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Review

Tissue-specific mechanisms of fat metabolism that focus on insulin actions

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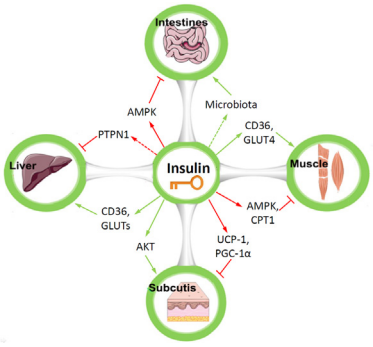
HIGHLIGHTS

- Tissue-specific fat metabolism serves as a trigger for developing abnormal fat metabolism.
- Tissue-specific fat metabolism is a compensatory agent for regulating normal fat metabolism.
- Outcomes of *de novo* lipogenesis and adipogenesis differ in different tissues.
- Insulin signaling pathways regulate lipo-/adipogenesis.
- Regulating insulin actions may be a key measure on fat deposition and metabolism.

GRAPHICAL ABSTRACT

AKT, serine/threonine protein kinase; AMPK, AMP-activated protein kinase; CD36, cluster of differentiation 36; CPT1, carnitine palmitoyltransferase-1; GLUTs, glucose transporters; GLUT4, glucose transporter 4; PGC-1α, PPARγ coactivator-1α; *PTPN1*, protein tyrosine phosphatase nonreceptor type 1.



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ABSTRACT

Background: The accumulation of ectopic fats is related to metabolic syndromes with insulin resistance, which is considered as the *first hit* in obesity-related diseases. However, systematic understanding of the occurrence of ectopic fats is limited, since organisms are capable of orchestrating complicated intracellular signaling pathways to ensure that the correct nutritional components reach the tissues where they are needed. Interestingly, tissue-specific mechanisms lead to different consequences of fat metabolism with different insulin sensitivities.

Aim of Review: To summarize the mechanisms of fat deposition in different tissues including adipose tissue, subcutis, liver, muscle and intestines, in an attempt to elucidate interactive mechanisms involving insulin actions and establish a potential reference for the rational uptake of fat.

Key Scientific Concepts of Review: Tissue-specific fat metabolism serves as a trigger for developing abnormal fat metabolism or as a compensatory agent for regulating normal fat metabolism. Outcomes of *de novo* lipogenesis and adipogenesis differ in the subcutaneous adipose tissue (SAT), liver and muscle, with the participation of insulin actions. Overload of lipid metabolic capability results in SAT fat expansion,

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and ectopic fat accumulation implicates impaired lipo-/adipogenesis in SAT. Regulating insulin actions may be a key measure on fat deposition and metabolism in individuals.

Contents

Introduction

Diet-induced metabolic syndromes such as hyperlipidemia, diabetes and nonalcoholic fatty liver disease (NAFLD) are found in individuals with or without obesity [1]. As the second essential energy supply nutrient for organisms, fats serve as an energy storage workshop to prevent energy depletion. The subcutis is the largest and safest storage site for excess fats. However, the accumulation of ectopic fat occurs once diet-derived energy is excessively stored beyond the lipid buffering capacity of the subcutis, resulting in metabolic syndromes and insulin resistance. High-fat diet (HFD) has been demonstrated to promote obesity more effectively than a high-sugar diet, and a HFD may induce intestinal carcinogenesis independent of obesity [2]. Absorption of short-chain fatty acids (SCFAs) by G-protein-coupled receptors (GPRs) in the posterior intestines contributes to liver lipogenesis, and SCFAs are vital to the production of saturated fatty acids (SFAs) or monounsaturated fatty acids (MUFAs). A HFD contributes to oxidative stress, inflammatory response and a series of negative cascades because excessive fat-catabolized lipids (e.g., free fatty acids, ceramide, and lipid peroxides) are a group of toxic substances that lead to cell injury unless their concentrations are controlled. Our previous studies have demonstrated that a HFD can induce insulin resistance potentially through oxidative stress and inflammation caused by endotoxins from imbalanced intestinal flora, and thus impair intestinal immune system [3,4]. Although the pathological mechanisms of diet-induced metabolic syndromes are still not clear, increasing attention has been given to the crosstalk between lipid metabolism disorders, insulin resistance and intestinal microecological imbalances [5,6]. Considering the tissue-specific properties of fat metabolism, we have reviewed the accumulated data of the absorption and catabolism of fats in the gastrointestinal tract and attempted to illustrate the cellular mechanisms of fat deposition in different tissues as well as their interactive mechanisms involving insulin actions.

Fat deposition in adipose tissue

The primary stages of adipose tissue during the lifetime include adipose mesenchymal stem cells (AMSCs), adipose mesenchymal precursor cells (AMPCs), preadipocytes, and mature adipocytes with actions of adipogenesis, lipogenesis, lipolysis and lipophagy (Fig. 1). The wingless-type MMTV integration site (WNT)/β-catenin signaling pathway is the classic regulator of the growth and differentiation of AMSCs/AMPCs [7]. The multipotency of AMSCs/AMPCs helps them acquire a white or a brown phenotype, which are referred to as white adipose tissue (WAT) and brown adipose tissue (BAT). As an indispensable endocrine tissue, adipose tissue secretes well-functioning molecules such as leptin, adiponectin [8], visfatin, fatty acid esters of hydroxy fatty acids (FAHFAs), and non-well-functioning molecules such as tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), retinol binding protein-4 (RBP4) and resistin. Unlike the impaired status of the excessive expansion of WAT, BAT participates in critical events named thermogenesis. In these events, mitochondrial uncoupling protein-1 (UCP-1) located in the inner mitochondrial membrane might be the key factor [9]. FA-activated UCP-1 uncouples mitochondrial respiration from the generation of adenosine triphosphate (ATP), which dissipates chemical energy as heat [10]. Adenosine monophosphate (AMP)-activated protein kinase (AMPK) plays an essential role in maintaining mitochondrial quality in BAT for thermogenesis by regulating dysfunctional mitochondrial mitophagy with the help of the autophagy protein light chain-3B (LC3B) in mouse and human [11]. It is well established that bile acids (BAs) promote energy expenditure by the G-protein coupled receptor (Takeda G protein-coupled receptor 5, TGR5) in HFD-fed mice and cells, suggesting that the BA–TGR5–cyclic-AMP (cAMP)–type 2 iodothyronine deiodinase (D2) signaling pathway is crucial for energy expenditure in BAT, and bone morphogenetic protein (BMP) family members such as BMP7 may regulate the committed development of BAT, while BMP2/4 regulates the committed development of WAT and the transformation of BAT from WAT [12].

Adipogenesis is a way for adipose tissue to develop through the recruitment and differentiation of new preadipocytes. Distinct from expansion via hypertrophy of cells, adipogenesis is triggered by the adipocyte cell size reaching a threshold, and the transcription of peroxisome proliferator-activated receptor γ (PPARγ) plays a critical role in the regulation of adipogenesis [13]. Crosstalk of BMP4/zinc-finger protein 423 (ZFP423)/PPARγ regulates the adipogenic commitment of WAT through the dissociation of the WNT1 inducible signaling pathway protein 2 (WISP2) and

