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Chapter 14

Ectopic fat accumulation in the liver and glucose homeostasis

Toshinari Takamura[1)], Hirofumi Misu[1)], Shuichi Kaneko[2)]

[1)] Department of Comprehensive Metabology, and [2)] Disease Control and Homeostasis, Kanazawa University Graduate School of Medical Sciences, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8641, Japan

Corresponding author: Toshinari Takamura MD, PhD,

E-mail: ttakamura@m-kanazawa.jp

Department of Comprehensive Metabology, Kanazawa University Graduate School of Medical Sciences, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8641, Japan

Tel: +81-76-265-2711; Fax: +81-76-234-4250

Abstract

Liver fat was associated not only with enhanced hepatic glucose production, but also with skeletal muscle insulin resistance, supporting a central role of fatty liver in systemic insulin resistance and existence of a network between the liver and skeletal muscle. Palmitate and cholesterol act as toxic lipids to cause hepatic insulin resistance via mitochondria-derived oxidative stress. Obesity mediated disruption in crosstalk among protein-, glucose- and lipid-metabolism pathways results in hepatic insulin resistance, enhanced gluconeogenesis and liver steatosis by impairing proteasome function. The liver plays as an endocrine organ to produce functional hepatokines and thereby mediates fatty liver-associated skeletal muscle insulin resistance through unique mechanisms. Selenoprotein P is upregulated through FoxOs and hyperglycemia, and causes resistance to insulin, angiogenesis and exericise through reductive stress. LECT2 is upregulated in satiety through AMPK inactivation, and contributes to the development of muscle insulin resistance and obesity by activating JNK and by impairing myogenesis, respectively.

Therefore, overnutrition evokes remodeling of nutrient homeostasis by toxic lipids and proteasome dysfunction in the liver. The remodeling also results in overproduction of hepatokines that disrupt inter-organ network leading to pathology of diabetes.

(10-15 lines or 150-200 words)

Keywords. 3-5 keywords

Fatty liver, insulin resistance, hepatokine, selenoprotein P, LECT2

14.1 Introduction

Insulin resistance is a core pathology of type 2 diabetes mellitus, nonalcoholic fatty liver disease (NAFLD), and cardiovascular diseases. The severity of insulin resistance may differ among the major insulin-target organs, the liver, skeletal muscle, and adipose tissue, suggesting that these organs cross-talk each other to keep whole body energy homeostasis. Disruption of inter-organ networks leads to insulin resistance. Over-nutrition is one of the major environmental factors that disrupt the inter-organ networks (1). Although obesity is less common (2), diabetes is a huge and growing problem in Asia (3), suggesting that Asian people may be feasible to obesity-associated metabolic dysregulation. Accumulating evidence suggests that ectopic fat accumulation in insulin-target organs leads to development of insulin resistance in each organ by altering oxidative stress (4, 5) and gene expression profiles (6, 7). Specifically, the liver functions as a center to maintain whole body energy homeostasis by sensing nutrient stimuli and by producing a variety of nutrients and bioactive substances.

In this review, we show the clinical evidence for significance of liver fat in whole body glucose homeostasis, remodeling of nutrient homeostasis in the liver, and interorgan networks via liver-derived hormone hepatokines.

14.2 Ectopic fat accumulation and organ-specific insulin resistance

Disruption of hepatic insulin signaling in liver-specific insulin receptor knockout (LIRKO) mice results in fasting and postprandial hyperglycemia and the subsequent development of peripheral (muscle) insulin resistance (8), whereas glucose homeostasis remains normal in mice of disrupted insulin signaling both in the skeletal muscle and

adipose tissue (9). These observations suggest that hepatic insulin resistance is the primary event leading to diabetes and the subsequent development of peripheral tissue insulin resistance. Indeed, liver steatosis is associated with whole-body insulin resistance, independently of body mass index (BMI), in Japanese patients with NAFLD (10). However, the role of intramyocellular fat accumulation in insulin sensitivity is also on debate, and no previous studies have demonstrated the association among the insulin targeting organs comprehensively and simultaneously. Therefore, to understand organ networks that sense excessive energy and regulate insulin action, elucidating the association between fat accumulation and organ-specific insulin resistance among the liver, skeletal muscle, and adipose tissue is important, especially in humans.

