 expression to classical BAT. A study suggests that brown adipocyte-specific aryl hydrocarbon receptor nuclear translocator-like protein 1 (Bmal1) in PVAT in particular is involved in the regulation of angiotensinogen expression and the ensuing increase in angiotensin II, which acts on smooth muscle cells in the vessel walls to regulate vasoactivity and blood pressure[172,173].

Adipokines are considered to be a link between obesity and CVD[174] (Fig. 3). EAT and PVAT secrete adipokines, such as leptin, adiponectin, resistin, visfatin, and inflammatory cytokines, all of which may modulate vascular tone, smooth muscle cell migration and proliferation, neointimal formation, inflammation and oxidative stress, thereby increasing the risk of CVD factors and CVD[175]. Resistin serves as an important risk factor for cardiovascular disease by affecting insulin sensitivity and coronary calcification[176−178]. Adiponectin regulates vascular steady state by decreasing the activity of C reactive protein (CRP)[179] and suppressing the signal mediated by TNF-α and NF-κB[180,181]. Adiponectin also activates endothelial NO synthase (eNOS) to enhance salt-induced hypertension by activating PI3K/AKT signaling and increasing the production of NO[182,183]. Obese individuals with low levels of adiponectin show an increased incidence of cardiovascular disease. Leptin inhibits cardiac systole by promoting the production of endothelin-1 (ET-1) and activating NADPH oxidase-mediated pathways[184,185].

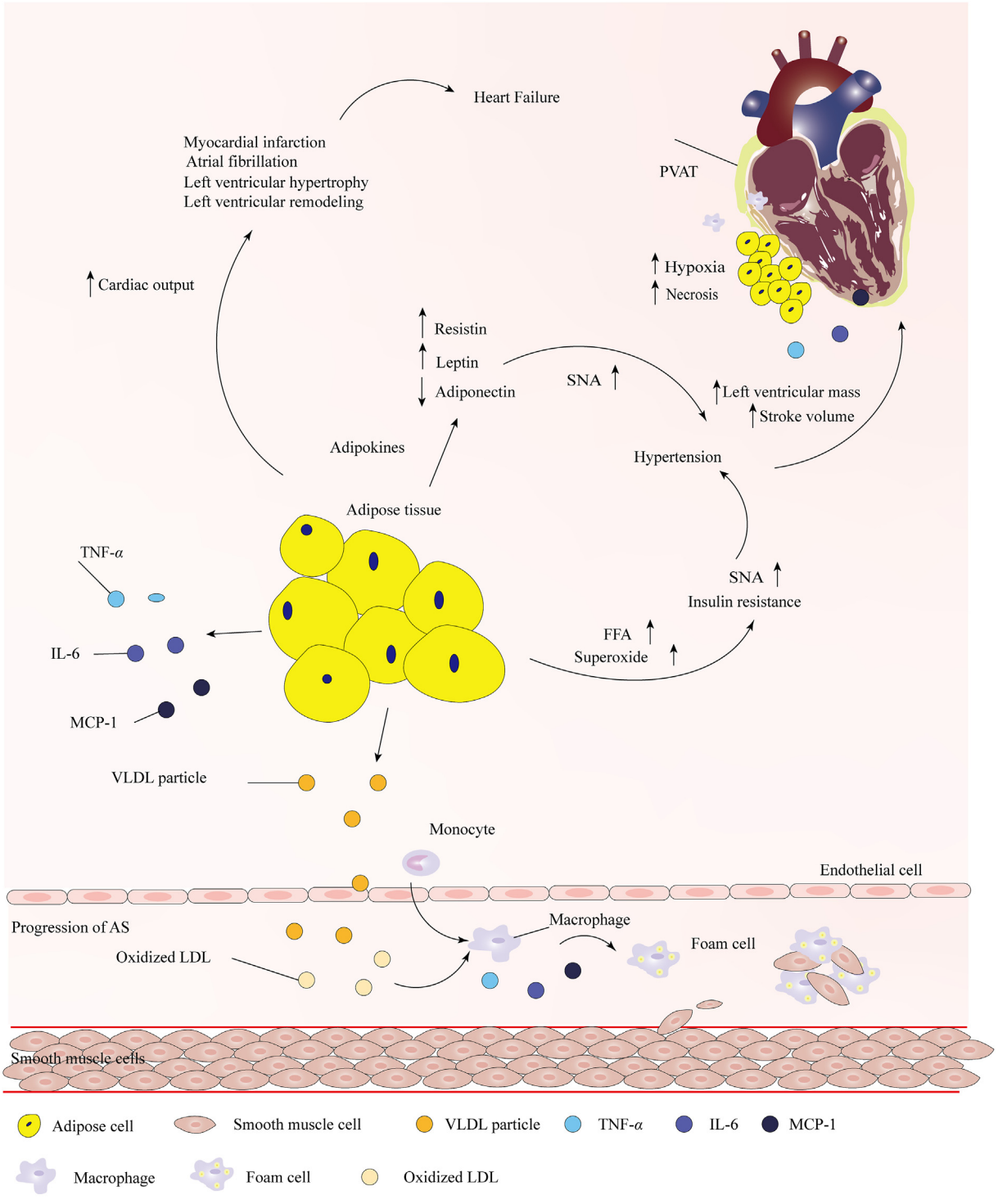

Figure 3 Schematic representation of the role of obesity in the promotion of cardiovascular diseases. Adipose tissue hypertrophy and ectopic deposition around the heart and coronary arteries impair angiogenesis, promote local tissue hypoxia and necrosis, and induce left ventricular hypertrophy and remodeling, which contribute to heart failure. Adipokines, free fatty acids (FFAs) and superoxides secreted by adipose tissue activate sympathetic nerve activity to induce hypertension and then increase left ventricular mass, stroke volume and cardiac output. Triglycerides (TG) in ectopic fat is transported by very low-density lipoprotein (VLDL) into the circulation. Low-density lipoprotein (LDL) undergoes oxidation and other modifications to combine with macrophages, forming foam cells, a hallmark of early atherosclerosis (AS) lesions.