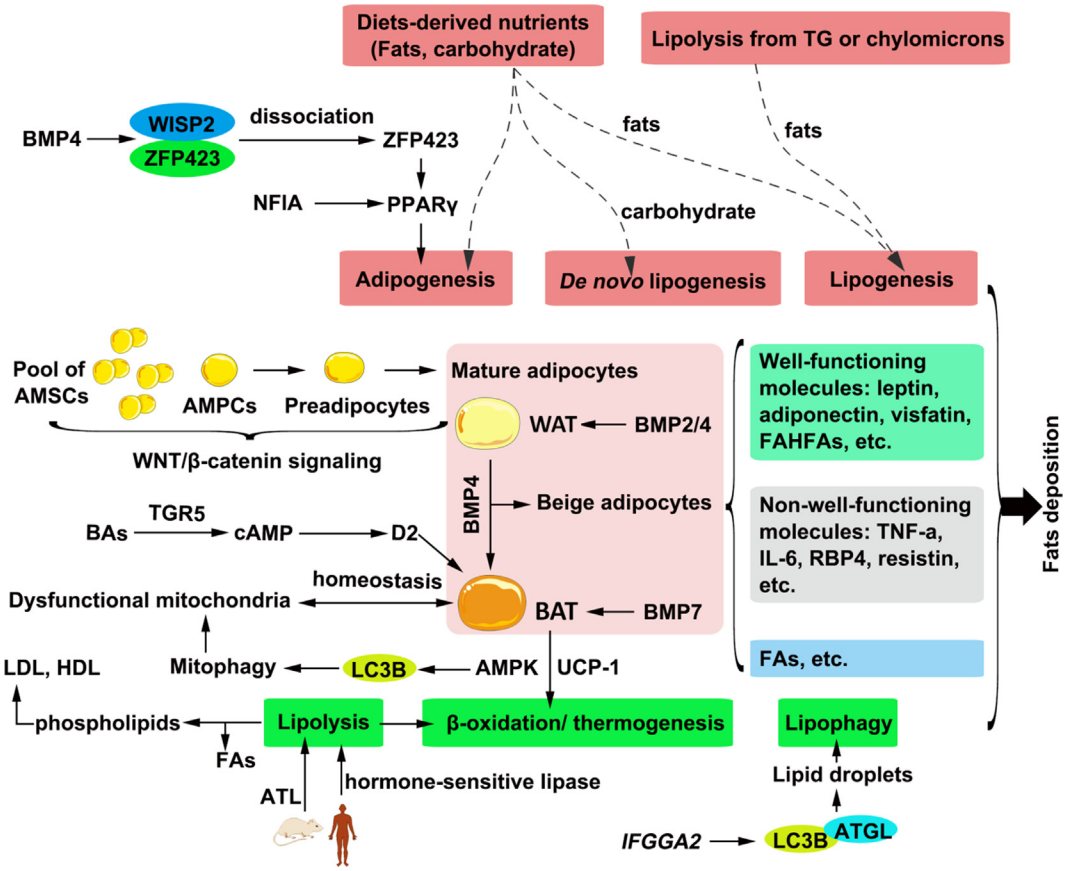

Fig. 1. Fat Deposition in adipose tissue. Classical WNT/β-catenin signaling regulates the growth and differentiation of AMSCs/AMPCs, leading to the acquisition of a white or a brown phenotype. With the help of the BMP family (e.g. BMP4), WAT can transform to beige adipocytes and BAT. Diet-derived fats or carbohydrates contribute to lipogenesis or *de novo* lipogenesis in adipocytes. Lipolysis from TGs or chylomicrons also supplies fats for lipogenesis. Furthermore, fat lipolysis is an adaptive mechanism in the production of LDL and HDL, and prepares substrates for β-oxidation/thermogenesis in adipocytes (mainly BAT). Lipophagy occurs in states of insufficient nutrients, in which lipid droplets are broken down by the autophagy protein LC3B and its partner lipase ATGL. AMPCs, adipose mesenchymal precursor cells; AMPK, AMP-activated protein kinase; AMSCs, adipose mesenchymal stem cells; ATGL, adipose triglyceride lipase; ATL, adipocyte triglyceride lipase, BAs, bile acids; BAT, brown adipose tissue; BMP, bone morphogenetic protein; cAMP, cyclic-AMP; D2, type 2 iodothyronine deiodinase; FAs, fatty acids; FAHFAs, fatty acid esters of hydroxy fatty acids; HDL, high density lipoprotein; IL-6, interleukin-6; LC3B, light chain-3B; LDL, low density lipoprotein; NFIA, Nuclear factor I-A; PPARγ, peroxisome proliferator-activated receptor γ; RBP4, retinol binding protein-4; TG, triglyceride; TGR5, Takeda G protein-coupled receptor 5; TNF-α, tumor necrosis factor α; UCP-1, uncoupling protein-1; WAT, white adipose tissue; WISP2, WNT1 inducible signaling pathway protein 2; WNT, wingless-type MMTV integration site; ZFP423, zinc-finger protein 423.

ZFP423 complex, which enters the nucleus to activate PPARγ [14]. Nuclear factor I-A (NFIA) induces brown adipogenesis by activating brown fat enhancers and facilitating the binding of PPARγ [15]. Lipogenesis in adipose tissue comes from diet-derived fats and lipolysis-derived fats, and the *de novo* production of fats come from non-fats (mainly sugars), which is called *de novo* lipogenesis. The key elements in FA transport, including cluster of differentiation 36 (CD36) and fatty acid transport proteins (FATPs), or the key elements in glucose transport, including glucose transporter 4 (GLUT4) and carbohydrate response element binding protein (ChREBP) in adipocytes, can promote lipogenesis or *de novo* lipogenesis [16]. Sterol-regulatory-element-binding protein-1c (SREBP-1c), ChREBP, liver X receptors (LXRs), mechanistic target of rapamycin (mTOR), acetyl-CoA carboxylase (ACC), fatty acid synthase (FASN), AKT (serine/threonine protein kinase, also known as protein kinase B), and AMPK are key factors in regulating lipogenesis or *de novo* lipogenesis. Inhibition of ACC helps reduce hepatic lipotoxicity by decreasing *de novo* lipogenesis and promoting the β-oxidation of fatty acids (FAs) in human primary hepatic stellate cells or in rats [17]. FASN, the key enzyme of *de novo* lipogenesis, participates in metabolic processes controlled by neural stem cells in adults [18]. As a way to mobilize FAs, lipolysis is instrumental for the energy expenditure of fats and the further β-oxidation of FAs. Lipolysis of triglycerides (TGs) or chylomicrons is an essential way to produce non-diet-derived FAs, and their assembly with phospholipids is important for the formation of low density lipoprotein (LDL) or high density lipoprotein (HDL). In contrast, a key regulator of lipolysis in murine adipose cells is adipocyte triglyceride lipase (ATL), which is hormone-sensitive lipase in human adipose cells. Overexpression of *IFGGA2*, one type of immunity-associated GTPase, enhances the production of the autophagy protein LC3B, which degrades lipid droplets via its partner lipase (adipose triglyceride lipase, ATGL) and thus promotes lipophagy in mice and humans [19].

Subcutaneous fat deposition

Excessive accumulation of ectopic fats induces local and systemic insulin resistance, which leads to the development of metabolic-related diseases, and less subcutaneous adipose tissue (SAT) is associated with higher mortality in female with cirrhosis and predicts mortality in male [20]. The ability of SAT to store excessive fats depends on the genetics of different individuals. An assessment of 3001 participants showed that most metabolic risk factors are correlated with visceral adipose tissue (VAT) rather than SAT, and the increase in VAT was observed in individuals with an increased prevalence of hypertension and impaired fasting