We have addressed the association of ectopic fat accumulation with organ-specific insulin resistance among the liver, skeletal muscle, and adipose tissue in Japanese patients with NAFLD, systematically using reliable methods including liver biopsy, assessment of glucose metabolism measured by an euglycemic hyperinsulinemic clamp study with stable-isotope, bioelectrical impedance analysis, and proton magnetic resonance spectroscopy (^{1}H-MRS) (11). As shown in Table 1, both histological iver steatosis score and intrahepatic lipid (IHL) are significantly correlated negatively with a muscle insulin sensitivity index Rd and positively with a hepatic insulin resistance index HGP × fasting plasma insulin (FPI) (Table 1). In the multiple regression analysis, liver steatosis score is significantly correlated with both HGP × FPI ($\beta = 0.284$, $P < 0.05$) and Rd ($\beta = -0.300$, $P < 0.01$) after adjusted with age, sex, and BMI. Unexpectedly, intramyocellular lipid (IMCL) is associated neither with their own organ-specific insulin resistance nor any of organ-specific insulin resistance index (Table 1). Adipose tissue

mass is correlated with HGP × FPI and Rd, but not with % suppression of free fatty acids, an adipose tissue insulin sensitivity index (Table 1) (11). Therefore, indices of fat accumulation in the skeletal muscle and adipose tissue are not associated with their own organ-specific insulin resistance (Figure 1). It is known that IMCL is increased not only with obesity but also by enhanced physical fitness (12). Therefore, absolute fat contents do not always predict insulin resistance in the skeletal muscle. Rather, toxic lipids that cause insulin resistance in the skeletal muscle should be further researched. On the other hand, hepatic steatosis per se is central surrogate pathology indicative of insulin resistance in both liver and skeletal muscle in patients with NAFLD (Figure 1). There may be a network between the liver and skeletal muscle to maintain whole body energy homeostasis (Figure 1). To date, whether hepatic steatosis is a consequence or cause of skeletal muscle insulin resistance remains uncertain because a longitudinal observation of the relationship is lacking. However, some possibilities are assumed for the link as follows: 1) Skeletal muscle insulin resistance causes obesity and subsequent hepatic steatosis as experimentally shown in mice with muscle-selective insulin resistance (13). Indeed, Flannery et al. recently reported that skeletal muscle insulin resistance promotes increased hepatic de novo lipogenesis and hepatic steatosis in the elderly (14). 2) The neuronal pathway from the liver might modulate peripheral insulin sensitivity (15). 3) Some nutrients, such as fatty acids and amino acids, might link hepatic steatosis and skeletal muscle insulin resistance (16). 4) A liver-derived hormone named as hepatokine affects the distant organ insulin sensitivity (17). Molecular mechanisms underlying the link between liver fat and altered glucose metabolism are discussed in the following sections.

14.3 Possible molecular mechanisms underlying mystery of the selective insulin resistance in the type 2 diabetic liver

In the liver, insulin suppresses glucose production and enhances lipogenesis. Indeed, total insulin resistance in the liver observed in the LIRKO mice present hyperglycemia without fatty liver (8). However, in the liver with type 2 diabetes, insulin fails to suppress gluconeogenesis but still activates lipogenesis, the pathology of which is regarded as a 'selective insulin resistance'-like phonotype (18) (Figure 2). Notably, the indices for hepatic fat accumulation are associated with HGP × FPI, but not with % suppression of HGP during the hyperinsulinemic clamp (Table 1) (11), suggesting that the liver fat is associated with basal HGP itself, possibly independently of insulin resistance. Indeed, HGP is not solely regulated by insulin, but also by other hormones such as glucagon and glucocorticoid. Transcription factors such as forkhead box protein O (FoxO), cAMP response element-binding protein (CREB), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), hepatocyte nuclear factor 4 (HNF4α), and glucocorticoid receptors are involved in regulation of gluconeogenesis by the hormones and nutrients. In addition, hepatic steatosis also occurs independently of insulin resistance. Of the triacylglycerol accumulated in the liver of patients with NAFLD, 59.0% arises from non-esterified fatty acids mainly derived from the adipose tissue and 14.9% from the diet, whereas only 26.1% from *de novo* lipogenesis (19). Transcription factors such as liver X receptor (LXR), sterol regulatory element-binding protein-1c (SREBP-1c), and carbohydrate response element binding

protein (ChREBP) are involved in the *de novo* lipogenesis. Of these, SREBP-1c is a master regulater of hepatic *de novo* synthesis of fatty acids and is activated not only by insulin, but also by glucose, fatty acids, amino acids, SREBP-1c itself, LXR, mechanistic target of rapamycin complex 1 (mTORC1) and endoplasmic reticulum (ER) stress (20).