Atrial natriuretic peptide (ANP) is primarily secreted from cardiomyocytes[186] and is an important hormone with pronounced lipolytic effects on WAT[187]. ANP induces lipid mobilization and oxidation and enhances insulin sensitivity[188]. ANP exhibits anti-inflammatory effects by inhibiting proinflammatory cytokines expression and secretion from human AT explants[189], such as IL-6 and TNF-α. Considering that AT and systemic inflammation are associated with insulin resistance[190]. This could be one mechanism by which ANP preserves insulin sensitivity in humans. ANP also plays a critically important role in regulating salt and water reabsorption by inhibiting secretion of vasopressin from the posterior pituitary, which in turn has important effects on blood pressure[191]. Furthermore, ANP lessens cardiac and pulmonary baroreceptor and chemoreceptor activity, thus reducing sympathetic outflow to the heart. This decrease in sympathetic activity together with the increase in vagal afferent activity result in a reduction in heart rate and cardiac output[192]. ANP also reduces vascular smooth muscle tone and peripheral vascular resistance[193]. In obesity, lower concentrations of ANP are seen among those with higher BMI, which has been proposed as an independent risk factor for development of cardiovascular disease, including hypertension[194].

Multiple epidemiological studies have demonstrated a strong association between being overweight/obese and HF[195], with up to 35%−45% of patients with heart failure being either overweight or obese. People with obesity had a two-fold higher risk of developing heart failure than in those of normal weight; every 1 kg/m^2 increment in BMI was found to increase the risk of HF by 5%−7%[195,196]. The link between obesity and HF is thought to occur through myocardial fibrosis and cardiac stiffening triggering atrial fibrillation (AF) and coronary atherosclerosis and myocardial infarction (MI) resulting in left ventricular remodeling with impaired systolic function[197,198]. Obesity is likely to increase the risk for AF, including increased cardiac output and development of HTN, by exerting increased preload and afterload on the left ventricle and leading to left ventricular hypertrophy[199]. Obesity also affects thyroid function, which may predispose to AF and subsequent HF[200]. AT secrete adipokines and multiple inflammatory cytokines contributing to the development of HF[201].

Currently, obesity-associated HTN is a serious risk factor for CVD[202]. The link between obesity and HTN is influenced by multiple factors[203] (Fig. 3). Reabsorption of sodium ions in the renal tubules and vasoconstriction have been observed in obesity. Dysfunctional sodium excretion and renal tubular reabsorption of sodium increase cardiac load capacity and raise blood pressure[204,205]. Blocking the angiotensin II receptor can significantly reduce the activity of sympathetic nerve activity (SNA) and control blood pressure[206]. High levels of FFA and superoxide activate SNA along with causing vasoconstriction, high blood pressure and insulin resistance[207]. Leptin also increases the activity of SNA[208,209]. Obese patients with hypertension have increased left ventricular mass and have higher stroke volume and cardiac output[210].

Atherosclerosis (AS) is the leading cause of CVD, and obesity is a major risk factor for AS[211]. The accumulation of TG in ectopic fat showed a strong relationship with the development of AS in obese patients[212−214] (Fig. 3). Excess TG is transported by very low-density lipoproteins (VLDL) in the circulation[215]. Large epidemiological studies confirmed that the elevation of triglyceride-rich lipoproteins (TGRLs) in circulation is atherogenic[215,216]. These small dense LDL particles easily enter the arterial wall, and they undergo oxidation and other modifications to produce proinflammatory and immunogenicity[217,218]. Macrophages combine with lipoproteins to become foam cells, a hallmark of early atherosclerotic lesions[218−220]. The excessive accumulation of EAT and PVAT can increase inflammatory cytokines[138], TNF-α, IL-6 and IL-1β, which in turn promote macrophage migration to AT and increase the number of foam cells. Adiponectin is the most abundant anti-inflammatory and vasculoprotective adipokine secreted by AT[221,222]. It can induce NO production, suppress proliferation and superoxide generation, and enhance eNOS activity in endothelial cells treated with oxidized low-density lipoprotein[223]. Adiponectin suppresses the expression of class A macrophage scavenger receptors and consequently reduces foam cell formation, decreases the secretion of proinflammatory cytokines, and limits the initiation of atherosclerotic plaque formation[224,225]. Increasing adiponectin levels have been suggested as a potential therapeutic target to reduce the AS risk associated with obesity.

Despite the strong relationship between obesity and development of CVDs, a large body of evidence has demonstrated an 'obesity paradox' in patients with CVD, where many types of CVD may have a better prognosis in the overweight or obese population compared to their leaner counterparts[226]. For example, overweight and obese patients have a better short- and intermediate-term prognosis compared with leaner patients with similar degrees of HF after adjustments for confounders[227]; overweight/obese people with coronary heart disease have a lower risk of total and CVD mortality compared with underweight and normal weight coronary heart disease patients[228]. Describing the obesity paradox is certainly not to promote being overweight or obese or a suggestion that weight gain is beneficial[226], and the balance of data still supports purposeful weight reduction in the prevention and treatment of CV diseases[229]. It is important to be cautious in judging disease risk only dependent on the BMI.

4. Obesity and T2DM

Obesity is known to be the main risk factor for T2DM[230,231], and approximately one-third of obese people develop T2DM. Adults with BMI >35 kg/m^2 are 20 times more likely to develop T2DM than those with a BMI between 18.5 and 24.9 kg/m^2. Moreover, 80% of T2DM patients are overweight or obese[232,233]. It is commonly believed that the primary cause of T2DM is obesity-driven insulin resistance in non-adipose tissues, combined with insufficient secretion of insulin by pancreatic β-cells to overcome this resistance[234].

