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Review Article

Roles of follicle stimulating hormone and its receptor in human metabolic diseases and cancer

Di Sun[1,3*], Mingzhu Bai[1,3*], Yanyu Jiang[1,2*], Meiyan Hu[1,2], Sufang Wu[3], Wenxin Zheng[4,5], Zhenbo Zhang[1,2,3]

[1]Reproductive Medicine Center, Department of Obstetrics and Gynecology, Shanghai General Hospital, Shanghai Jiaotong University, Shanghai 200080, China; [2]Department of Obstetrics and Gynecology, Shanghai First People's Hospital, Baoshan Branch, Shanghai 201900, China; [3]Department of Obstetrics and Gynecology, Shanghai General Hospital, Shanghai 200080, China; [4]Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA; [5]Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA. [*]Equal contributors.

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Abstract: Follicle stimulating hormone (FSH) and its receptor (FSHR) play an important role in human metabolic diseases and cancer. Evidence showed that FSHR is not only distributed in ovary and testis but also in other cells or organs such as osteoclast, adipocytes, liver, pituitary cancer and so forth. Moreover, FSH is associated with lipogenesis, inflammation, insulin sensitivity, thermogenesis, skeletal metabolism, osteogenesis and ovarian cancer, all of which have been confirmed closely related to metabolic diseases or metabolic-related cancer. Therefore, FSH and FSHR may be potential therapeutic targets for metabolic diseases and metabolic-related cancer. Epidemiological researches revealed close relationship between FSH/FSHR and metabolic diseases or cancer. Experimental studies elucidated the underlying mechanism both in vivo and in vitro. We reviewed the recent researches and present an integrated framework of FSH/FSHR and metabolic diseases and cancer, which provides potential targets for the treatments of metabolic diseases and cancer.

Keywords: Follicle stimulating hormone/receptor, lipogenesis, inflammation, insulin resistance, thermogenesis, skeletal metabolism

Introduction

Follicle stimulating hormone is a glycoprotein polypeptide secreted by anterior pituitary gland, which is commonly considered involving in human growth, development, pubertal maturation and reproduction [1]. It is a heterodimer consisting of an alpha unit and a beta unit. The alpha subunit of FSH consists of 92 amino acid, and it is identical to the alpha subunits of luteinizing hormone, thyroid-stimulating hormone and human chorionic gonadotropin (HCG). The beta subunit of FSH consists of 111 amino acids which endows FSH with the ability to combine FSHR and exerts its specific biological function. FSHR is a G-coupled receptor (GPCR) generally expressed in gonads, namely ovary and testis [2]. Recently, emerging studies have revealed that FSHR is universally expressed in various cells and tissue, including osteoclast [3-7], adipocytes [8, 9], liver [10], pituitary cancer [11] and so on.

A range of studies have shown that FSH is a pivotal regulator for lipogenesis, inflammation [12, 13], insulin sensitivity [13], thermogenesis [14], skeletal metabolism and osteogenesis and so forth. FSH should not be ignored in the development of obesity, cardiovascular disease (CVD), osteoporosis, diabetes, etc. Additionally, accumulating studies have proved the regulative role of FSH in these diseases. Therefore, we conclude that FSH is an important regulator for metabolic disorders and it might be a potential target for relevant metabolic diseases.

FSHR expression in multiple organs related to metabolic diseases

It's generally considered that FSHR is located in gonads, furthermore, merging evidence

revealed that FSHR is also expressed in adipose tissue, liver, bone and even in the endothelium of intra- and/or peritumoral blood vessels of various cancers including ovarian cancer, human pituitary adenomas, adrenal tumors and thyroid tumors (**Figure 1**, Key Figure) [15].

FSHR in ovary

It is generally believed that FSH, performing a function through FSHR in ovary, stimulates the maturation of oosphere and regulates ovulation. What's more, FSH promotes and maintains bone matrix metabolism by stimulating estrogen secretion with the help of FSHR in granulosa cells [16, 17]. Apart from healthy ovary, FSHR is also expressed in fallopian tubal epithelium and ovarian epithelial tumors (OET) [15, 18, 19]. Deepa Bhartiya and Jarnail Singh have revealed that the interaction of FSH and FSHR3 in ovary surface epithelium triggers the proliferation of ovarian stem cell, and the interference of FSH-FSHR-stem cells signaling results in the stagnation of stem cell proliferation, leading to the premature ovary failure (POF). Conversely, persistent stimulation of FSH-FSHR-stem cells is associated with ovarian cancer because of the everlasting proliferation of the ovarian stem cells [20]. Our research also agrees with this conclusion. We found that FSH promotes the proliferation and differentiation of the cancer cell through OCT4-mediated Notch, Sox2 and Nanog upregulation [21]. Our previous investigation showed decreasing prohibitin and RII-β production and elevated HER-2/neu, C-Myc and EGFR expression in benign OET cells after overexpressing FSHR, comparable with the level of malignant ovarian epithelial cancer (OEC) cells, which indicates a potential pathway stimulating OET cells proliferation and invasion through FSH [22]. In subsequent studies, we found that FSH-reactive oxygen species (ROS)-Nrf2-hypoxia inducible factor 1α (HIF1α)-vascular endothelial growth factor (VEGF) pathway is associated with angiogenesis in ovarian cancer [21]. Furthermore, we found that FSH and FSHR are capable of motivating the migration and invasion in OEC cells via phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt)-Snail signaling pathway. Additionally, the invasive process of OEC can be attenuated by inhibiting PI3K/Akt pathway or knocking down FSHR expression [23]. Recently, it has been found that FSH promotes Gankyrin expression through activating PI3K/Akt signal pathway, which increases HIF-1α degradation and reduces the negative regulation to cyclin D1. As a result, elevated cyclin D1 prompts cancer cells proliferation [24]. Accumulating evidence suggest that ovarian cancer is an immunogenic tumor, which opens up the possibility for immunotherapy to redirect T cells into ovarian cancer cells. However, lacking of specific target is bound to result in serious side effect [25-32]. It is believed that FSHR is normally expressed in most ovarian cancer types but it can hardly be found in any ovarian healthy tissues. Therefore, they creatively provide FSHR-target T cells for immunotherapy in an effort to reduce the toxicity and side effect [33, 34]. Likewise, as the non-specific chemotherapy causes serious side effect, studies have been done to prove the feasibility of FSHR-target chemotherapeutic drug. Intriguingly, this process greatly reduces the chemotherapeutic side effect as well as improving the antitumor and anti-proliferation effect [24]. In summary, these researches showed that FSHR in ovary is not only closely related to neo-oogenesis and skeletal metabolism, but also involved in ovarian carcinogenesis and its development, invasion and migration.