Triglyceride itself is not a toxic lipid and rather may be protective to prevent toxic effects of free fatty acids. Rather, free cholesterol and saturated free fatty acid palmitate are regarded as toxic lipids that cause hepatic insulin resistance via oxidative stress (17)as follows:

1) Mice fed an atherogenic diet rich in cholesterol and cholate show steatohepatitis, oxidative stress, and hepatic insulin resistance (4). In the liver of this model, *SREBP-1c* is upregulated possibly via cholesterol-mediated LXR activation, suggesting *de novo* lipogenesis in the liver. In addition, hepatic expression of insulin receptor substrate (IRS)-2 was downregulated by cholesterol diet. Shimano et al. discovered that SREBP-1c binds to E-box in the promoter of *IRS-2* competitively with TFE3 and FoxO1, and thus down-regulates *IRS-2* (21). These findings may link lipogenesis and insulin resistance in the liver.

2) In an *in vitro* fatty liver system using H4IIEC3 hepatocytes, a saturated fatty acid palmitate, but not an unsaturated fatty acid oleate, inhibits insulin-stimulated tyrosine phosphorylation of insulin receptor substrate 2 and serine phosphorylation of Akt, through c-Jun NH_2-terminal kinase (JNK) activation (5). In this model, mitochondrial β oxidation-derived reactive oxygen species (ROS) play a causal role in the palmitate-induced JNK activation (5). Therefore, toxic lipid-induced mitochondrial ROS may also underlie the link between steatosis and insulin resistance in the liver.

Indeed, in human, genes involved in mitochondrial oxidative phosphorylation (OXPHOS) are coordinately upregulated and positively correlated with those involved in a ROS-related pathway in the livers of obese type 2 diabetic patients compared with those of non-obese type 2 diabetic patients (7). These findings in toxic lipids-induced hepatic steatosis also contribute to the selective insulin resistance-like phonotype in type 2 diabetic livers (18).

14.4 Cross-talk among glucose, protein and lipid metabolic pathways in the liver

Growing evidence suggests that chronic endoplasmic reticulum (ER) stress in the liver is a major contributor to obesity-induced insulin resistance (22, 23). ER is responsible for protein quality control (24). The burden of unfolded proteins in the ER lumen is identified as an ER stress by several ER stress sensors, known as ATF6, PERK and IRE-1. The ER stress sensors trigger cellular adaptation for unfolded protein accumulation to restore normal function of the cell, which is called as the unfolded protein response (UPR). Chronic UPRs are causally linked to the pathogenesis of human metabolic diseases such as obesity and type 2 diabetes. Accumulating evidence suggests that obesity promotes ER stress, which is detected as an enhanced UPR signaling, that activates c-jun N terminal kinase (JNK) and impairs insulin signaling at the level of IRSs in the liver and adipose tissue (25). However, the molecular mechanisms linking obesity and ER stress are not fully understood.

In searching for metabolic pathways that are significantly altered by obesity in the livers of people with type 2 diabetes, we found that genes involved in ubiquitin-proteasome pathways are coordinately upregulated in obese individuals (7).