Insulin is an important hormone released by pancreatic β cells, with important physiological roles, including stimulation of the uptake and utilization of glucose, promotion of lipogenesis, inhibition of gluconeogenesis and glycogenolysis, and prevention of protein breakdown and lipolysis[235]. Insulin binds to cell surface receptors primarily on skeletal muscle, adipose tissue, and liver[236], and subsequently promotes receptor autophosphorylation and phosphorylation of insulin receptor substrates (IRSs)[237]. This process further leads to the activation of AKT (also known as PKB), and recruits glucose transporter 4 (GLUT-4) to the plasma membrane to facilitate glucose uptake into the cell[235,238] (Fig. 4). This IRS/PI3K/Akt pathway has an important role in the activation of metabolic, especially biosynthetic processes[238].

Insulin resistance (IR) is defined as the inability of insulin target tissues − such as skeletal muscle, liver, and AT − to carry out adequately the physiologic effects (such as glucose uptake and

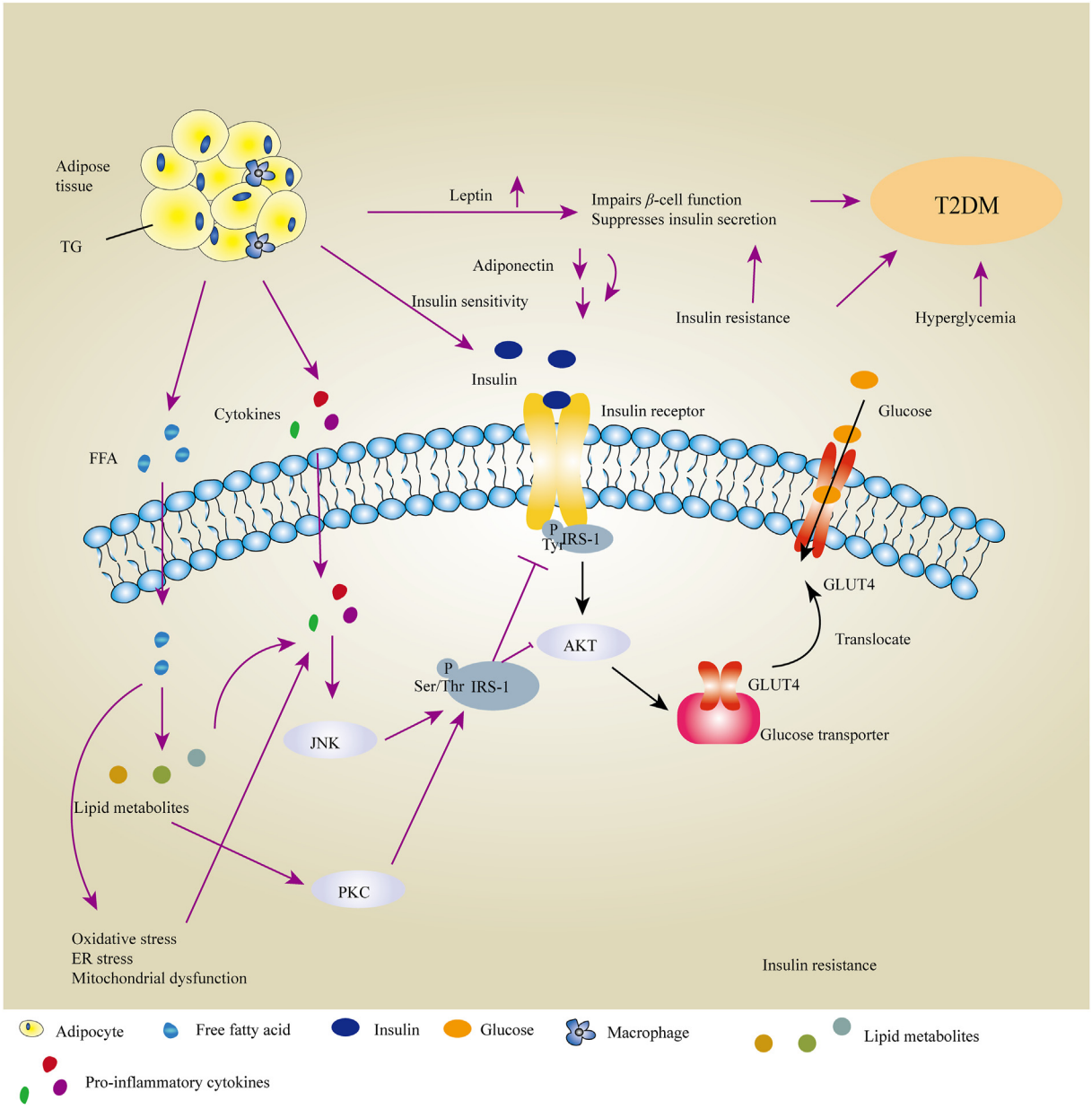

Figure 4 Schematic representation of the links between obesity and insulin resistance and their internal mechanisms associated with T2DM. Free fatty acids (FFAs) and their metabolites activate protein kinase C and promote Ser/Thr phosphorylation of insulin receptor substrates 1 (IRS-1), in turn reducing normal Tyr phosphorylation of IRS-1 and impairing the control of the glucose transporter GLUT4, inducing insulin resistance and thus poor glucose tolerance. Proinflammatory cytokines secreted by adipose tissue activate the JNK signaling pathway and indirectly inhibit the translocation of GLUT4 to promote insulin resistance. Elevated leptin and low adiponectin levels, along with insulin resistance, impair β-cell function, suppressing insulin secretion and leading to T2DM. The black line indicates the normal mechanism underlying the insulin-stimulated uptake of glucose involving translocation of the glucose transporter GLUT4 to the plasma membrane. The purple line indicates the defective process(es) in obese individuals.