FSHR in fat tissue and adipocytes

FSHR in fat tissue and adipocytes affects body fat and thermogenesis. FSH stimulates adipocytes to produce FSHR. FSHR regulates genes associated with lipogenesis namely Rdh10, dgat2 (related to Retinoic acid metabolism), Acsl3, Dci (related to Fatty acid metabolism), AdipoQ, lipoprotein lipase (Lpl), RarB (related to PPAR [peroxisome proliferator-activated receptor] signaling pathway), and fatty acid synthase (Fas, relate to inflammation and insulin resistance) [35]. FSHR promotes lipogenesis and lipid accumulation through regulating these genes. According to previous studies, combination of FSH and FSHR promotes the production of lipid droplets in preadipocytes and the expression of genes related to lipogenesis including: peroxisome proliferator-activated receptor γ (PPARγ, link to the metabolism of fatty acids and triglycerides), CAAT/enhanced binding proteins α (C/EBPα), FAS, Lpl and perilinpin [36]. Further research revealed that FSH regulates lipogenic genes through Ca^{2+}

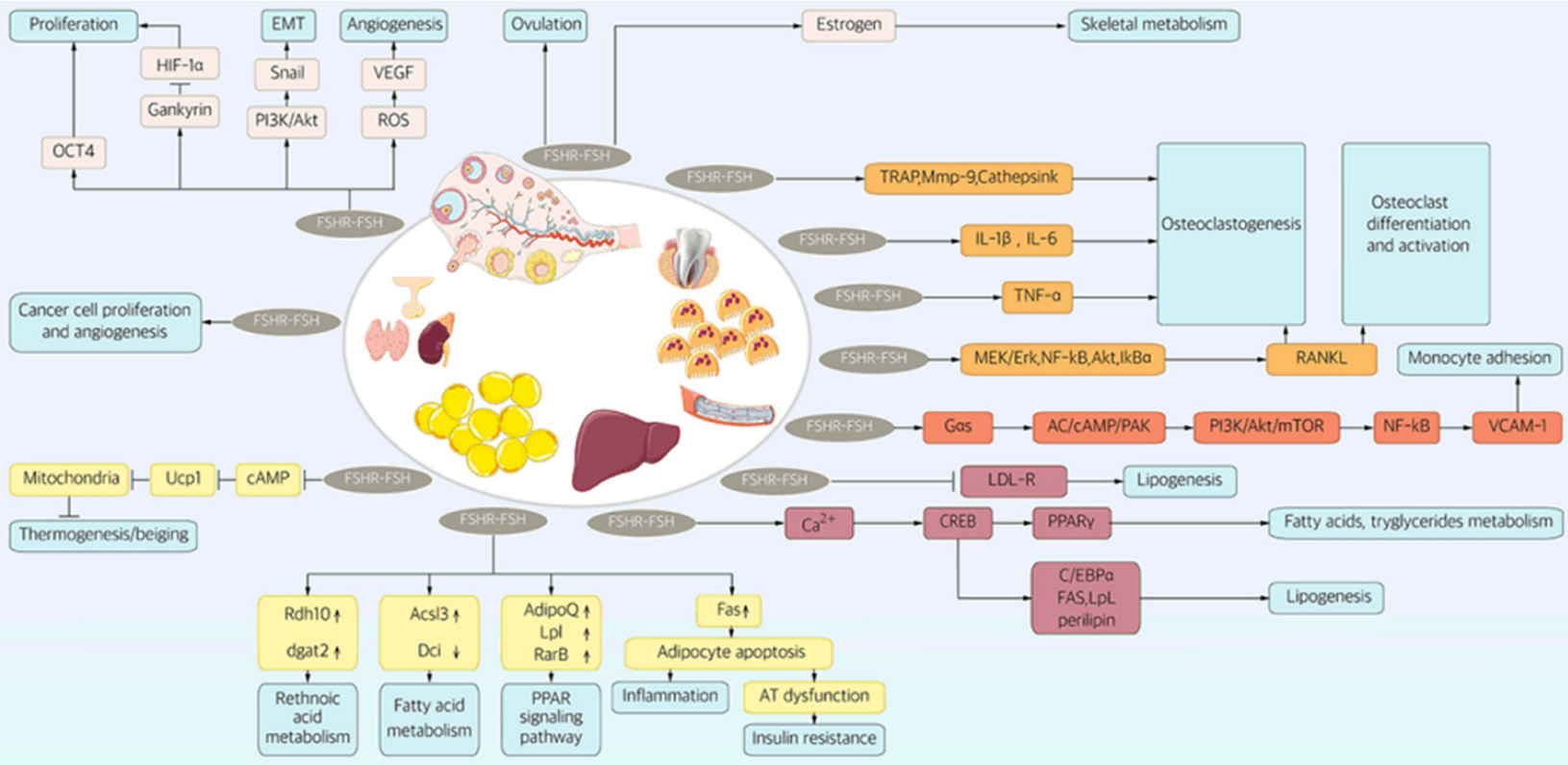

Figure 1. FSHR is expressed in multiple organs related to metabolic diseases and FSH/FSHR participates in the regulation of cellular activities and metabolic processes. FSHR in adipose tissue regulates thermogenesis/beiging of white adipocytes through cAMP-Ucp1-mitochondria pathway. Also, it regulates retinoic acid metabolism, fatty acid metabolism, PPAR signaling pathway and adipocyte apoptosis by regulating Rdh10, dgat2, Acsl3, Dci, AdipoQ, Lpl, RarB and Fas respectively. Meanwhile, FSHR upregulates Ca^{2+} and CREB by binding with FSH. CREB can not only promotes lipogenesis through upregulating C/EBPα, Fas, Lpl and perilipin, but also increase fatty acids and tryglyceride level by activating PPARγ signaling pathway. FSHR in liver and HepG2 cells regulates LDL-R and reduces the endocytosis of LDL-C, which then contributes to lipid accumulation. The binding of FSH to FSHR in vascular endothelial cells activates Gαs, AC/cAMP/PAK, PI3K/Akt/mTOR, NF-kB and VCAM-1 successively, and finally causes monocyte adhesion. FSHR in osteoclast and their precursors enhances MEK/Erk, NF-kB, Akt and Ik-Bα phosphorylation, which then promotes RANKL induced osteoclastogenesis and osteoclast differentiation and activation. Besides, FSHR promotes osteoclast differentiation and activation through TRAP, MMP-9, CathepsinK, IL-1β, IL-6 and TNF-α. FSHR in the ovary is associated with oosphere stimulation and ovulation, and modulate skeletal metabolism by regulating estrogen. FSHR in ovarian epithelial tumors stimulates OCT4 and Gankyrin induced cancer cell proliferation and also enhances EMT through PI3K/Akt-Snail signaling pathway. Also, FSHR upregulates VEGF and angiogenesis in ovarian cancer by triggering ROS expression. FSHR in non-gonadal endocrine tumors is supposed to be involved in cancer cell proliferation and angiogenesis.

dependent signaling pathway and cAMP-response-element-binding protein (CREB) [36].

Apart from promoting lipogenesis, FSH also inhibits thermogenesis and beiging of white adipocytes through the downregualtion of the expression of cyclic adenosine monophosphate (cAMP), uncoupling protein1 (Ucp1: induces the biogenesis of mitochondrial) and mitochondrial density. This, in turn, induces obesity (the reduction in mitochondrial density brings about the decrease in beiging which leads to the accumulation of white adipose tissue, and finally induces the body fat) [14].

In general, FSH and FSHR induces lipogenesis directly or indirectly (through FSH-Ca^{2+}-CREB pathway) while FSH-cAMP-Ucp1 signaling pathway induces obesity by reducing thermogenesis and beiging of white adipocytes.

FSHR in liver and HepG2

FSHR is also expressed in liver and HepG2 cells. FSH increases total cholesterol in serum and increases the level of low-density-lipoprotein cholesterol (LDL-C) by inhibiting the expression of LDL receptor (LDLR), both of which increase the incidence of CVD [10, 37, 38]. In conclusion, FSH reduces LDL resorption and induces cholesterol production, and the increasing serum LDL and cholesterol level are the acknowledged risk factors of CVD.