Proteasomes play fundamental roles in processes that are essential for cell viability by degrading misfolded proteins (26). Unexpectedly from the expression data, liver proteasome activity was reduced by approximately 30-40% in mouse models of obesity, such as genetically obese ob/ob mice, diabetic db/db mice, and C57BL/6 mice fed a high fat diet (HFD) (27). As a consequence, ubiquitinated proteins were accumulated in the liver of these obese model mice. These results suggest that liver proteasome activity is reduced in animal models of obesity. Thus, coordinate upregulation of the genes involved in the ubiquitin-proteasome pathway in obese patients and mouse models of obesity may compensate for impaired proteasome function. Therefore, we hypothesized that proteasome dysregulation in the liver is involved in the development of hepatic insulin resistance in obesity and type 2 diabetes. To test this hypothesis, we generated PA28α-PA28β-PA28γ triple-knockout (PA28 KO) mice, the genes of which are up-regulated in the livers of patients with obesity and in those of mice fed HFD (27), as a model of impaired proteasome function and investigated their metabolic phenotypes as follows: 1) Hepatic proteasome activity in PA28 KO mice fed a standard chow was reduced by 35% as compared with wild-type mice. As expected, ubiquitinated proteins were accumulated in the liver of the PA28 KO mice. 2) Electron micrographs revealed massive expansion of the ER in the livers of PA28 KO mice, suggestive of an unfolded protein response (UPR). Indeed, the liver in PA28 A28 KO mice showed the evidence of ER stress, such as increased levels of Grp78, CHOP, p-PERK, p-eIF2α, and p-IRE-1α, as well as ER stress-inducible mRNAs encoding CHOP and the spliced form of XBP-1 (XBP-1s), as compared with wild-type mice. 3) Phosphorylation of JNK and its downstream target c-Jun were significantly increased in the livers of PA28 KO mice as

compared with those of wild-type mice. 4) Although body weight was not altered, PA28 KO mice fed the standard chow presented glucose intolerance. Hyperinsulinemic-euglycemic clamp experiments and western blot analysis of the insulin signaling pathway revealed that PA28 deficiency impairs insulin signaling mainly in the liver, but not in the skeletal muscle, and thereby induces systemic glucose intolerance in vivo. These findings illustrate that proteasome dysfunction causes ER stress, JNK activation, and thereby cause insulin resistance in the liver (Figure 3). Yang et al. reported that hepatic autophagy is downregulated in the livers of ob/ob mice and that defective autophagy in Atg7 KO mice causes ER stress and hepatic insulin resistance (28). Therefore, it is possible that both proteasome- and autophagy-mediated protein degradation are impaired in the livers of obese individuals, further exacerbating ER stress.

5) PA28 KO mice showed hepatic steatosis associated with upregulated *Srebf1* and *Acc1*, and increased cleaved/active SREBP-1c (Figure 3). SREBP-1c is activated by ER stress (20). In addition, proteasome dysfunction results in increased protein levels of SREBP-1c because proteasome is responsible for degradation of SREBP-1c (29).

6) FoxO1 protein amounts dramatically increased in both cytoplasmic and nuclear fractions, probably due to proteasome dysfunction in the liver of PA28 KO mice (Figure 3). Spliced XBP-1 directly binds FoxO1 and promotes its protein degradation via the proteasome (30). In the liver of PA28 KO mice, spliced XBP1 protein was increased, probably due to increased phosphorylation of IRE1α, an endonuclease for *XBP1* gene. In addition, hepatic insulin resistance caused by ER stress/JNK pathway and increased SREBP-1c that downregulates IRS-2 further accumulates FoxO1 in the nucleus, leading

to induction of genes involved in gluconeogenesis such as *Pepck1*.

These findings suggest that proteasome dysfunction may be a primary event linking obesity and ER stress-induced insulin resistance in the liver. In addition, there seems to be a crosstalk among protein-, glucose- and lipid-metabolism pathways (Figure 3). Notably, activation of SREBP-1c and FoxO1 occurred independently of insulin resistance, and may mimic so-called 'selective insulin resistance' in the liver with type 2 diabetes, that is, coexistence of fatty liver and enhanced gluconeogenesis (Figure 2).

Proteasome function seems to be altered differently in different tissues. Insulinopenic hyperglycemia impairs proteasome activity in the liver and kidney (31, 32), whereas proteasome activity is enhanced in the wasted muscle of obese diabetic db/db mice (33). Taken together, these results indicate that obesity predominantly induces proteasome dysfunction in the liver. This clarifies the previous finding that ER stress causes insulin resistance in the liver together with the adipose tissue (22) and brain (34). Significance of enhanced proteasome activity in the skeletal muscle of obese model mice should be investigated in future.