utilization) of circulating insulin[239,240]. Elevated levels of FFAs are observed in obese individuals. High level of FFAs in the circulation become deposited in insulin-sensitive non-adipose tissues, resulting in lipotoxicity, which is an important cause of insulin resistance[241]. Lipid metabolites from FFA, such as long-chain fatty acyl CoAs, diacylglycerol (DAG) and ceramides, activate some forms of PKC, the inhibitor of nuclear factor κB kinase b (IKKb), and Jun kinase (JNK), which induce Ser/Thr phosphorylation of IRS-1[242,243] and in turn inhibit normal insulin-stimulated tyrosine phosphorylation of IRS-1, resulting in the impairment of insulin signaling[235,244,245]. Additionally, proinflammatory pathways (for example, NF-κB) are activated, promoting the secretion of proinflammatory cytokines, including TNF-α, MCP-1, and IL-6[246]. Elevated levels of cytokines activate the JNK signaling pathway and thus inhibit the normal pathway of insulin-stimulated tyrosine phosphorylation of IR and IRS-1, ultimately inhibiting the translocation to the plasma membrane of the insulin-sensitive glucose transporter GLUT-4[39,247,248] (Fig. 4).

FFAs also activate NADPH oxidase and induce ROS production. ROS-induced oxidative stress results in dysregulated production of proinflammatory cytokines and promotes insulin resistance[237].

Adipokines can regulate β-cell function and glucose metabolism. APN appears to improve insulin sensitivity by inducing phosphorylation and activation of AMPK and PPARα signaling, promoting phosphorylation (and inhibition) of ACC, and increasing fatty acid oxidation and glucose uptake[249−251]. It thus also activates the LKB1/AMPK/TSC1/2 pathway to antagonize inhibition by mTORC1/p70 S6K of insulin signaling[252,253] and enhance the ability of insulin to stimulate IRS-1 tyrosine phosphorylation and AKT phosphorylation[254,255]. Moreover, APN could promote fat storage preferentially in subcutaneous AT rather than in liver or skeletal muscle to reduce VAT mass and inflammation, improving glucose and fat metabolism and enhancing insulin sensitivity[180]. Obese individuals show lower adiponectin secretion, which impairs insulin sensitivity. In contrast, leptin deficiency causes insulin resistance and T2DM[256]. Leptin activates the IRS/PI3K pathway to improve insulin sensitivity in peripheral tissues and triggers the translocation of GLUT4 from cytosol to cell surface to increase glucose uptake[256−258]. Obesity in humans is usually associated with high circulating leptin levels. However, ample evidence suggests that common forms of obesity are associated with hypothalamic leptin resistance[259,260]. The potential of leptin monotherapy in obese humans with T2DM in clinical trials have failed to demonstrate therapeutic activity, with no observation of important weight loss or metabolic improvements (insulin sensitization, amelioration of glucose and lipid metabolism)[261−263]. Furthermore, leptin has been reported to impair β-cell function and suppress insulin secretion[264,265]. Leptin could induce β cell hyperpolarization through activating PI3K-dependent PDE3B and the K_{ATP} channel to inhibit insulin secretion[266,267]. VAT regulates metabolic homeostasis and progressive insulin resistance thereby increasing the risk of T2DM[268]. It also enhances the production and secretion of pro-inflammatory adipokines by these adipose tissues[269], which can promote IL-1β-induced apoptosis in β-cells by activating the NF-κB and JAK/STAT signaling pathways[270]. Insulin-induced hyperlipidemia leads to the accumulation of lipids in β-cells and induces β-cell apoptosis[271]. Hyperglycemia induced by insulin resistance triggers β-cell apoptosis through glucotoxic effects on β-cells that show adverse effects on insulin secretion[272,273].

Here, we will introduce novel targets involved in the process of obesity and T2DM, the MNKs. MNKs (mitogen-activated protein kinase-interacting protein kinases), including MNK1 and MNK2, phosphorylate eIF4E (eukaryotic initiation factor 4E) at Ser209 and then control the translation of certain mRNAs[274,275]. eIF4E participates in the eukaryotic initiation factor complex 4F, along with the RNA helicase eIF4A and the scaffolding protein eIF4G[276]. eIF4E directly binds the 5′-cap structure of cytoplasmic mRNAs and plays a crucial role in protein synthesis[277]. Phosphorylation of eIF4E has been shown to regulate the translation efficiency of some mRNAs, encoding proteins which are involved in tumor development, progression and metastasis[278]. MNKs are the only kinases that phosphorylate eIF4E at Ser209 *in vivo* and eIF4E is their only known *in vivo* substrate MNK double knockout mice show no overt phenotype under normal vivarium conditions, so appear to be a safe target for disease therapy. Inhibition the activity of MNKs and the phosphorylation of eIF4E has shown good effect on tumor treatment and obesity induced by HFD[274].

When MNK1-KO or MNK2-KO mice are fed a high-fat diet, they show different phenotypes[279]. MNK2-KO mice show less weight gain and improved glucose tolerance compared to control mice given an HFD, as well as better insulin sensitivity and reduced adipose tissue inflammation. HFD-fed MNK1-KO mice show better glucose tolerance and insulin sensitivity. MNK-DKO or hypomorphic eIF4E$^{+/-}$ mice are protected from HFD-induced obesity[280,281]. Elevated energy expenditure and changes in expression of proteins linked to lipolysis, mitochondrial function, and oxidative metabolism were observed.