glucose, while transplantation of SAT into the VAT area can decrease body weight and improve insulin sensitivity in mice [21]. Thus, SAT is believed to have a higher capacity to expand its capillary network than VAT, but morbid obesity can decrease the capacity of angiogenesis in SAT with insulin resistance [22]. Angiopoietin-2–integrin α5β1 signaling in SAT specifically enhances FA transport via CD36 and FATP3, which further reduces ectopic fat accumulation [23]. Angiopoietin-2 produced from SAT regulates angiogenesis and integrin α5β1 acts as a ligand with angiopoietin-2 for the activation of CD36/FATP3 [24]. Gremlin-1 secreted by (pre)adipocytes is an antagonist of BMP4/7, whose production inhibits adipogenesis in WAT in subjects with hypertrophic obesity [25]. Vascular endothelial growth factors (VEGFs) and their receptors (VEGFR-1, also known as Flt1, and VEGFR-2) control angiogenesis to activate thermogenesis in SAT by activating UCP-1 and PPARγ coactivator-1α (PGC-1α), and thus increase the basal metabolic rate to prevent HFD-induced obesity [26]. Moreover, impaired lipolysis of SAT is linked to weight gain and impaired glucose metabolism [27]. *De novo* lipogenesis is involved in the process of the tricarboxylic acid (TCA) cycle, which metabolizes derivatives of sugars and various lipids with the help of GLUT4. Insulin-activated 3-phosphoinositide dependent kinase-1 (PDK1) and mTOR complex 2 (mTORC2) potentially regulate the conversion of glucose-derived citrate through the activation of AKT at phosphorylating sites Thr308/309 and Ser473/474, respectively, in WAT. This drives ChREBPβ, the lipogenic transcription factor, to promote *de novo* lipogenesis and improve insulin sensitivity [28]. Therefore, SAT has a direct and beneficial capability to regulate body weight and energy metabolism due to its cell-specific property associated with angiogenesis and lipid buffering capacity for the prevention of ectopic fat deposition. Restoring or improving the capability of SAT provides effective targets for the treatment of obesity-related complications, and homeostasis of SAT capabilities is an essential index for monitoring metabolic syndromes (Fig. 2).

Fat deposition in muscle

Based on embryonic development, both muscle tissue and BAT are derived from the same $Pax7^{+}/Myf5^{+}$ progenitor cells (Fig. 3). The pivotal switch that regulates the choice between muscle tissue and BAT is turning on the *MyoD*/*Myf5*-*E2F4* axis, which transcriptionally promotes the formation of myoblasts or brown preadipocytes [29]. Endothelial cells influence the development and energy balance of muscle. It has been reported that endothelial fat-related gene *FTO* may induce insulin resistance in muscle cells, and knockout of *FTO* gene can protect mice from insulin resistance by increasing AKT phosphorylation [30]. Moreover, adipo-myokines produced by skeletal muscle or adipose tissue may contribute in the mediation of the health benefits of exercise and physical inactivity probably leads to an altered adipo-myokine profile, which could provide a potential mechanism for the association between sedentary behavior and many chronic diseases like diabetes [31].

Muscle tissue is the primary site for the β-oxidation of fats when the glucose supply is insufficient. Most FAs uptake for lipogenesis in muscle tissue demands the lipolysis of TGs, circulating very low-density lipoproteins (VLDLs) and chylomicrons, while glucose uptake for *de novo* lipogenesis in muscle tissue relies on GLUTs. Lipoprotein lipase (LPL) is synthesized by myocytes or adipocytes to hydrolyze TG into FAs [32]. It can be transported into the capillary lumen surface with the help of glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1 (GPIHBP1), a protein of the lymphocyte antigen 6 (Ly6) family [33]. The insulin-inactivated RalGAPα1/β complex is vital to accelerate the uptake of FAs and glucose in muscle. In this process, the complex is inactivated by the phosphorylation of RalGAPα1, followed by the activation of RalA due to a lack of the inhibitory function of the RalGAPα1/β complex, and the activated guanosine triphosphate (GTP)-loaded RalA can promote the docking and translocation of CD36 and GLUT4 to further promote FA and glucose uptake, which can be reversed by insulin resistance in muscle [34]. Carnitine palmitoyltransferase-1 (CPT1) located in the mitochondrial outer membrane is a rate-limiting enzyme of β-oxidation that acts in response to FA uptake. The NAD^{+}-dependent deacetylase sirtuin 1 (SIRT1) signaling pathway can be activated by low glucose levels and then promote the transcription of mitochondrial metabolic genes, such as isocitrate dehydrogenase alpha subunit (*IDH3α*, gene of TCA), cytochrome *c* (*cyt c*, gene of respiratory chain), and *CPT1-b* (gene of FA utilization), through PPARγ and its coactivator PGC-1α [35]. The AMPK signaling pathway is another adaptive mechanism for the β-oxidation of FAs in muscle tissue [36]. AMPK-activated ACC2 phosphorylation contributes to the β-oxidation of FAs, but prolyl hydroxylase 3 (PHD3)-hydroxylated ACC2 results in the repression of β-oxidation under high energy conditions in mice, mouse cell lines and human cell lines [37]. Exercise promotes kynurenine biotransformation in skeletal muscle, which protects against neuroinflammation and leads to peripheral kynurenic acid accumulation and activate G-protein coupled receptor 35 (GPR35) in adipose tissue to increase energy expenditure [38], but high-level phosphate can induce physical inactivity and reduce FA oxidation in skeletal muscle [39]. Moreover, caspase-1-activated interleukin-18 (IL-18) in inflammasome complexes may increase lipolysis in adipose tissue, and enhance fat oxidation in skeletal muscle by activating AMPK to suppress fat accumulation in HFD-fed mice [40].

Fat metabolism in the liver

All intestinally-derived FAs (including SCFAs), lipolysis-derived FAs, and diet-derived sugars (glucose or fructose) are basic resources for lipogenesis or *de novo* lipogenesis in liver based on CD36 or GLUTs [41]. As shown in Fig. 4, excessive accumulation of fat in liver leads to lipolysis in adipose tissue, and the flux of non-esterified fatty acids (NEFAs) aggregate in the liver due to insufficient β-oxidation of FAs and increased hepatic *de novo* lipogenesis. Triose kinase (TK), a critical modifier of fructose metabolism, accelerates fructolysis to promote hepatic *de novo* lipogenesis, and TK deficiency inhibits hepatic TG accumulation [42]. Some TGs can be stored as lipid droplets in the liver, while others exit the liver after being packaged into VLDL by thioesterase superfamily member 2 (Them2) [43]. Acetyl-CoA-derived cholesterols comprise another pivotal part of fats in the liver. Lipolysis-derived cholesteryl esters (CEs) from chylomicrons participate in intrahepatic circulation as CE and free cholesterol (FC). Together with hepatic TGs, hepatic CEs further contribute to the formation of VLDL, and cholesterols are transported in either LDL or HDL. The hepatic low-density lipoprotein receptor (LDLR) pathway facilitates the uptake of LDL-c and thus decreases the amount of LDL-c in circulation. LXRs interact with lipogenic genes and improve insulin sensitivity by regulating PPARγ and ChREBPβ [44]. *In vitro* studies have shown that LXRs inhibit the uptake of LDL-c by disrupting the LDLR pathway through the inducible degrader of the LDLR (Idol), which is an E3 ubiquitin ligase targeting LDLR for degradation [45]. Noncoding RNAs, such as long noncoding RNAs (lncRNAs), microRNAs (miRNAs) [46] and circular RNAs (circRNAs), have recently received increasing attention due to their integral regulation of organismal complexity [47]. MicroRNA-148a can regulate LDLR expression to control circulating lipoprotein levels [48], and microRNA-206 may prevent hepatic lipogenesis by inhibiting sterol response element-binding protein 1c (SREB1c) signaling and the degradation of protein tyrosine phosphatase nonreceptor