14.5 Role of hepatokines that mediate inter-organ network during remodeling of energy homeostasis

As described above, we hypothesized that a liver-derived hormone, hepatokine, affects the distant organ insulin sensitivity. Human hepatic gene expression information accmulated by using serial analysis of gene expression (SAGE) technique and DNA chip methods (35, 36) were used to identify genes with signal peptides whose hepatic expression levels were significantly correlated with glycemic control (HbA1c), obesity

(BMI), or insulin resistance (HOMA-R and metabolic clearance rate). Expression of the candidates hepatokine genes were further referred to the various animal models of diabetes, obesity and fatty liver (4, 37-39). Based on these approaches, we isolated 62 candidate genes for hepatokines associated with insulin resistance, hyperglycemia, and obesity (35).

14.5.1 Selenoprotein P

Of these, we identified a gene encoding selenoprotein P, the expression levels of which were positively correlated with insulin resistance and hyperglycemia (40). Indeed, serum levels of selenoprotein P are elevated in people with type 2 diabetes, and significantly correlated with fasting plasma glucose and HbA1c levels (40). Selenoprotein P (in humans encoded by the *SEPP1* gene) is upregulated through FoxOs (Figure 4). Insulin downregulates *SEPP1* by phosphorylating and inactivating FoxO1 (41), whereas antidiabetic metformin activates AMPK, phosphorylates and inactivates FoxO3a, and thereby downregulates *SEPP1* in hepatocytes (42).

Selenoprotein P causes insulin resistance in the liver at least in part by inactivating AMP-activated protein kinase (AMPK) (40) (Figure 4). Selenoproein P also impairs angiogenesis by inducing VEGF resistance in vascular endothelial cells (43).

Specifically, selenoprotein P acts as a redox protein by activating glutathione peroxidase. Unexpectedly in the large-scale intervention study, selenium supplementation was paradoxically associated with an increased risk for diabetes in humans (44). Also, in our previous study in a cultured hepatocyte cell line, anti-oxidant reagents, N-acetyl-L-cysteine, rescued palmitate-induced insulin resistance only partly,

whereas it effectively suppressed palmitate-induced activation of JNK (5). To solve this paradox, we addressed the concentration-dependent effects of ROS on insulin signaling in hepatocytes. Treatment with high concentrations of H_2O_2 reduced insulin-stimulated Akt phosphorylation by activating JNK, whereas lower concentrations of H_2O_2 enhanced insulin-stimulated phosphorylation of Akt by suppressing PTP1B activity (45). Therefore, depending on its concentration, H_2O_2 can have the positive or negative effect on insulin signal transduction in hepatocytes. It might be possible that selenoprotein P deprives a physiologic ROS burst that is required for insulin signal transduction and thereby causes insulin resistance, the condition referred to a reductive stress. Indeed, similar to the selenoprotein P KO mice, mice lacking one of the selenoproteins involved in the elimination of physiological ROS, glutathione peroxidase 1, are reported to be protected from high-fat-diet-induced insulin resistance (46).

Interestingly, supplementation with antioxidants may preclude health-promoting effects of physical exercise in humans (47). Consistent with the concept of mitohormesis, exercise-induced oxidative stress ameliorates insulin resistance and causes an adaptive response promoting endogenous antioxidant defense capacity. In this regard, we recently identified a putative skeletal muscle receptor for selenoprotein P. Molecular mechanisms how selenoprotein P causes skeletal muscle insulin resistance are under investigation through investigating the skeletal muscle-specific selenoprotein P KO mice (Figure 4).

Serum levels of selenoprotein P are inversely associated with serum levels of adiponectin (48) that enhance skeletal muscle insulin sensitivity (49). Therefore, overproduction of selenoprotein P in association with hepatic steatosis, by directly or indirectly lowering adiponectin levels, causes skeletal muscle insulin resistance.