In HFD-fed MNK-DKO mice, some genes or proteins showed increased expression, for example, ATGL (adipose triglyceride lipase), HSL (hormone-sensitive lipase), AGPAT9 (1-acylglycerol-3-phosphate *O*-acyltransferase 9), which are involved in lipid metabolism in AT; *ATP6*, *ND1*, *ND5*, *COX1*, *NRF2*, *PPARG*, *PGC1α* and *YY1* which are involved in oxidative metabolism are also elevated in AT of MNK-DKO mice. These changes may underlie, at least in part, the metabolic phenotype of MNK-DKO mice, which show higher energy expenditure and oxidative metabolism. In turn, this likely contributes to their lower weight gain on an HFD; interestingly, no significant difference in weight gain was seen for WT and MNK-DKO mice on the normal diet. Furthermore, levels of the mRNA for SFRP5, which negatively regulates expression of certain genes involved in mitochondrial function, were found to be lower in AT from MNK-DKO mice.

A subsequent study, using HFD-fed eIF4E$^{+/-}$ mice, employed tandem mass tag labelling−mass spectrometry (TMT−MS) to identify target proteins (and thus potentially mRNAs affected by eIF4E phosphorylation). The levels of a number of proteins (CD36, ELOVL5, LPIN2, APOC3, APOH and PLIN2) involved in fat storage were found to be decreased from the liver of HFD-fed eIF4E$^{+/-}$ mice. eIF4E normally promotes the translation of a set of mRNAs which encode proteins involved in fatty acid oxidation. Moreover, each of two MNK inhibitors was found to inhibit weight gain in HFD mice. ETC-206 and eFT508 prevent weight gain induced by excessive energy consumption (the HFD)[280,281]. These findings point to a potential new way to prevent weight gain induced by a high-fat diet without causing toxicity owing to the safety of MNKs as drug targets, *i.e.*, the pharmacological inhibition of the MNKs.

5. Obesity and liver diseases

Obesity affects multiple metabolic functions of the liver. It is associated with the development of non-alcoholic fatty liver disease (NAFLD), associated steatosis and inflammation and promotes the progression of several other liver diseases, including hepatitis C and alcoholic liver disease. NAFLD is a common cause of chronic liver disease and has emerged as the most rapidly growing cause of hepatocellular carcinoma (HCC)[282−285]. Associated and serious pathological states include liver cell necrosis, liver fibrosis and cirrhosis of the liver[283]. NAFLD is a complex liver disease that develops from simple steatosis to steatosis with lobular inflammation and cellular injury, which may develop nonalcoholic steatohepatitis (NASH)[286]. NASH patients have an increased risk of liver fibrosis, liver cirrhosis, and HCC[287]. A meta-analysis reported that over 40% of NAFLD patients have progressive fibrosis[288]. NAFLD is a multisystem disease, affecting other organs and regulatory pathways. For example, NAFLD increases risks for T2DM, CVD, and chronic kidney disease (CKD)[289]. A meta-analysis showed that NAFLD increased overall mortality by 57% mainly from liver-related and CVD causes, and

increased the risk of incident T2DM by approximately twofold[290]. Additionally, increasing attention has also focused on NAFLD-related CKD and a further recent meta-analysis reported that NAFLD was associated with an approximate twofold increased risk of CKD[291].

TG accumulation is likely the first step in the pathophysiology of NAFLD and results from an imbalance between TG synthesis and utilization[292]. In healthy individuals, excess carbohydrate that accumulates in the liver is converted into FFAs by *de novo* lipogenesis (DNL)[293,294]; some of these FFAs are esterified into TG in AT for storage, and others are stored in the liver directly[293] (Fig. 5). Increased intracellular glucose levels activate the glucose sensor carbohydrate response element-binding protein (ChREBP), which promotes glycolysis and gene expression of DNL genes in the liver[295]. The newly synthesized TG is mostly packaged into very low-density lipoproteins (VLDL) and exported to AT[284]. Adipose tissue extracts lipids from VLDL through the action of lipoprotein lipase. In obesity, insulin resistance causes a decreased insulin-dependent inhibition of lipolysis and adipocytes cannot accept TG from VLDL or hydrolyze intracellular TG, which causes more FFAs to be released into the circulation[296,297].

Excess energy intake or limited energy expenditure make redundant fat accumulate in SAT preferentially. Compared with VAT, SAT is more insulin-sensitive and has high avidity for FFAs and TGs, preventing their deposition in non-adipose tissue[21,298]. Hypertrophic subcutaneous adipocytes have been shown to have a pro-inflammatory gene expression and are associated with greater rates of lipolysis, increased cytokine release, and IR[299]. When the storage capacity of SAT is exceeded, or when normal lipid metabolism is impaired in obese patients, fat begins to accumulate in other non-adipose tissue organs, which promote the formation of VAT. Each standard deviation increase in subcutaneous AT (SAT) mass decreases the likelihood of IR by 48%, whereas each standard deviation increase of visceral AT (VAT) mass increases likelihood of IR by 80%[300]. VAT enlarged in the liver contributes to fatty liver.

In states of insulin resistance, insulin continues to support DNL, while its capacity to reduce hepatic gluconeogenesis is impaired in the liver, which upregulates the level of FFA and inhibits FFA β-oxidation, further promoting hepatic fat accumulation[301,302]. Excess FFA in the liver can be disposed of through oxidation pathways, mainly in mitochondria, but also in peroxisomes and microsomes[40,286,303]. β-Oxidation of FFAs in mitochondria produces ROS that induce FFA peroxidation and cause damage to mitochondrial DNA and proteins[304]. VAT in the liver induces hypoxia by affecting vascularization and then promoting