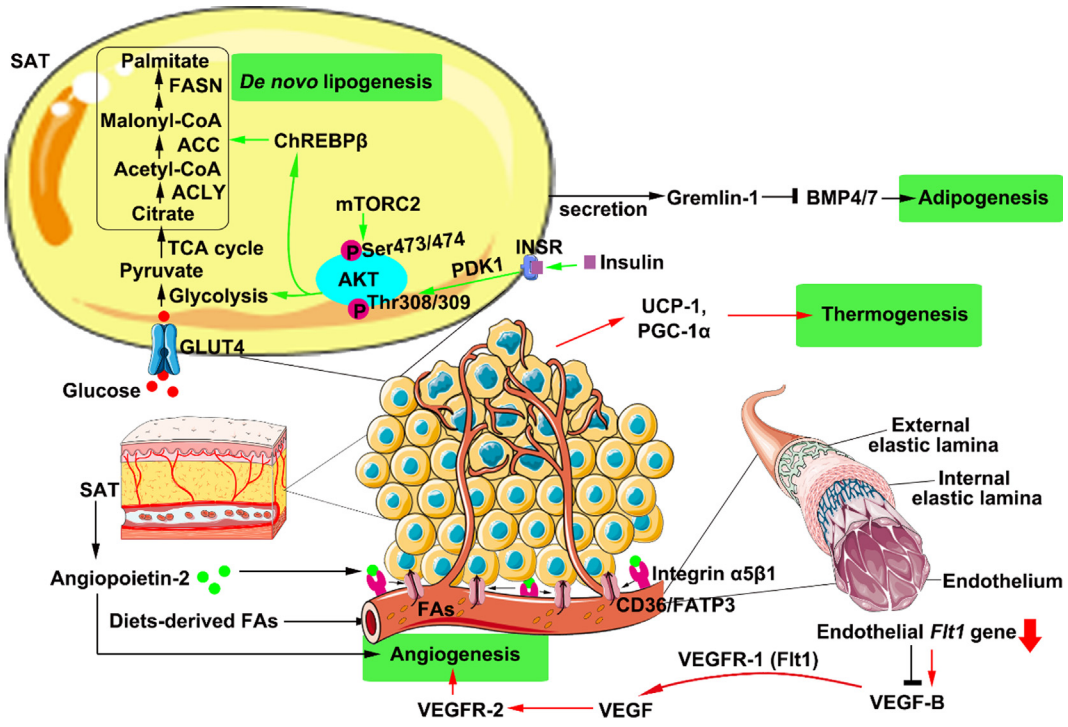

Fig. 2. Subcutaneous fat deposition. Diet-derived fats enter SAT with the help of CD36/FATP3, and SAT-secreted angiopoietin-2 contributes to angiogenesis and the activation of CD36/FATP3 by binding with integrin α5β1, which accelerates the transport of FAs. The endothelial *Flt1* gene inhibits VEGF-B, and the deletion of the *Flt1* gene contributes to VEGFR-2-stimulated angiogenesis. This is followed by enhanced thermogenesis in SAT through UCP-1 and PGC-1α. Both insulin and mTORC2 promote *de novo* lipogenesis by activating AKT at phosphorylation sites Thr308/309 and Ser473/474, respectively. This drives ChREBPβ to increase *de novo* lipogenesis in SAT. Furthermore, Gremlin-1 secreted by (pre)adipocytes is an antagonist of BMP4/7, whose production inhibits adipogenesis in WAT with hypertrophic obesity. ACC, acetyl-CoA carboxylase; AKT, serine/threonine protein kinase; ACLY, ATP citrate lyase; BMP, bone morphogenetic protein; FAs, fatty acids; FASN, fatty acid synthase; FATP3, fatty acid transport protein-3; GLUT4, glucose transporter 4; INSR, insulin receptors; mTORC2, mTOR complex 2; PDK1, phosphoinositide dependent kinase-1; PGC-1α, PPARγ coactivator-1α; SAT, subcutaneous adipose tissue; TCA, tricarboxylic acid; UCP-1, uncoupling protein-1; VEGF, vascular endothelial growth factor.

type 1 (*PTPN1*) [49]. Glucagon-stimulated inositol triphosphate receptor 1 (*INSP3R1*) may also regulate intrahepatic lipolysis by enhancing ATL, hepatic gluconeogenesis, the acetyl-CoA content and hepatic mitochondrial oxidation [50]. BAs are oxidative products that derived from cholesterol with the help of the rate-limiting enzyme cholesterol 7α-hydroxylase (CYP7A1). While unconjugated BAs are secreted into bile, BAs conjugated with glycine or taurine contributes to reduce the accumulation of potentially cytotoxic BAs in the liver [51]. BAs are essential in the homeostasis of hepatic lipogenesis because they activate BA receptors, such as farnesoid X receptors (FXRs), followed by the activation of short heterodimer partner (SHP) to reduce SREBP-1c, which is the master regulator of hepatic lipogenesis [52].

Fat metabolism in intestines

Leucine-rich-repeat-containing G-protein-coupled receptor 5 intestinal stem cells (*Lgr5* ISCs) remodel the intestinal composition by modulating the production of their daughter cells (progenitor cells), and these cells differentiate into all types of intestinal cells including Paneth cells and absorptive cells. As shown in Fig. 5, interspersed between Paneth cells and *Lgr5* ISCs neutralize competition to maintain the homeostasis of self-renewing small intestinal crypts. As multifunctional guardians of ISCs, Paneth cells exert functions against the intestinal microbiota through the production of antimicrobial (poly)peptides [53]. HFD-derived FAs potentially promote the proliferation of ISCs and make progenitor cells more stem cell-like through PPARδ/WNT/β-catenin signaling cascades [54]. Neurotensin (NT) is a 13-amino acid peptide that predominantly located in specialized enteroendocrine cells of the small intestine, and can be stimulated by fat absorption to facilitate the translocation of FAs based on NT receptors such as NT receptor 1 (NTR1) [55]. NT-deficient mice have been observed to reduce intestinal fat absorption and protect against HFD-induced obesity through the activation of AMPK signaling in enteroendocrine cells [56]. Circulating peptides and GPRs, such as NTR1, have received increasing attention due to their functions as essential agents for fat absorption in the small intestine [57]. In recent studies, metformin has been newly identified as a peptide hormone that inhibits intestinal FA absorption, neurotensin secretion, and insulin resistance-related obesity by promoting AMPK signaling. This occurs through its receptor GPRC6A, which is an endogenous receptor of osteocalcin [58]. Metabolitin can downregulate NT expression in enteroendocrine cells and further reduces the NTR-induced uptake of FAs in enterocytes to inhibit FA absorption in enterocytes [59].

Intestinal microorganisms including parasites, bacteria and viruses play a critical role in fat metabolism, as lipid droplets provide energy to the intestinal microbiota but also mediate an innate immune defense against the intestinal microbiota by both reprogramming cell metabolism and eliciting protein-mediated antimicrobial mechanisms [60]. Microbial colonization has been reported to influence the metabolic process in mice fed diets enriched with lard and primary bile acids [61]. Microbiota harvested from cecum of conventionally raised animals can promote the absorption of monosaccharides and increase the expression of mRNAs encoding two key enzymes in the *de novo* FA biosynthetic pathway in adult germ-free mice to increase body fat and insulin resistance [62]. Moreover, the transplantation of intestinal microbiota from