FSHR in bone and osteoclast

L. Sun et al. have identified FSHR in human and mouse osteoclast and their precursors. The activation of FSHR leads to the enhancement of the phosphorylation of MEK/extracellular regulated protein kinases (Erk), the nuclear factor kappa-light-chain-enhancer of the activated B cells (NF-kB) and the Akt (receptor activator of nuclear factor kappa B ligand (RANKL) sensitive kinases), thereupon transduces the proresorptive action of RANKL that contribute to hypogonadal (high FSH) osteoporosis [4]. RANKL, tartrate-resistant acid phosphatase (TRAP), matrix metallopetidase 9 (MMP-9) and Cathepsin K are associated with osteoclastic phenotypes and function, which is responsible for the differentiation of osteoclast. FSH stimulates these cytokines to favor the differentiation of osteoclast and contribute to bone loss [4, 6].

Periapical periodontitis is featured with periapical bone loss. HUA QIAN et al. reported that FSH aggravates salceolar bone loss in periodontitis [5]. FSH administration significantly increases RANKL expression while the osteoprotegerin (OPG) levels are relatively stable, which results in the increase of RANKL/OPG ratio, this, in turn increased bone resorption and bone loss in periapical periodontitis. FSH also stimulates macrophages and granulocytes to produce TNF-α in the bone marrow. TNF-α triggers osteoclastogenesis and promotes osteoclast differentiation and activation through cooperating with IL-1 and RANKL. Moreover, FSH triggers osteoresorptive cytokine IL-1β expression as well, which affects the density of bone mineral. As described above, FSH promotes osteoclast differentiation and activation through variant cytokines and RANKL, meanwhile, it stimulates osteogenesis through RANKL pathway, both of which contribute to osteoporosis.

FSHR in non-gonadal endocrine tumors

FSHR is expressed in non-gonadal endocrine tumors such as human pituitary adenomas, adrenal tumors and thyroid tumors [39, 40]. According to Marek Pawlikowski, immunostaining of FSHR in pituitary adenomas, benign and malignant adrenal tumors and thyroid cancer and benign lesions mostly is positive in the endothelium of intra- and/or peritumoral blood vessels, which indicates that the FSHR relates to cancer cell proliferation and angiogenesis [11]. In summary, FSHR should not be ignored in the carcinogenesis, angiogenesis, proliferation, invasion and migration of non-gonadal endocrine tumors.

In a nutshell, FSHR is expressed in multiple metabolic-related organs and it plays an important role in the development of human life, including neo-oogenesis, skeletal metabolism, lipogenensis, thermogenesis, beiging, cholesterol and LDL production and resorption, osteogenesis; and it also plays a vital part in carcinogenesis, angiogenesis, proliferation, invasion and migration of ovarian cancer and non-gonadal endocrine tumors.

The metabolic phenotypes of different FSH and FSHR status

Significant changes in metabolic phenotypes have been identified in different FSH and

Table 1. The metabolic phenotypes of different FSH and FSHR status

Dispose	FSH/FSHR status	Metabolic status	References
$FSHR^{+/-}$	FSHR↓	Body fat↓	[14]
		LM/TM↑	[14]
		BMD↑	[14]
FSHR antibody	FSHR↓	Body fat↓	[14]
		LM/TM↑	[14]
		BMD↑	[14]
OVX[a]	FSH↑	TC[b], LDL-C[c]↑	[10]
OVX+GnRHa+FSH	FSH↑	TC, LDL-C↑	[10]
OVX+GnRHa	FSH↓	TC, LDL-C↓	[10]
$FSHR^{-/-}$	FSHR↓	Prevent bone loss	[3]
$FSH\beta^{-/-}$	FSH↓	Prevent bone loss	[3]
$FSH\beta^{+/-}$	FSH↓	Prevent bone loss	[3]
OVX	FSH↑	Induce bone loss	[5]
OVX+LE	-	Reduce bone loss by OVX	[5]
FSH adoption	FSH↑	EMT[d] of EOC[e]↑	[23]
FSHR re-expression	FSHR↑	EMT of EOC↑	[23]
FSHR depletion	FSHR↓	EMT of EOC↓	[23]

a: ovariectomy; b: total cholestoral; c: low-density-lipid; d: epithelial-mesenchymal transition; e: epithelial ovarian cancer.

FSHR status (**Table 1**). Knocking down of FSHR ($FSHR^{+/-}$) and adopting of FSHR antibody exhibits identical transition in body fat and thermogenesis. For instance, FSHR antibody treatment in mice reduces body fat and increases lean mass/total mass (LM/TM) ratio accompanied with significant augment in bone mineral density (BMD), FSHR deficient mice exhibit the same phenotype as antibody treatment [14].

Inversely, after ovariectomy, FSH in mice increases because of negative feedback mechanism, and the serum TC and LDL-C levels elevate equally. Ovariectomy+GnRHa+FSH elevates FSH levels through administration of exogenous FSH and at the same time excludes the effects of other gonadal hormone (especially estrogen). Similarly, the increase of the FSH level induces both the serum TC and LDL-C expression and leads to lipid metabolism disorder. Accordingly, ovariectomy+GnRHa blocks FSH secretion and reduces serum TC and LDL-C level, which sequentially reduces lipogenesis in mice [10].

Hypogonadal FSH receptor null mice ($FSHR^{-/-}$) and FSH null mice ($FSH^{-/-}$) both prevent bone loss and even elevate bone mass by reducing bone resorption, whereas eugonadal FSHβ haplodeficiency ($FSH\beta^{+/-}$) increases bone mass in spine and femur [3]. We attribute the elevation of bone mass in eugonadal $FSH\beta^{+/-}$ mice to the normal secretion of estrogen (estrogen loss is the main reason of bone loss in postmenopausal women) and the reduced FSH-FSHR combination, while hypogonadal $FSHR^{-/-}$ and $FSH^{-/-}$ mice are severely hypogonadal which reduces or even blocks estrogen secretion in a large scale, and reduces its ability to prevent bone loss.

With high serum FSH levels, ovariectomized mice were induced bone loss seriously, especially in lumbar spine area [3]. Ovariectomy also exacerbates bone loss in periapical lesions. Consistently, administration of FSH inhibitor leuprorelin (LE) reduced bone loss [5].

When adopted with FSH or transfected with FSHR-plasmid, epithelial ovarian cancer cells showed increased epithelial-mesenchymal transition (EMT), namely migration and invasion. On the contrary, knocking down of FSHR inhibited the invasion and migration by blocking PI3K/Akt pathway [23].

FSH expression or level in patients with metabolic diseases

As described above, FSHR is expressed in diverse organs and tissues involved in adipogenesis, neo-oogenesis, skeletal metabolism and carcinogenesis. Additionally, modification of FSHR and FSH in mice or human plays an important role in metabolic status. Therefore, metabolic diseases show corresponding changes in FSH level (**Table 2**). It is widely acknowledged that menopausal osteoclast is closely associated with high FSH level. Likewise, the elevation of FSH is observed in menopausal periapical periodontitis [5, 41, 42]. Polycystic ovarian syndrome (PCOS) is featured with hyperandrogenism, chronic anovulation, and defect in glucose homeostasis accompanying reduced FSH level [43-47].