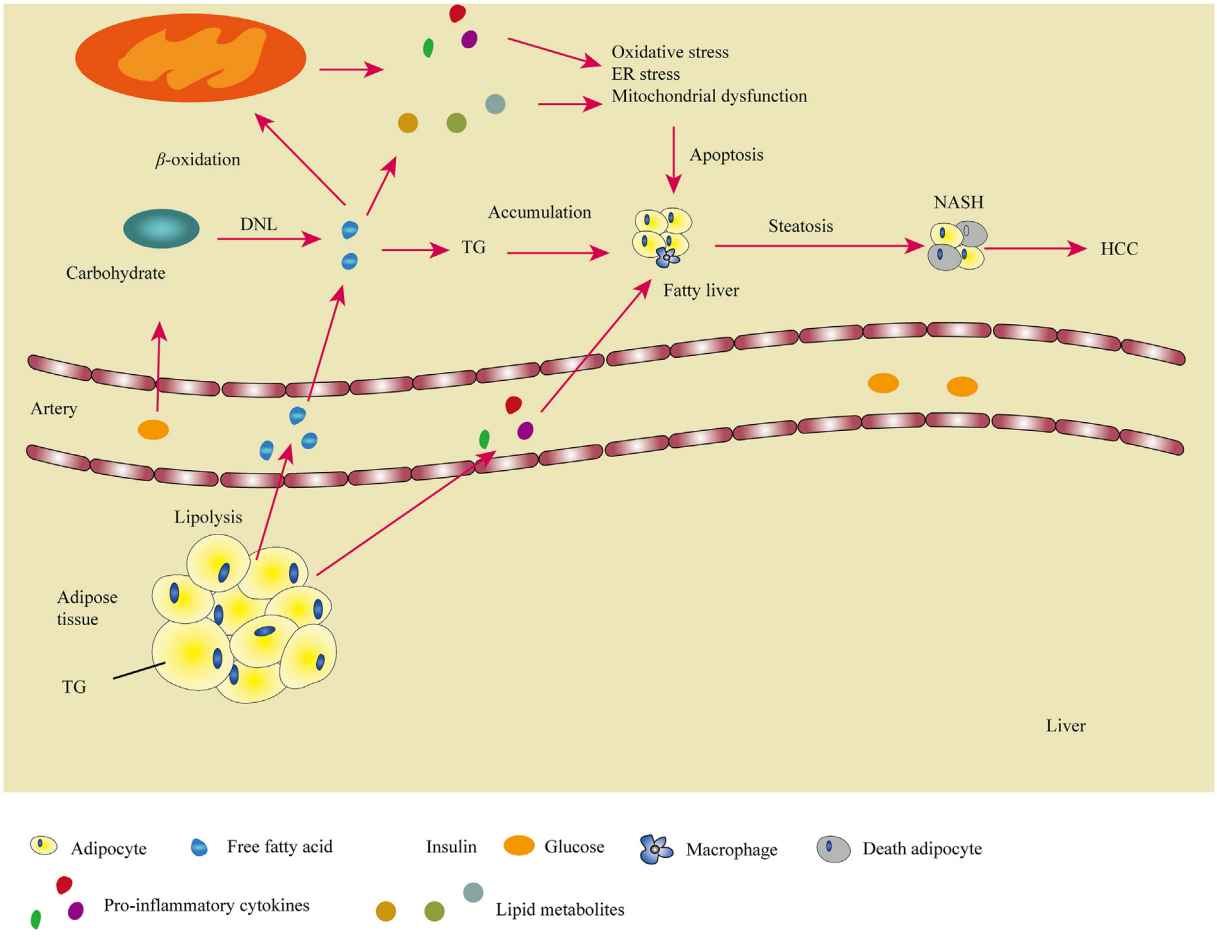

Figure 5 Schematic representation of the links between obesity and liver diseases. Free fatty acids (FFAs) and glucose from the circulation accumulate in the liver and support *de novo* lipogenesis (DNL) of FAs to form triglycerides (TG), which causes fatty liver. Under the 'second hit' of inflammation induced by oxidative stress, ER stress and reactive oxygen species (ROS) cause adipocyte apoptosis, which eventually leads to NASH and sometimes to HCC.

adipocyte apoptosis, which increases the infiltration of macrophages into AT and enhances the production of proinflammatory cytokines[305,306]. These changes increase the risk of NASH[292]. With the deterioration of obesity, inflammation develops when the influx of FFAs to the liver overwhelms physiologically adaptive mechanisms, leading to ROS formation, ER stress, and hepatocellular dysfunction and injury by lipotoxicity[307,308].

The progression to NASH also involves hepatic increased infiltration of different subtypes of immune cells, such as macrophages, Kupffer, dendritic and hepatic stellate cells (HSCs), and the immune cells produce cytokines (such as TGF-β, IL-10) and other factors contributing to inflammation[309]. Hepatocyte injury followed by inflammation and activation of the innate immune system leads to liver fibrosis mediated by activation of HSCs and to secretion and deposition of extracellular matrix (ECM)[308,310,311]. In the obese state, hyperglycemia and hyperinsulinemia promote profibrogenic signals in the HSCs[312,313], which mediates profibrotic activity, either directly or as a cofactor of TGF-β, a key cytokine mediating the induction and promotion of fibrogenesis[314].

NAFLD and NASH are reversible, and not all patients progress to HCC[282]. A recent report indicated that obesity contributes to NASH and HCC through independent mechanisms. Obesity-induced oxidative stress in the liver inhibits the activity of protein tyrosine phosphatases (PTPs) that results in the activation of STAT-1 and STAT-3 to promote the development of NASH and HCC respectively[315,316].