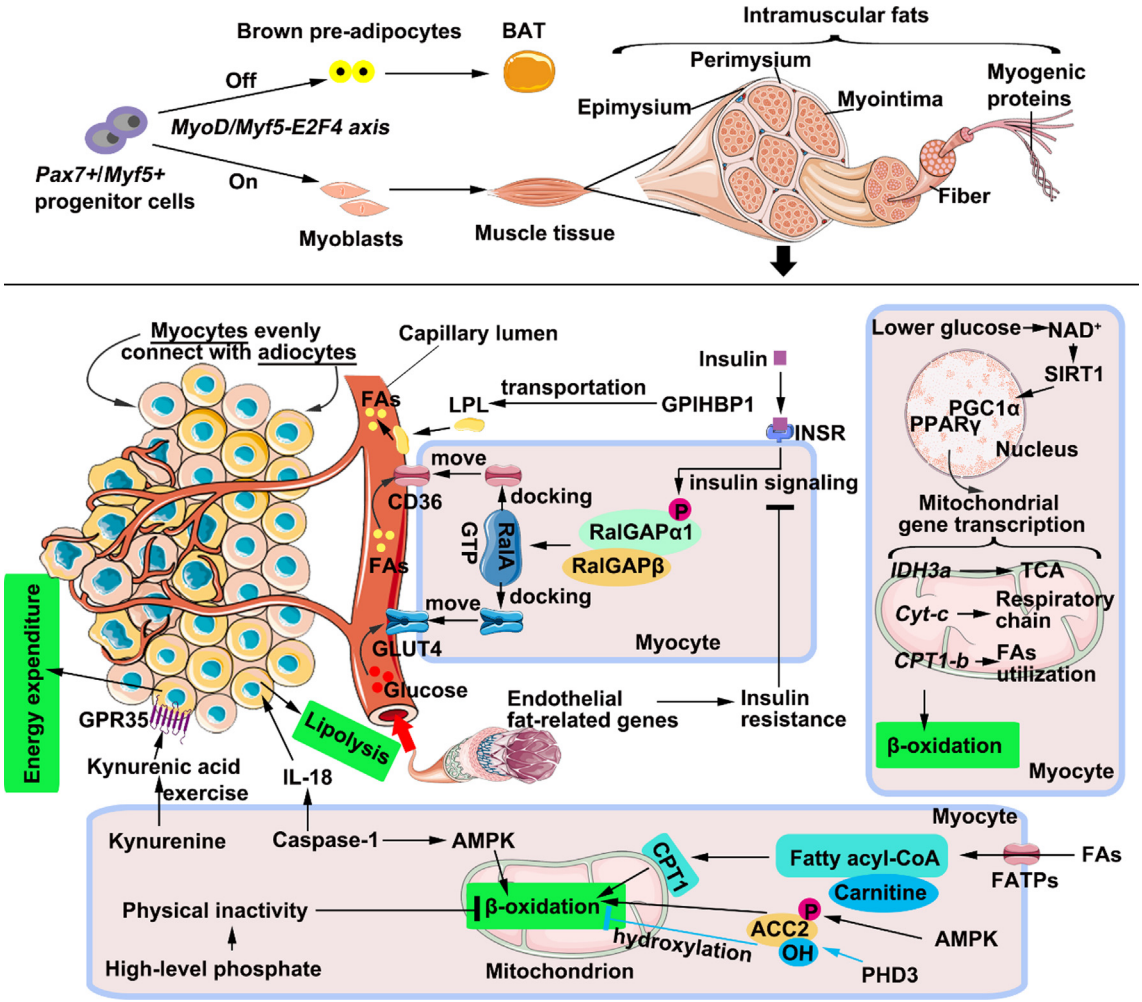

Fig. 3. Fat Deposition in Muscle. Insulin promotes the phosphorylation of RalGAPα1 and breaks down the RalA complex. GTP-loaded RalA promotes the docking and translocation of CD36 and GLUT4, which promote FA and glucose uptake. However, muscle endothelial fat-related genes (e.g. FTO) promote insulin resistance and influence the transport of FAs and glucose. Under condition of low glucose level, NAD^+ induces the activation of PGC-1α through the SIRT1 signaling pathway. This is followed by the promotion of genes related to TCA, the respiratory chain, and FA utilization, and ultimately promotes the β-oxidation of FAs. CPT1 and AMPK play essential roles in mitochondrial β-oxidation. PHD3 or high-level phosphate inhibits mitochondrial β-oxidation by the hydroxylation of ACC or decreasing physical activity, respectively. Caspase-1-activated IL-18 increases lipolysis in adipose tissue and promotes AMPK-dependent β-oxidation. Moreover, exercise changes the metabolic programs of kynurenine, which leads to peripheral kynurenic acid accumulation to activate GPR35 and increase energy expenditure. ACC2, acetyl-CoA carboxylase 2; AMPK, AMP-activated protein kinase; BAT, brown adipose tissue; CD36, cluster of differentiation 36; CPT1, carnitine palmitoyltransferase-1; cyt c, cytochrome *c*; FAs, fatty acids; FATPs, fatty acid transport proteins; GLUT4, glucose transporter 4; GPIHBP1, glycosylphosphatidylinositol- anchored high density lipoprotein-binding protein 1, GPR35, G-protein coupled receptor 35; GTP, guanosine triphosphate; IDH3α, isocitrate dehydrogenase alpha subunit; IL-18, interleukin 18; INSR, insulin receptors; LPL, lipoprotein lipase; Myf5, myogenic factor 5; MyoD, myogenic differentiation; PGC-1α, PPARγ coactivator-1α; PHD3, prolyl hydroxylase 3; PPARγ, peroxisome proliferator-activated receptor γ; RalGAP, RalGTPase-activating protein; SIRT1, sirtuin 1;TCA, tricarboxylic acid.

cold-exposed mice can reduce HFD-induced obesity in germ-free recipient mice, suggesting a mechanism involving a leaner phenotype with the production of conjugated BAs and activation of AMPK [63]. Nevertheless, HFD-derived saturated FAs induce alterations in the composition of the intestinal microbiota, and can also promote the expansion of *Bilophila wadsworthia* in IL-10 $^{-/-}$ mice to cause a proinflammatory T_H1 immune response with colitis [64]. Intestinal microbiota may regulate fat absorption and export in intestinal epithelial cells through the control of the circadian clock. This regulates the uptake and storage of fats through nuclear factor interleukin-3 (NFIL3), which is a basic leucine zipper transcription factor that controls a circadian fat metabolic program [65]. Consuming a HFD can disrupt circadian metabolites in a tissue-specific manner [66], and the circadian clock controls cytoplasmic polyadenylation element-binding 4 (CPEB4) mRNA transcription, which is required for HFD-induced endoplasmic reticulum (ER) stress, to maintain mitochondrial homeostasis [67].

Interactive mechanisms of fat deposition centering on insulin actions

As one of the most important factors in regulating glucolipid metabolism, insulin plays an irreplaceable role in regulating fat deposition (Fig. 6). Excessive accumulation of FAs in blood reduces glucose uptake but increases hepatic glucose production, resulting in glucose intolerance, hyperinsulinemia and insulin resistance. On the one hand, excessive fat deposition increases the secretion of non-well-functioning molecules that deliver to peripheral tissues, and abnormal FAs can induce a series of inflammatory cytokines to disrupt the integrity of insulin receptors (INSR) and cause systemic insulin resistance. Additionally, saturated FAs may induce gut microbiota disturbance and cause inflammation [64]. On the other hand, adipose tissues can also secret well-functioning molecules such as leptin, adiponectin and FAHFAs, which attenuate insulin resistance. It has been reported that adiponectin can