Catherine Kim et al. have reported that obesity is related to low FSH level. However, as described before, high FSH level brings about

Table 2. FSH expression or level in patients with metabolic diseases

Metabolic disease	FSH level	References
Osteoporosis	↑	[41, 42]
Periapical periodontitis	↑	[5]
PCOS[a]	↓	[43-47]
Obesity	↓	[48, 49, 80, 81]
CVD[b]	↓	[51]
NAFLD[c]	↓	[52]
Diabetes	↓	[53-55]

a: polycystic ovarian syndrome; b: cardiovascular disease; c: non-alcoholic fatty liver disease.

the increase in body mass. Therefore, we hypothesize that high level of FSH induces obesity, and the increased mesenchymal adipose tissue facilitates the production of endogenous estrogen, which reduces FSH level through negative feedback [48].

Previous studies found that postmenopausal women with higher BMI have lower FSH level, indicating negative correlation between FSH level and obesity in postmenopausal women [49]. In the meantime, Kim C et al. have found that weight loss in overweight and obese postmenopausal women can increase FSH level. Hetemaki N et al. explained it with elevated endogenous estrogen produced by mesenchymal adipose tissue [48, 50]. Researches described above corroborate our hypothesis that high FSH level leads to postmenopausal obesity, which in turn promotes endogenous estrogen production, and an increased estrogen reduces FSH level through negative feedback (FSH-obesity-estrogen-FSH regulatory loop). Decreased FSH is also found in diabetes, non-alcoholic fatty liver disease (NAFLD) and CVD attributed to obesity [51-55].

Diverse role of FSH in metabolic diseases and cancer

As mentioned above, FSHR is expressed in metabolic-related organs and conversion of FSH level is found in metabolic diseases, which suggest close relationship between FSH and metabolic diseases. Here, we review recent data demonstrating the important role of FSH in metabolic diseases (**Table 3**).

FSH and obesity

The consumption of adipose and the increase of thermogenesis are two vital pathways to reduce body weight. On the contrary, accumulation of adipose and reduction of thermogenesis both contribute to obesity (**Figure 2**).

FSH and adipose accumulation

Previous studies revealed that FSH triggered FSHR in adipocytes, which affects genic expression associated with retinoic acid metabolism (Rdh10, dgat2), fatty acid metabolism (Acsl3, Dci), PPAR signaling pathway (AdipoQ, Lpl, RarB), inflammation and insulin sensitivity (Fas) [9, 56]. Fas is one of the members of tumor necrosis factor (TNF) family, and it induces apoptosis in various cells [57-59]. Once Fas induces adipose cell apoptosis, it impairs insulin sensitivity and obstructs lipolysis and glucose uptake, which contributes to lipid accretion and obesity. What's more, Fas effectively upregulates inflammatory cytokines (IL-1β, IL-6, MCP-1), which contributes to adipose tissue dysfunction and lipid accumulation [12, 13]. Another research shows that FSH induces lipid droplets formation through CREB-PPARγ/C/EBPα/FAS/Lpl/perilinpin pathway, what's more, FSH-Ca^{2+} signaling pathway upregulates CREB [36]. In general, FSH induces lipogenesis by affecting multiple genes in lipid metabolism, and results in adipose accumulation.

FSH and thermogenesis

The consequence described above confirmed that FSH promotes obesity by increasing adipose. Accordingly, we speculate that dosing with FSHR antibody (compared to mice dosing with IgG) will cut down body weight in mice with high fat diet. Nonetheless, there exists no difference between these two groups, indicating FSHR antibody does not protect mice with high fat diet from obesity by lessening accumulation of adipose. Therefore, it probably works through encouraging thermogenesis. Further studies revealed that FSHR antibody helps cut down body fat and increases LM/TM while reduces FM/TM compared with the adoption of IgG. Most importantly, mice treated with FSHR antibody have decreased white adipose tissue (WAT) in visceral and subcutaneous tissue. By the same token, $FSHR^{+/-}$ mice resembles phenotypes with mice in the adoption of FSHR antibody, suggesting that this change is working through FSH related pathway. In-depth study revealed the potential mechanism in FSH induced obesity. Firstly,

Table 3. Diverse roles of FSH in metabolic diseases

Metabolic disease	Signaling pathway	Effect	References
Obesity	FSH-c AMP-Ucp1	Thermogenesis/beiging of white adipocytes	[9]
	FSH-Rdh10/dgat2	Lipogenesis	[56]
	FSH-Acsl3/Dci		[56]
	FSH-AdipoQ/Lpl/RarB		[56]
	FSH-Ca^{2+}-CREB[a]-PPARγ/C/EBPα/FAS/Lpl/perilinpin		[36]
	FSH-Fas	Insulin resistance	[12, 13]
	FSH-Fas-IL-1β/IL-6/MCP-1	Inflammation	[12, 13]
CVD[b]	FSH-LDLR-LDL-C	Lipogenesis	[10]
	FSH-Rdh10/dgat2		[56]
	FSH-Acsl3/Dci		[56]
	FSH-AdipoQ/Lpl/RarB		[56]
	FSH-Fas	Insulin resistance	[12, 13]
PCOS[c]	FSH-NFkB/AP2-AMH-aromatase activity	Skeletal metabolism	[60]
	FSH-NFkB/AP2-AMH-follicular growth	Infertility/polycystic ovary	[60]
EOC[d]	FSH-stem cell	Proliferation	[20]
	FSH-OCT4-Notch, Sox2, Nanog	Proliferation and differentiation	[21]
	FSH-ROS-Nrf2-HIF1α-VEGF	Angiogenesis	[68]
	FSH-PI3K/Akt-Snail	EMT[e]	[23]
	FSH-PI3K/Akt-Gankyrin-HIF1α-Cyclin D1	Proliferation	[24]
	FSH-TRPC3	Proliferation	[67]
Periapical periodontitis	FSH-RANKL	Osteogenesis	[5]
	FSH-RANKL/TNF-α/IL-1β/IL-6	Osteoclast differentiation	[5]
Osteoporosis	FSH-MEK/Erk/NFkB-RANKL	Osteogenesis	[3]
	FSH-RANLK/TRAP/MMP9/CathepsinK/TNF-α/IL-1β/IL-6	Osteoclast differentiation	[4]
T2DM	FSH-Fas	Insulin resistance	[12, 13, 53, 75]
	FSH-adipogenesis	Adiposity	[9, 53]
NAFLD	FSH-Fas	Insulin resistance	[12, 13]
	FSH-adipogenesis	Adiposity	[9, 53]

a: cAMP-response-element-binding protein; b: cardiovascular disease; c: polycystic ovarian syndrome; d: epithelial ovarian cancer; e: epithelial mesenchymal transition.

FSH antibody triggered cAMP via Arb3 signaling, which in turn activated Ucp1 expression in mice. Likewise, FSH deficient mice resemble the phenotypes of antibody treated mice by the increasing density of Ucp1 and beige-like adipocytes in white adipose tissue. What's more, these mice have shown increased mitochondrial density in both WAT and BAT, which increases thermogenesis in BAT and induces beiging in WAT and together prevents mice from obesity. Conversely, FSH-FSHR combination inhibits Ucp1 by blocking cAMP, and through the same pathway weakens BAT thermogenesis and WAT beiging which results in obesity [9].

FSH and estrogen

As described above, FSH induces obesity via thermogenesis and accretion of adipose. For this reason, we assume that obese patients have high FSH level. Interestingly, most obese patients possess relatively lower FSH level than non-obese patients. To explain it, we hypothesize that the increased mesenchymal adipose induced by high FSH level promotes estrogen production, which in turn inhibits FSH expression.