Adipokines secreted by VAT also play important roles in the progression of liver diseases. Adiponectin can enhance insulin sensitivity and inhibit inflammation[317,318], oppose fatty acid synthesis and promote mitochondrial β-oxidation by activating AMPK, thereby helping to prevent liver diseases[319]. Adiponectin lowers intracellular lipid content by two mechanisms to upregulate insulin signaling. First, adiponectin treatment increases the lipoprotein lipase activity in WAT, which may lead to increased uptake of TG into WAT, thus diverting circulating TG away from storage in liver and skeletal muscle[320]. Second, adiponectin contributes to the activation of AMPK, PPARα and eNOS, which promotes fatty acid oxidation and glucose uptake[255]. APN activates AMPK through activating the LKB1 and CaMKK pathways, and then AMPK suppression of ACC lowers malonyl-CoA production to increase the oxidation of long chain fatty acids and circumventing insulin stimulated lipid synthesis[320]. Moreover, AMPK lowers liver G6Pase and PEPCK mRNA expression[321] by promoting transducer of regulated cAMP response element−binding protein 2 (TORC2) phosphorylation and blocking its nuclears accumulation to decrease the production of hepatic glucose and plasma glucose[322,323]. APN increases fatty-acid combustion and energy consumption *via* PPARα activation which leads to decreased triglyceride content in the liver and skeletal muscle and thus increased insulin sensitivity[254]. Lipotoxicity can be linked to the abundance of specific lipids and result in NAFLD and insulin resistance. Diacylglycerols (DAGs) and ceramides are the two best-studied mediators of lipid-induced insulin resistance[324,325]. Ceramides are bioactive sphingolipids produced by the liver that interfere with insulin signaling by activating protein phosphatase 2 (PP2A) and protein kinase C epsilon (PKCε)[326−330]. In contrast, plasma membrane *sn*-1,2-DAGs, the key DAG stereoisomer, impair insulin action *via* activation of PKCε in liver and subsequently inhibit insulin receptor kinase (IRK, tyrosine kinase) activity[331,332]. One study has found that 2 weeks of gAcrp30 treatment reversed whole-body insulin resistance in HFD-fed mice by reducing plasma membrane DAG content, resulting in decreased translocation of PKCε to the plasma membrane in liver, leading to increased insulin signaling[325]. Adiponectin lowers liver ceramide content by activating hepatic ceramidase[333] through AdipoR1 and AdipoR2, and stimulates deacylation of ceramides at neutral pH in a dose-dependent manner producing sphingosine, S1P and dihydrosphingosine-1-phosphate, which reduce insulin resistance[120].

Leptin exerts a dual action on NAFLD. On one hand, leptin inhibits hepatic *de novo* lipogenesis, whereas it stimulates fatty acid oxidation, thereby reducing lipid content in livers. On the other hand, leptin upregulates TGF-β1 and other matrix remodeling enzymes to enhance inflammation and hepatic fibrosis[334]. NAFLD is related to insulin resistance, hepatic steatosis and diabetes and its pathology is adversely affected by obesity[335], but not all patients with obesity develop NAFLD[336]. Despite not having obesity, these individuals often have central adiposity, which predisposes to the metabolic syndrome and is associated with insulin resistance[337]. Furthermore, some patients with NAFLD are lean. These people belong to the 'metabolically obese, normal weight' phenotype[338], which refers to individuals who are non-obese, frequently sedentary, and who have impaired insulin sensitivity, increased cardiovascular risk and increased liver lipid levels, the consequence of decreased capacity for storing fat and reduced mitochondrial function in adipose tissue and increased hepatic *de novo* lipogenesis[339].

Although NAFLD is the most common liver diseases impacted by obesity, obesity and hepatic steatosis also influence the development and progression of other forms of liver disease[340]. Steatosis is frequently seen in individuals with concurrent hepatitis C infection, especially the genotype 3 hepatitis C virus (HCV) infection[341]. In addition, weight gain and insulin resistance are both associated with progressive fibrosis in chronic HCV infection[340]. In individuals with chronic hepatitis C, weight gain itself is associated with progressive liver disease. It has been estimated that approximately 20% of individuals infected with HCV are obese. Obesity in these individuals is associated with steatosis and the progression of fibrosis[342]. HCV proteins have been proven to regulate the host's glucose and lipid metabolism[343] through stimulating DNL and increasing the process of lipogenesis[340]. HCV increases TGF-β1 expression through induction of ROS, and activation of the p38 MAPK, JNK, ERK, and NF-κB pathways[344] to promote the development of HCC.

6. Treatment

Obesity and associated diseases have attracted great attention in recent years on account of their widespread and increasing prevalence. Controlling or losing weight to prevent further worsening of obese individuals seems to be an effective method but can be very challenging for people to adhere to in the longer term. For example, people with biopsy-confirmed NASH showed a 5% reduction in BMI has been shown to result in a 25% relative reduction in liver fat[345], and people who have weight loss over 10% with T2DM would reduce the end points of CVD by 21%[346]. The methods of weight loss include increased physical activity, diet changes, bariatric surgery and drug interventions. Dietary modification is central to obesity treatment, which includes nutritional restriction and nutraceutical intervention. Caloric restriction (CR) is a long-term dietary intervention by reducing caloric intake, which represents an effective strategy to reduce weight, influences adipose tissues plasticity and modifies

Table 1 Antiobesity drugs on the market.

Drug	Mechanism	Approval	Side effect
Phentermine	Sympathomimetics agent	1959	Palpitations, elevated blood pressure
Topiramate/Phentermin	Sympathomimetic/anticonvulsant	2012	Depression, suicidal ideation
Cathin hydrochloride	Sympathomimetics agent	1975	Tachycardia, increase in blood pressure
Sibutramine	Sympathomimetics agent	1997	Non-fatal myocardial infarction and stroke
Fenfluramine	Sympathomimetics agent	1973	Cardiac valvular insufficiency
Rimonabant	CB1 receptor blocker	2006	Depression, suicidal ideation
Bupropion/Naltrexone	Opioid receptor antagonist/dopamine and noradrenaline reuptake inhibitor	2014	Seizures, palpitations, transient blood pressure elevations
Orlistat	Pancreatic lipase inhibitor	1999	Gastrointestinal symptoms, liver injury
Liraglutide	GLP-1R agonists	2014	Nausea/vomiting, diarrhea, gallstones
Semaglutide	GLP-1R agonists	2021	Nausea/vomiting, diarrhea