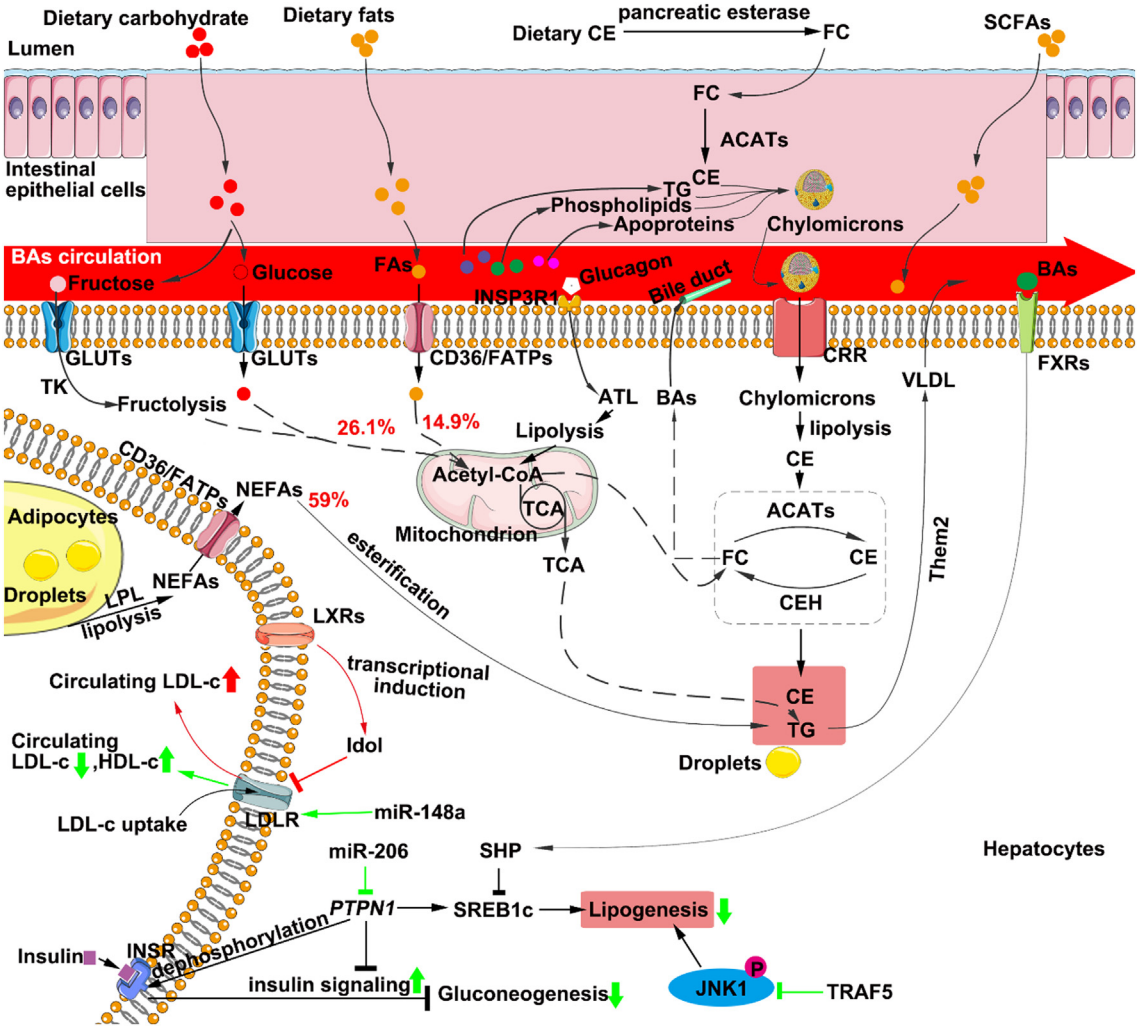

Fig. 4. Fat deposition in the liver. Diet-derived fats, sugars (glucose and fructose), and NEFAs from lipolysis account for 14.9 %, 26.1 %, and 59 % to comprise the TG pool respectively, in the liver. TG is stored as lipid droplets or assembled into VLDL to enter BA circulation. Cholesterol is another form of fat in the liver that maintained in two forms, FC and CE, and a sustainable conversion between these two forms occurs with the help of ACATs and CEH. The intrahepatic circulation of cholesterol relies on CE from the intestinal absorption of FC. Intrahepatic glucagon is decomposed based on ATL, which contributes to the production of acetyl-CoA and FC. The activation of LDLR facilitates the uptake of LDL-c and thus decreases the levels of circulating LDL-c, while LXR-induced transcription of Idol degrades the structure of LDLR. However, miR-148a increases the expression of LDLR, which decreases the circulating LDL-c but increases HDL-c. Activated insulin actions help decrease gluconeogenesis, and *PTPN1* gene dephosphorylates INSR to disrupt insulin actions. Moreover, *PTPN1* increases the expression of SREB1c and promote lipogenesis in the liver, which can be reversed by miR-206 and FXR-dependent BAs, and TRAF5 inhibits liver lipogenesis by suppressing JNK1. ACATs, acylcoenzyme A:cholesterol acyltransferases; ATL, adipocyte triglyceride lipase; BAs, bile acids; CD36, cluster of differentiation 36; CE, cholesteryl ester; CEH, cholesteryl ester hydrolase; CRR, chylomicron remnant receptor; FAs, fatty acids; FATPs, fatty acid transport proteins; FC, free cholesterol; FXRs, farnesoid X receptors; GLUTs, glucose transporters; HDL-c, high-density lipoprotein cholesterol; INSP3R1, inositol triphosphate receptor 1; INSR, insulin receptors; JNK1, c-Jun *N*-terminal kinase 1; LDL-c, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; LXRs, liver X receptors; miR, micro RNA; NEFAs, non-esterified fatty acids; *PTPN1*, protein tyrosine phosphatase nonreceptor type 1; SCFAs, short-chain fatty acids; SHP, short heterodimer partner; SREB1c, sterol response element-binding protein 1c; TCA, tricarboxylic acid; TG, triglyceride; TK, triose kinase, TRAF5, TNF Receptor Associated Factor 5; VLDL, very low-density lipoprotein.

activate AMPK and decreased IL-33-NF-κB signaling [8], and FAHFAs may increase GLUT4 expression, *de novo* lipogenesis and insulin sensitivity [16]. Moreover, adipose tissues may play different roles under various physiological conditions, such as perivascular adipose tissue (PVAT) exerts vasodilatory and anti-inflammatory functions in lean individuals, but obesity results in PVAT inflammation, characterized by imbalance between pro- and anti-inflammatory cells as wells as adipokines [68].

HFD can lead to obesity with insulin resistance through the mTOR/S6 kinase 1 (S6K1) signaling pathway, and S6K1-deficient mice demonstrate improved insulin sensitivity through a negative response to insulin receptor substrate 1 (INSRS1) [69]. Dietary ω-3 FAs can prevent metabolic disorders through the inactivation of NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, and promote insulin sensitivity through G protein-coupled receptor 120 (GPR120) [70]. Uric acid can induce hepatic fat accumulation and insulin resistance by activating the NLRP3 inflammasome in hyperuricemia-inducing diet-fed mice [71]. Diacylglycerols (DAGs) and ceramides are considered as key factors in the inhibition of lipid-induced insulin signaling. A potential therapy for the amelioration of insulin resistance could act to either inhibit the formation of double bonds in ceramides or inhibit the production of dihydroceramide desaturase-1 (DES1) [72]. DAG-activated protein kinase C-ε (PKCε) has been reported to inhibit the activity of INSR by phosphorylating INSR at Thr^{1160} *in vitro*, and HFD-fed mice with a threonine-to-alanine mutation at the homologous residue Thr^{1150} can protect against hepatic insulin resistance but not skeletal muscle insulin resistance [73]. These findings suggest the tissue-specific importance of maintaining the integrity of INSR for insulin actions. The latest evidence has demonstrated that