FSH and cardiovascular disease (CVD)

Cardiovascular disease is closely related to lipogenesis, obesity and insulin resistance. As illustrated before, high FSH along with high FSHR level leads to lipid accumulation via various pathways. Besides, FSH induces adipose tissue accumulation and obesity through interfering thermogenesis and beiging. Importantly, lipid accumulation and obesity play a vital role in CVD development [9] (**Figure 3**). Additionally, OVX mice with elevated FSH level tend to have reduced LDLR in liver and HepG2 cells. As LDLR in favor of endocytosis of LDL-C, this subsequently results in high LDL-C level [10]. Consistent with this result, postmenopausal women have high LDL-C level, which we attri-

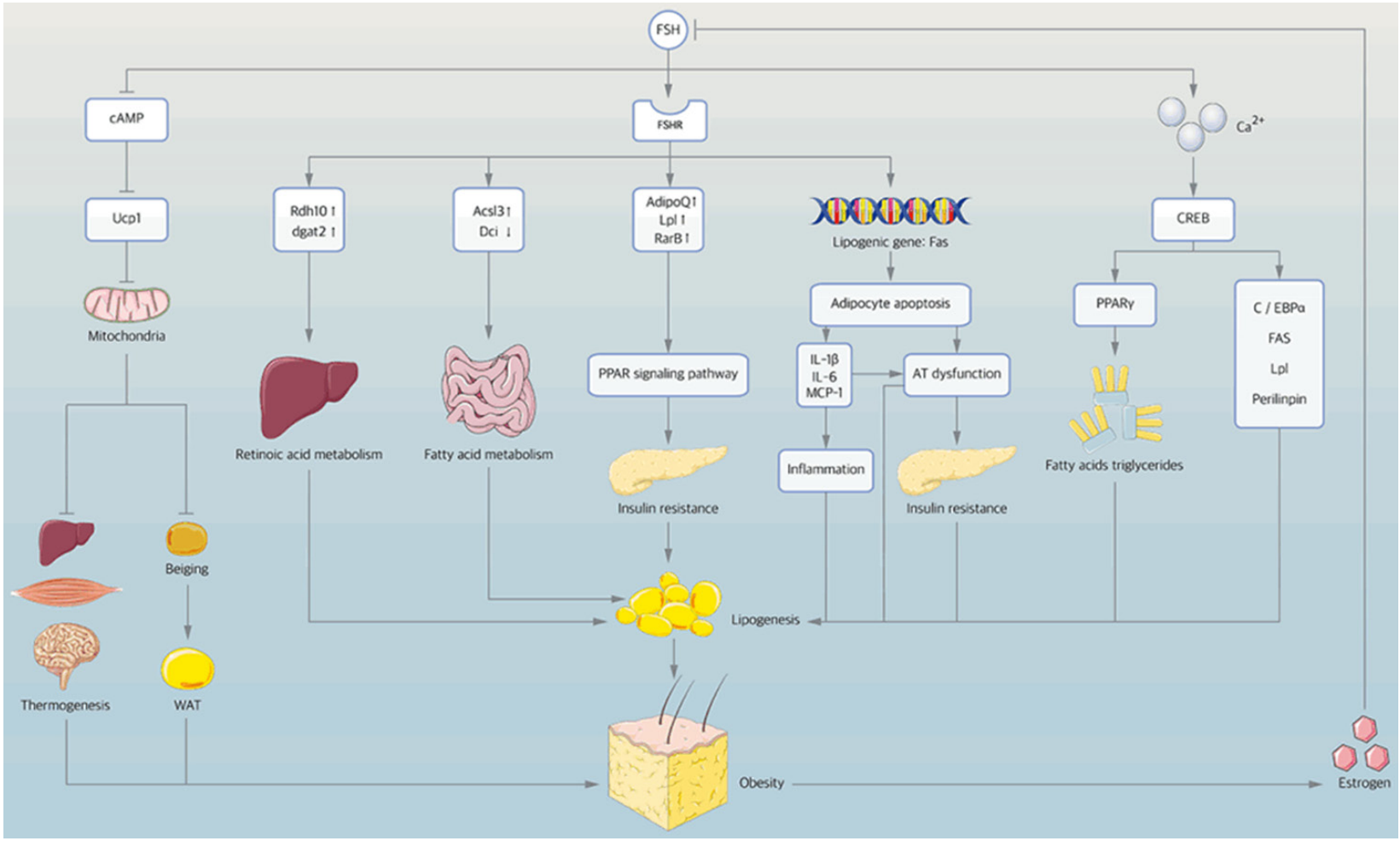

Figure 2. FSH and obesity. FSH upregulates FSHR in adipocytes, and consequently affects multiple genes expression, which in turn triggers lipogenesis over various pathway including retinoic acid metabolism, fatty acid metabolism, insulin resistance, inflammation and adipose tissue dysfunction. FSH activates Ca^{2+} and then activates CREB-PPARγ/C/EBPα/FAS/Lpl/perilinpin signaling pathway for lipid biosynthesis. Meanwhile, FSH reduces thermogenesis and beiging by reducing cAMP, Ucp1 and mitochondrial density.