endocrinological function of adipose tissue and skeletal muscle[347]. Diet intervention and exercise always require a long time (over 6 months) to achieve ideal goals for obese patients, and it is difficult for many people stick to these regimes and continue to lose weight[348,349]. Bariatric surgery is safe and highly effective in reducing weight, obesity-associated comorbidities, and mortality. Bariatric surgery is appropriate for patients who have a BMI $>$ 40 kg/m^2 alone or $>$35 kg/m^2 with comorbidities, or have failed in attempts to diet and exercise, or are free of significant psychological disease[350]. Bariatric surgery includes gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass, and/or biliopancreatic diversion with duodenal switch[351]. Whereas gastric banding and sleeve gastrectomy are purely restrictive in nature, the latter two procedures also result in significant malabsorption[352].

Drug treatment can enhance weight loss in the short (phentermine, amfepramone, cathin hydrochloride) and long-term use (sibutramine, fenfluramine, rimonabant and orlistat), although most of these drugs showed adverse cardiovascular effects or addictive potential (Table 1)[353]. Many reviews have discussed the development of drugs against obesity[353–355]. The agents approved by the FDA to treat obesity are involved in regulating mitochondrial function, sympathomimetics, fat absorption, and appetite regulation. However, several drugs have been removed from the market due to adverse effects, only a few are still being used. Phentermin, an agent of sympathomimetics drugs, was approved for short-term use since 1959[356]. It can cause some side-effects including increased pulse rate and blood pressure, headache and dry mouth. The combination of topiramate with phentermine at low doses showed greater weight loss and fewer side effects by affecting energy metabolism through modulation of GABAergic neurotransmission[353,357]. The main concern is the risk of oral clefts in infants exposed to topiramate in utero[353]. Orlistat as a lipase inhibitor to reduce the uptake of dietary fat has been approved as an anti-obesity drug since 1999[357]. It possesses excellent safety without inducing adverse cardiovascular effects, but has some gastrointestinal side effects. While its effects on weight loss were not obvious[358]. Bupropion/naltrexone combination is also approved in US for long term weight management by reducing food intake[359]. Although this combination may increase blood pressure or heart rate, no significant increase in cardiovascular events was found[360]. In recent years, glucagon-like peptide-1 (GLP-1) receptor agonists are increasingly being used for the treatment of T2DM. Liraglutide and semaglutide have been approved as anti-obesity drugs in 2014 and 2021 respectively[353]. They can not only reduce glucose concentrations and increase satiety, but also slow gastric emptying and reduce bodyweight in a dose-dependent manner. Both of them are well tolerated and show a low incidence of major adverse cardiovascular events, while the typical GLP-1-related adverse effects including nausea, diarrhea, vomiting and constipation still occur[361,362].

Most obesity-related deaths are due to CVD[363], and improving cardiovascular health becomes a primary objective for weight-loss drugs. None of the currently approved anti-obesity drugs have been shown to be effective for primary prevention of CVD or in reducing major adverse cardiovascular events or mortality among patients with obesity[356]. The exploration of next generation anti-obesity drugs is still ongoing.

7. Conclusions

Obesity remains the most serious risk factor for several cancers, cardiovascular diseases, type 2 diabetes, and liver diseases. Excess uptake of calories leads to accumulation of fat in adipose tissue thereby promoting adipose tissue expansion through adipocyte hypertrophy and hyperplasia. When the available fat exceeds the storage capacity of adipocytes, it will travel through the circulation and form ectopic deposits in other organs, giving rise to visceral fat. Visceral fat can impair vascularization and cause hypoxia, oxidative stress, and ER stress which contribute to the pathogenesis of other associated diseases. Furthermore, excess dietary fats are transformed into free fatty acids to synthesize triglycerides as an energy reserve. High levels of free fatty acids in serum and their metabolites activate the PKC and JNK-1 signaling pathways and change the initial process of ISR-1 to induce insulin resistance that will cause hyperglycemia, T2DM, and liver diseases directly. Adipose tissue, as an endocrine organ, secretes several adipokines, including leptin, adiponectin, and resistin. These adipokines play important roles in regulating the relationship between obesity and associated diseases. For example, elevated leptin activates intracellular signaling, such as the PI3K/AKT/mTOR and ERK/MAPK pathways, including in cancer cells. It impairs β-cell function and suppresses insulin secretion to result in a hyperglycemia state lower levels of adiponectin in obesity decrease insulin sensitivity and fat oxidation. Adipose tissue is in a state of inflammation. VAT secretes some inflammatory cytokines, such as TNF-α, IL-6 and MCP-1, which can activate the NF-κB and JAK/STAT signaling pathways and induce inflammation in the heart and liver. Fat accumulation in non-adipose tissue and inflammation induced by visceral fat are the most important causal factors for obesity-associated diseases. Decreasing the uptake of a high-fat or high-carbohydrate diet and proper physical

activity to control body weight and reduce the percent of visceral fat will help people who are overweight or obese lower the risk of other metabolic disorders. In view of the worldwide epidemic of obesity, it is important for us to control body weight and balance our diet. However, many people find it hard to stick to lower food consumption and higher levels of exercise. Therefore, understanding the links between obesity and other diseases and the internal mechanisms that underlie them could help us better prevent and treat obesity and related disorders. Novel therapeutic approaches to this need to be explored and validated.

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Author contributions

Xin Jin, Tingting Qiu and Li Li: Writing-Original draft preparation. Rilei Yu, Xiguang Chen, Changgui Li and Christopher G. Proud: Writing-Review & Editing. Tao Jiang: Supervision, Funding acquisition and Writing-Review & Editing. All authors have approved the final article.

Conflicts of interest

The authors declare no conflict of interest.

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