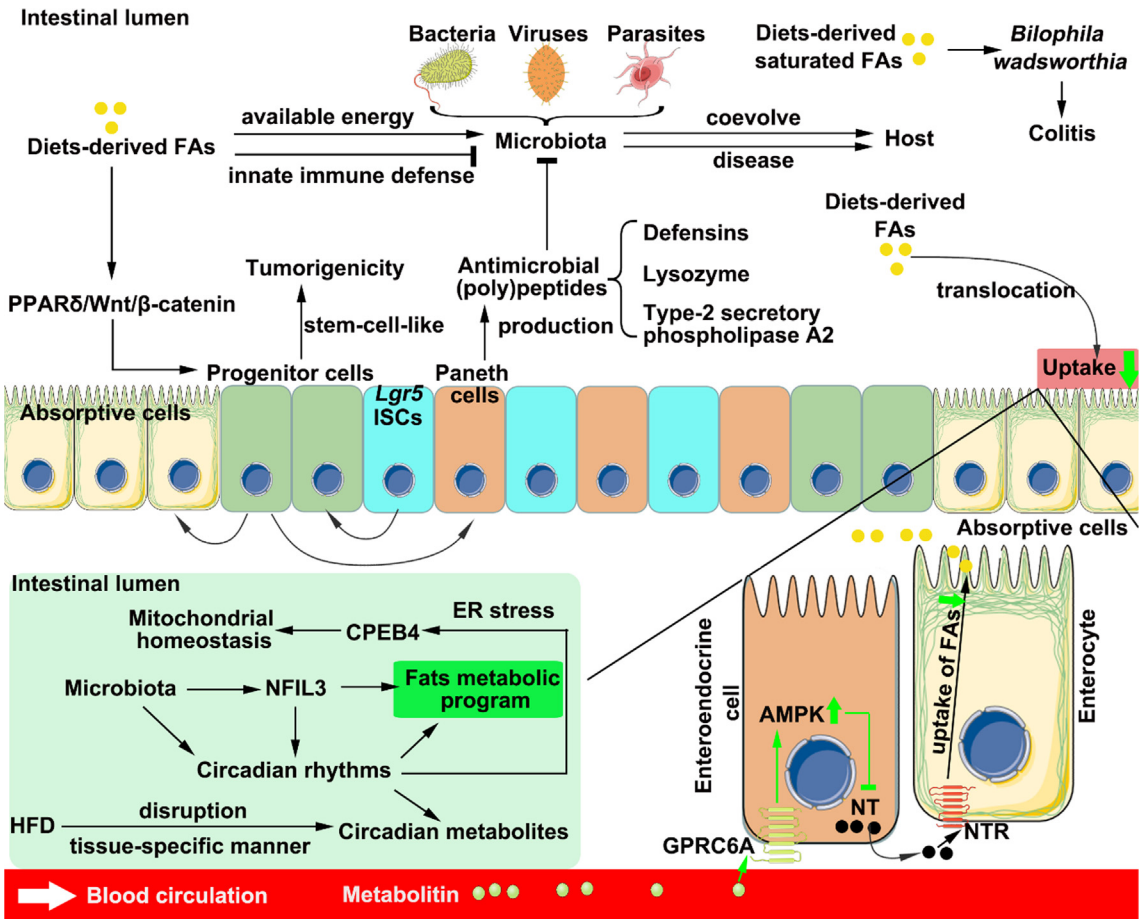

Fig. 5. Fat Metabolism in Intestines. Diets-derived FAs can induce more stem-cell-like progenitor cells through PPARδ/WNT/β-catenin signaling cascades, which cause progenitor cells to escape physiological regulation and initiate tumor formation. Fats provide intestinal microbiota with energy for growth to coevolve with the host or mediate an innate immune defense against intestinal microbiota associated digestive diseases (e.g. colitis). Homeostasis of fat metabolic program can be affected by microbiota through NFIL3 or circadian rhythms. Disrupted circadian rhythms or ER stress leads to a series of adaptive changes in a tissue-specific manner. The uptake of diet-derived fats relies on NT-stimulated NTR signaling. Activate AMPK in enteroendocrine cells through GPRC6A can reduce the production of NT and FA uptake in enterocytes. AMPK, AMP-activated protein kinase; CPEB4, cytoplasmic polyadenylation element-binding 4; ER, endoplasmic reticulum; FAs, fatty acids; HFD, high-fat diet; *Lgr5* ISCs, leucine-rich-repeat-containing G-protein-coupled receptor 5 intestinal stem cells; NFIL3, nuclear factor interleukin-3; NT, neurotensin; NTR, neurotensin receptor.

hepatic plasma membrane-bound *sn*-1,2-DAGs can cause hepatic insulin resistance, which promotes the translocation of the key factor PKCε to the hepatic plasma membrane. This translocation of PKCε leads to the phosphorylation of the insulin receptor at Thr^{1160} to influence subsequent cascades involved in AKT-2-mediated insulin signaling, and increases gluconeogenesis by promoting the expression of forkhead box protein O1 (FoxO1) but decreases glycogen synthesis by promoting glycogen synthase kinase-3 (GSK3) expression in rats and humans [74].

The development of insulin resistance-related lipid metabolism dysfunction involves considerable metabolic alterations and the rebuilding of host cell metabolism via a series of remodeling pathways. Hepatocytes may secrete dipeptidyl peptidase 4 (DPP4) to induce inflammatory adipose tissue macrophages and result in insulin resistance through the impaired pathway of insulin-mediated p-AKT in adipose tissue and liver [75]. Recent studies have shown that extracellular vesicles (EVs) are able to send messages between adipocytes and the liver [76]. The release of EVs can regulate the let-7e-5p/PGC-1α axis by remodeling adipose tissue via adipogenesis and lipogenesis in the liver, and short-term lipid overload led to adipogenesis induced by hepatic EVs, but long-term lipid overload led to lipogenesis, which can be reversed by the knockout of liver-specific geranylgeranyl diphosphate synthase (GGPPS) [76]. These findings suggest that acute or chronic HFD supplementation may increase the expression of GGPPS, resulting in EV production by geranylgeranylation of Rab27A, a Rab-GTPase that is responsible for the formation and release of EVs. It has also been reported that intestinal hypoxia-inducible factor-2α (HIF-2α) targets neuraminidase 3 (*NEU3*), a gene encoding key enzymes in the ceramide salvage pathway, and thus induces the production of ceramide to promote hepatic lipogenesis and insulin resistance, which ultimately inhibit hepatic β-oxidation in mice and human [77]. Skeletal muscle-specific glucocorticoid receptor knockout mice demonstrate increased muscle mass but smaller adipose tissues, which result in the depletion of plasma alanine and activate liver-fat communication by increasing the plasma levels of fibroblast growth factor 21 (FGF21), a peptide hormone that functions in FA oxidation and glucose metabolism, to activate lipolytic genes in adipose tissues and improve insulin sensitivity [78]. Moreover, lithocholic acid has also been reported to bind to vitamin D receptor (VDR) and thus accelerate the development of hepatic steatosis by promoting hepatic lipogenesis in HFD-fed mice with insulin resistance [79], whereas inactivation of endothelial cell surface expressed chemotaxis and apoptosis regulator (Ecscr) benefits insulin actions and adipose tissue angiogenesis [80].