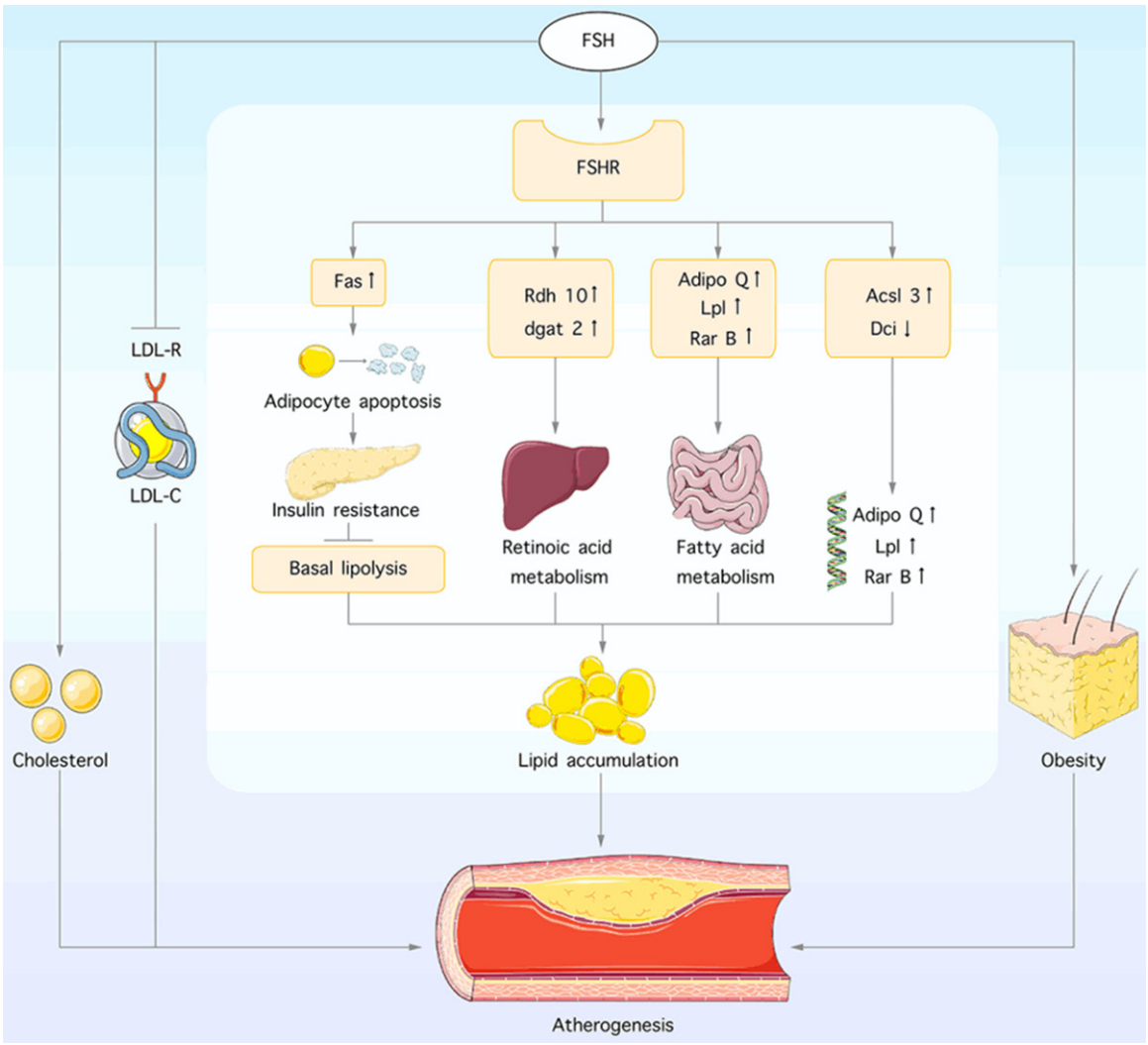

Figure 3. FSH and cardiovascular disease (CVD). FSH upregulates FSHR expression in adipocytes and affects numerous lipogenic genes expression, which contribute to lipid accumulation. High level of FSH reduces LDLR in liver and HepG2 cells, which sequentially blocks the endocytosis of LDL-C and promotes LDL-C level in serum. Additionally, FSH not only increases cholesterol level but also causes obesity through multiple pathways, both of which are major etiology of CVD.

bute to the high FSH level and is proved in animal models as described above. Besides LDL-C, FSH also induces cholesterol in serum, both of which are independent risk factors of CVD [38].

FSH and polycystic ovarian syndrome (PCOS)

It is reported that FSH can block anti-Mullerian hormone (AMH) in granulosa cells and trigger follicular development. Therefore, it is reasonable to hypothesize that FSH can treat infertility by improving follicular development [60] (**Figure 4**). AMH constricts estrogen production by reducing aromatase activity and results in bone loss. FSH is pivotal for gonadal germ cell growth and development in female, and it is indispensable for follicular growth, especially granulosa cells. Accordingly, low FSH level is responsible for poor follicular development and polycystic ovary [61].

FSH and ovarian cancer

FSH is pivotal for carcinogenesis, proliferation, invasion and migration in ovarian cancer [62-66] (**Figure 5**). Ovarian epithelial stem cells, including ovarian stem cells and very-small non-embryonic like stem cells, are closely related to neo-oogenesis and primordial follicle

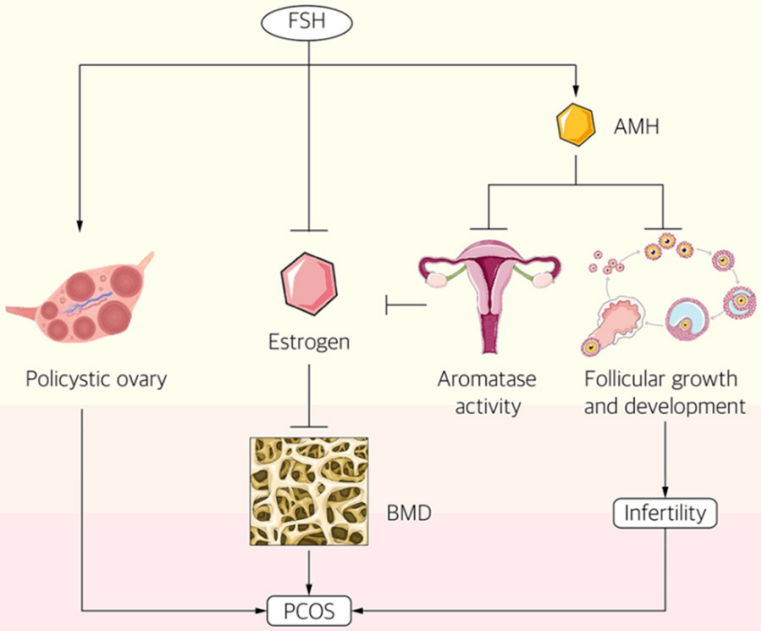

Figure 4. FSH and polycystic ovary syndrome (PCOS). FSH is closely related with multiple symptoms of PCOS. The reduced FSH level results in polycystic ovary in PCOS. Additionally, low FSH induces anti-Mullerian hormone (AMH) expression, which inhibits aromatase activity resulting in low serum estrogen and bone mineral density. More importantly, the expression of AMH prevents follicular growth and development, resulting in infertility.

assembly, therefore, overexpression of this two groups of stem cells motivates FSH-related carcinogenesis in ovary [20]. Further study revealed that FSH regulates ovarian cancer stem cell proliferation through octamer-binding transcription factor 4 (OCT4) cancer stem cell pathway [21]. Studies found that PI3K/Akt is closely related to ovarian cancer cell proliferation and invasion, and FSH regulates PI3K/Akt through transient potential channel C3 (TRPC3). PI3K/Akt pathway regulates variant molecules that participate in EMT, proliferation, differentiation and angiogenesis of ovarian cancer, including Snail, Gankyrin and HIF-1α. Snail stimulates ovarian cancer cell invasion and migration. Gankyrin stabilizes the expression of Cyclin D1 by degrading HIF-1α protein, which induces cancer cell proliferation, and Gankyrin also activates PI3K/Akt by reducing PTEN in cytoplasm [22-24, 67]. ROS-HIF1α-VEGF pathway facilitates OEC angiogenesis, which proved to be another signaling pathway associated with FSH-induced ovarian cancer development [68].

FSH and periapical periodontitis

Periapical periodontitis mainly attributes to periapical bone loss. In periapical periodontitis mice model, OVX mice had higher FSHR, RANKL, inflammatory cytokines (IL-1β, IL-6) in osteoclast than sham group. Additionally, FSH-treated group showed more obvious elevation of these cytokines than the other two control groups and the application of leuprorelin (FSH inhibitor) significantly reversed bone loss and reduced related cytokines production [5] (**Figure 6**).

FSH and osteogenesis

Perimenopausal osteoporosis has long been considered as the result of reduced estrogen production due to ovary dysfunction. However, increasing evidence showed that FSH plays an important role in bone loss independent of estrogen [6, 7, 69-72]. Researches have been done to clarify the underlying mechanism of FSH induced osteoporosis. First of all, FSH-treated human osteoclasts exhibit elevated MEK/Erk, NF-kB, Akt and NF-kB inhibitor alpha (IkBα) level. They are RANKL sensitive kinases which can activates RANKL, and RANKL promotes osteoporosis through prompting osteoclastogenesis and osteoclast differentiation [3] (**Figure 7**). Furthermore, FSH stimulates the production of TRAP, MMP-9, and Cathepsin K, which is crucial for osteoclast differentiation and activation [4]. Inflammatory cytokines, such as TNF-α, IL-6 and IL-1β, are found elevated in mononuclear cells incubated with FSH. Additionally, a series of studies indicated that TNF-α motivates osteoporosis through inducing osteoclast differentiation [73].

FSH and diabetes mellitus type 2 (T2DM)

Recent studies showed that the low FSH level is correlated with diabetes [54, 74]. Bertone-Johnson JR et al. found that FSH affects insulin resistance in older postmenopausal women and leads to incident T2DM [75]. Recent researches found the relationship between low FSH and diabetes in postmenopausal women, and attributed it to adiposity and insulin resistance [53]. In conclusion, insu-

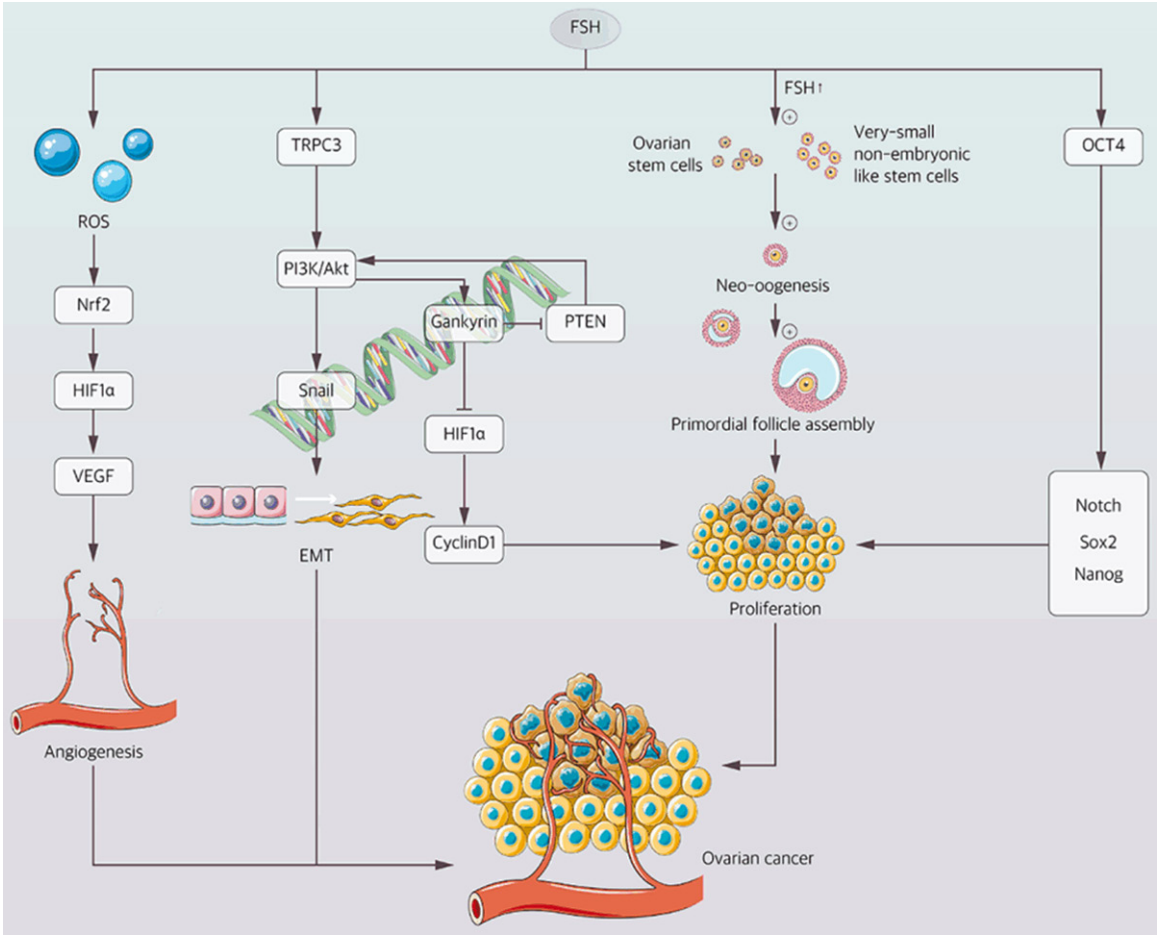

Figure 5. FSH and ovarian cancer. FSH stimulates ovarian stem cells and very small non-embryonic like stem cells, they are associated with neo-oogenesis and primordial follicle assembly in normal ovary. However, over-expressed FSH in ovarian cancer accelerates and exaggerates this process which leads to ovarian cancer cell proliferation. Additionally, OCT4 cancer stem cells signaling pathway are found stimulated in ovarian cancer, suggesting it involves in ovarian cancer cell proliferation. TRPC3 relays the signal from FSH to PI3K/Akt and its downstream target: snail, which is responsible for EMT. Meanwhile, PI3K/Akt degrades HIF-1α by stimulating Gankyrin. Gankyrin stimulates PI3K/Akt by modulating PTEN, consisting of positive feedback of PI3K/Akt signaling pathway. Furthermore, FSH interacts with ROS, leading to the upregulation of Nrf2 and HIF-1α, and in turn upregualtes VEGF level, which is associated with angiogenesis.

lin resistance and adiposity play vital roles in the relationship between FSH and T2DM.

FSH and non-alcoholic fatty liver disease

Previous researches found that NAFLD is accompanied with a lower level of FSH [76]. As described before, FSH regulates insulin sensitivity and adipogenesis. Further studies revealed that adiposity and insulin resistance contribute to FSH-induced hepatic steatosis, which causes NAFLD in women over 55 years old [9, 12, 13, 52]. Therefore, we conclude that insulin sensitivity and adipogenesis contribute to FSH relevant NAFLD.

Concluding and perspectives

According to the current studies, we reviewed multiple metabolic diseases involving in FSH and the underlying signaling pathway, which may be applied as potential targets for metabolic diseases treatments. In the past few years, scientists have found that FSH plays an essential role in increasing the body weight via multiple pathways, while epidemiological research found that postmenopausal women with obesity tend to have lower FSH levels than non-obese post-menopausal patients. Besides, the FSH level of postmenopausal women with CVD, T2DM or NAFLD tends to be