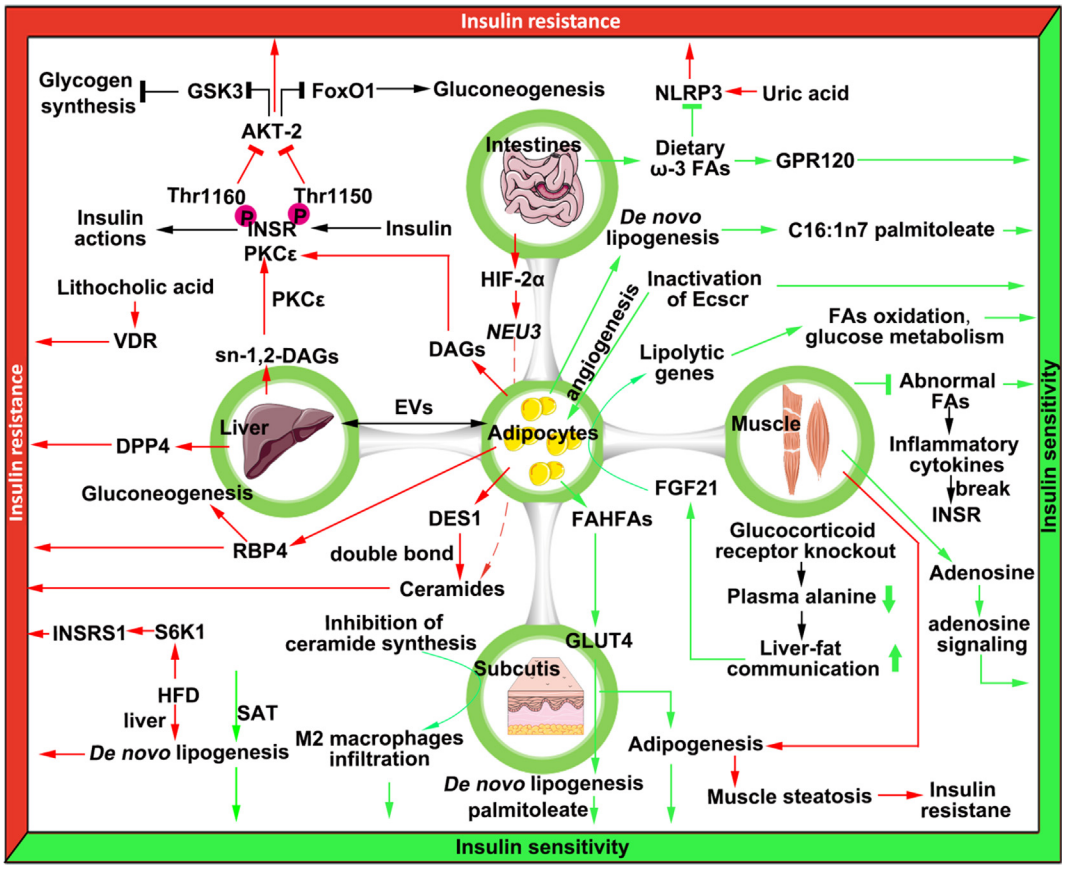

Fig. 6. Interactive mechanisms of fat deposition centering on insulin actions. Insulin actions can be activated through AKT activation based on INSR. Communications among the liver, intestines, muscle, subcutis and adipose tissue are dependent on different molecules (e.g. EVs, proteins and lipids), which affect tissue-specific or systemic insulin actions. Intestine ω-3 FAs benefits insulin sensitivity, while HIF-2α may lead to insulin resistance. Hepatic plasma membrane-bound *sn*-1,2-DAGs or adipocyte-produced DAGs can recruit or activate PKCε, which disrupts the integrity of INSR and leads to insulin resistance. Due to a tissue-specific mechanism, the beneficial effect of *de novo* lipogenesis in SAT (with increased levels of insulin-sensitizing palmitoleate) are in contrast to the detrimental effect of *de novo* lipogenesis in the liver (with increased TG level, insulin resistance and metabolic syndromes). Likewise, the beneficial effects of adipogenesis in SAT (with higher lipid buffering capacity) are in contrast to the detrimental effects of adipogenesis in muscle (with more fat infiltrates and muscle steatosis). AKT-2, serine/threonine protein kinase-2; DAGs, diacylglycerols; DES1, dihydroceramide desaturase-1; DPP4, dipeptidyl peptidase 4; Ecscr, endothelial cell surface expressed chemotaxis and apoptosis regulator; EVs, extracellular vesicles; FAHFAs, fatty acid esters of hydroxy fatty acids; FGF21, fibroblast growth factor 21; FoxO1, forkhead box protein O1; GLUT4, glucose transporter 4; GPR120, G protein-coupled receptor 120; GSK3, glycogen synthase kinase-3; HFD, high-fat diet; HIF-2α hypoxia-inducible factor-2α; INSR, insulin receptors; INSR, insulin receptors; INSRS1, insulin receptor substrate 1; NEU3, neuraminidase 3; NLRP3, NOD-like receptor family pyrin domain containing 3; PKCε, protein kinase C-ε; RBP4, retinol binding protein-4; SAT, subcutaneous adipose tissue; S6K1, S6 kinase 1; VDR, vitamin D receptor.

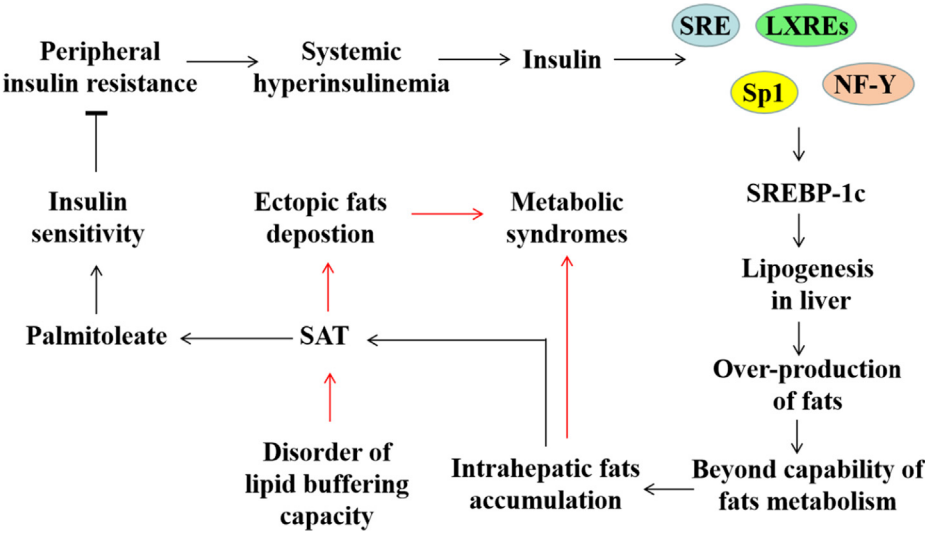

Fig. 7. Insulin actions in regulating fat deposition and metabolism. LXREs, LXR response elements; NF-Y, nuclear factor-Y; SAT, subcutaneous adipose tissue; Sp1, specificity protein 1; SRE, sterol response element; SREBP-1c, sterol-regulatory-element-binding protein-1c.

Outlook

Insulin resistance can reduce glucose utilization in cells, and the compensatory excessive secretion of insulin leads to hyperinsulinemia. As shown in Fig. 7, peripheral insulin resistance and the accumulation of glucose in the blood promote the vicious spiral of systemic hyperinsulinemia, which accelerates the lipogenesis pathway in the liver with the transcription of SREBP-1c via the full complement sites of the sterol response element (SRE), LXR response elements (LXREs), specificity protein 1 (Sp1) and nuclear factor-Y (NF-Y). Hyperinsulinemia-induced lipogenesis and FA accumulation cause cytotoxicity to hepatocytes, which induces hepatocyte injury and secondary inflammation/fibrosis during fatty liver disease. As the largest and safest storage site for excess fats, subcutaneous *de novo* lipogenesis and adipogenesis serve as compensatory agents for improving insulin sensitivity by producing insulin-sensitizing fatty acid palmitoleate. This compensatorily maintains the balance of insulin actions.

Due to the tissue-specific manner, outcomes of *de novo* lipogenesis and adipogenesis differ in the SAT, liver and muscle. The intestinal microbiota and their products play important roles in fat metabolism, and insulin actions are the essential events. Although *de novo* lipogenesis in WAT ameliorates insulin resistance by producing insulin-sensitizing fatty acid palmitoleate, increased *de novo* lipogenesis in the liver increases the risk of metabolic syndromes with insulin resistance. Overload of lipid metabolic capability results in SAT fat expansion, and ectopic fat accumulation implicates impaired lipo-/adipogenesis in SAT. This may be a key measure that regulating fat deposition and metabolism in individuals.

Compliance with ethics requirements

The manuscript had no animal experiments.

CRediT authorship contribution statement

Shusong Wu: Writing – original draft, Writing – review & editing. **Jijun Tan:** Writing – original draft. **Hongfu Zhang:** Writing – review & editing. **De-Xing Hou:** Writing – review & editing. **Jianhua He:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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