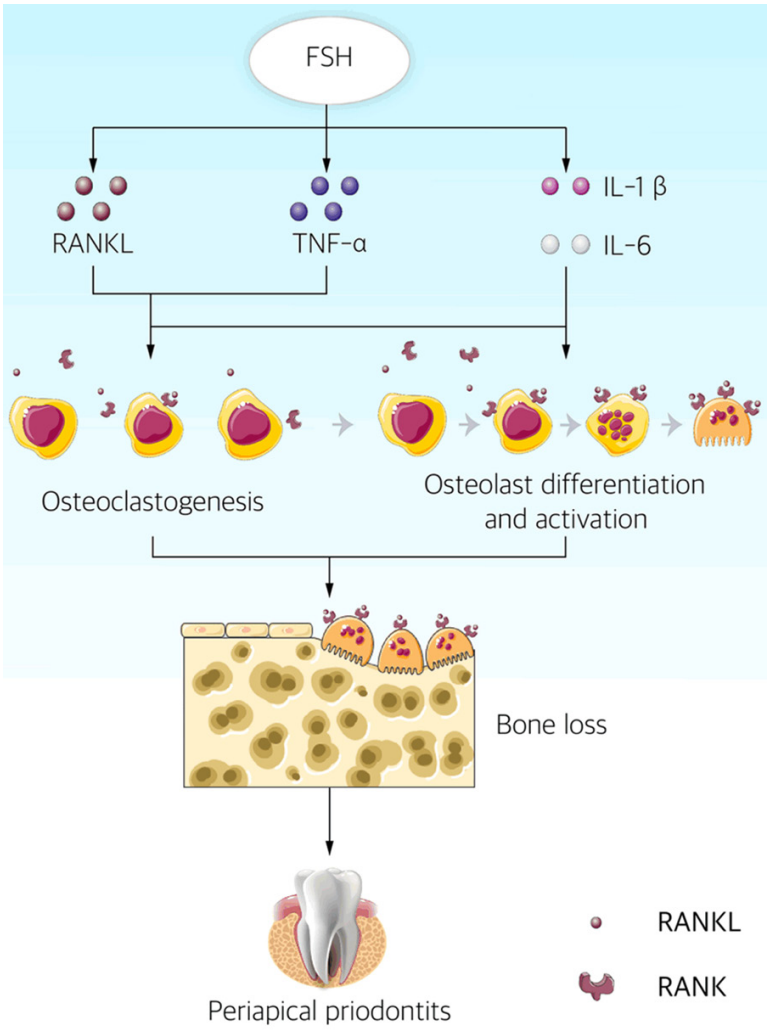

Figure 6. FSH and periapical periodontitis. Periapical bone loss is vital in the occurrence of periapical periodontitis. FSH transduces the action of RANKL and stimulates the production of TNF-α in the bone marrow, which cooperatively promotes osteoclastogenesis, osteoclast differentiation and activation. Moreover, FSH triggers osteoresorptive inflammatory cytokines IL-6 and IL-1β expression which affects the density of bone mineral. All of the above are direct causes of periapical bone resorption and bone loss.

lower than that in postmenopausal women who do not suffer from these diseases [9, 52, 77, 78]. To explain the contradictory result, we hypothesize that FSH induces obesity, and obesity increases estrogen level, which in turn reduces FSH level through negative feedback regulation. Yet, there is no research involved in this field to prove this hypothesis or to reveal new mechanisms attributing to this paradoxical consequence.

We hypothesized the possible signaling pathway by which FSH induces T2DM and NAFLD according to relevant studies, but studies with direct evidence of the pathways remains to be implemented in the future [9].

As we clarified that FSH induces metabolic diseases through multiple pathways, FSH antibody or inhibitor might be potential treatment to these diseases. Studies have reported that FSH antibody reduces adiposity while increasing BMD, also, HUA QIAN et al. discovered that FSH inhibitor leuprorelin plays a protective role in periapical bone loss. However, if the antibody or inhibitor of FSH can reverse other metabolic diseases like CVD, T2DM, NAFLD remains unclear [5, 8, 9, 79]. It is universally acknowledged that low FSH level and PCOS are interrelated, but few studies detect if supplementary exogenous FSH or FSH inducer can improve the syndrome of PCOS [61, 78]. Likewise, the elevated expression of FSHR in the endothelium of intra- and/or peritumoral blood vessels of pituitary adenomas, benign and malignant adrenal tumors and thyroid cancer and benign lesions is found in recent researches. According to Marek Pawlikowski and his team, immunostaining of FSHR in these diseases mostly happens in the endothelium of intra- and/or peritumoral blood vessels, suggesting that it is related to cancer cell proliferation and angiogenesis. Nonetheless, only a few studies focus on verifying the underlying mechanism [11].

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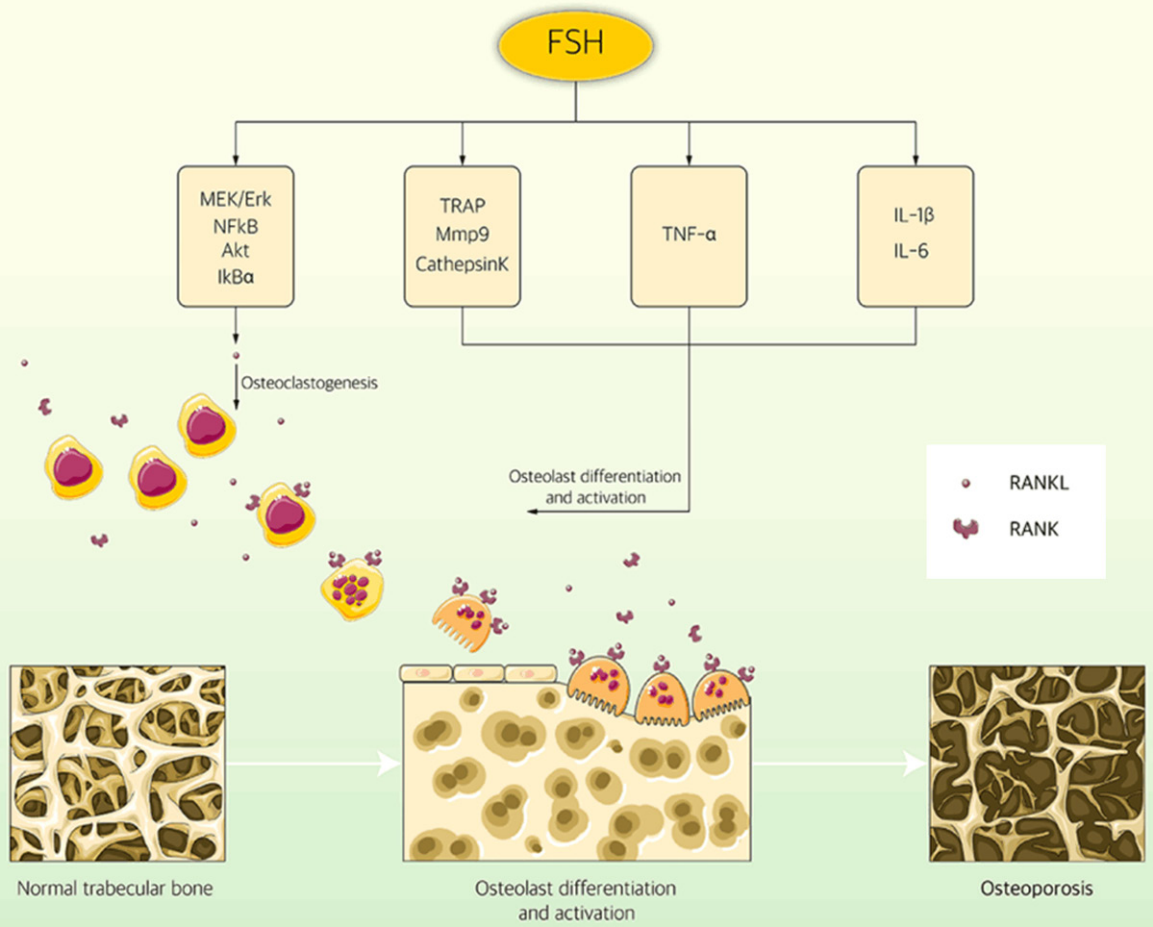

Figure 7. FSH and osteoporosis. FSH takes effects in osteoporosis with bone loss independent of estrogen. FSH activates RANKL by regulating RANKL sensitive kinases MEK/Erk, NFkB, Akt and IkBα, and RANKL plays an important role in osteoclastogenesis, osteoclast differentiation and activation. In addition, FSH can stimulate TRAP, MMP-9, CathepsinK and inflammatory cytokines including TNF-α, IL-6 and IL-1β expression, which are all vital to osteoclast differentiation and activation, in turn leading to bone loss.

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Disclosure of conflict of interest

None.

Address correspondence to: Zhenbo Zhang, Reproductive Medicine Center, Shanghai General Hospital, Shanghai Jiaotong University, 100 Haining Road, Shanghai 200080, China. Tel: +86-21-37798941; Fax: +86-21-63240090; E-mail: zhangzhenbozzb@aliyun.com

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