14.5.2 LECT2

Our second hepatokine is leukocyte cell-derived chemotaxin 2 (LECT2), the gene of which is most correlated with BMI (50). LECT2 is a 16 kDa secretory protein originally identified from cultured supernatant of human T-cell line as a neutrophil chemotactic factor (51). LECT2 (in humans encoded by the *LECT2* gene) is expressed preferentially by human adult and fetal liver cells and is secreted into the blood stream (52). LECT2 enhances macrophage function via the CD209a/DC-SIGN receptor and improves immunity in bacterial sepsis (53). More recently, it has been reported that LECT2 suppresses hepatocellular carcinoma by direct binding and inactivating hepatocyte growth factor (HGF) receptor MET (54). However, the role of LECT2 in the development of obesity and insulin resistance was unknown. We characterized molecular aspects of LECT2 as follows: 1) Serum Lect2 levels were correlated positively with BMI, waist circumference, HOMA-R, and HbA1c, and negatively with insulin sensitivity Matsuda index (50). These data indicate that the serum levels of LECT2 are positively associated with both adiposity and the severity of insulin resistance in humans. 2) *Lect2* was up-reguleted in HFD (vs. standard chow) feeding, fed (vs. fasted) state, and resting (vs. exercise) state. In these experimental conditions, AMPK phosphorylation was impaired. Indeed, *Lect2* expression in H4 hepatocytes was upregulated by dominant negative-AMPK infection, whereas downregulated by constitutive active-AMPK transfection. These findings indicate that AMPK down-regulates LECT2 expression in hepatocytes (Figure 5). 3) Glucose or insulin loading test revealed that *Lect2* KO mice showed lower blood glucose levels after glucose or insulin injection. 4)

Hyperinsulinemic-euglycemic clamp studies showed that glucose infusion rate and peripheral glucose disposal were increased in *Lect2* KO mice, whereas endogenous glucose production EGP was unaffected. These results indicate that *Lect2* KO mice have better insulin sensitivity in skeletal muscle but not in the liver. 5) In vitro in C2C12 myocytes, recombinant LECT2 protein phosphorylated JNK and decreased insulin-stimulated Akt phosphorylation, which was rescued by double knockdown of JNK1 and JNK2. 6) To further elucidate the role of LECT2 in the development of obesity-associated insulin resistance, we fed *Lect2* KO mice a 60% HFD. *Lect2* KO mice were protected from the HFD-induced weight gain. Serum levels of insulin decreased in the KO mice in both fasting and fed conditions. 7) *Lect2* KO mice presented higher heat production in both light and dark phases. This may be caused by enhanced myogenesis, because all of the subsets of myosin heavy chain were up-regulated in the *Lect2* KO mice. As a consequence, physical-exercise-assessed muscle endurance was significantly higher in *Lect2* KO mice than wild-type mice. These findings suggest that LECT2 decreases energy expenditure by inhibiting myogenesis (Figure 5).

In conclusion, LECT2 is a satiety-associated hepatokine that is induced by inactivating AMPK in the liver. Overproduction of LECT2 contributes to the development of muscle insulin resistance and obesity by activating JNK and by impairing myogenesis, respectively (Figure 5).

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Legends

Table 1. Univariate correlation between ectopic fat and organ-specific insulin resistance HGP, hepatic glucose production; FPI, fasting plasma insulin; SSPI, steady state plasma insulin; IHL, intrahepatic lipid; IMCL, intramyocellular lipid; VO_2, basal oxygen consumption rate per body weight. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. (modified from Ref. (11))

Figure 1. Relationship between intracellular lipid accumulation and origan-specific insulin resistance among 3 major insulin-targeting organs, the liver, skeletal muscle and adipose tissue.

Skeletal muscle insulin resistance is not associated with intramyocellular lipid accumulation, but with hepatic steatosis, suggesting that there is inter-organ network between the liver and skeletal muscle in human. (modified from Ref. (11))

Figure 2. Selective insulin resistance-like phenotype in the liver with type 2 diabetes.

In the liver with type 2 diabetes, insulin fails to suppress gluconeogenesis but continues to activate lipogenesis, which is regarded as a 'selective insulin resistance'-like phonetype.

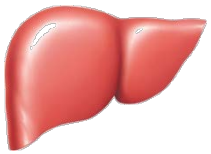
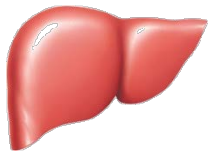
Figure 3. Cross-talk among protein, glucose and lipid metabolic pathways.

Proteasome function is impaired in the state of obesity, followed by endoplasmic reticulum (ER) stress, JNK activation and insulin resistance in the liver. Proteasome dysfunction also results in increased protein levels of FoxO1 and SREBP-1c because proteasome is responsible for degradation of FoxO1 and SREBP-1c, which are master

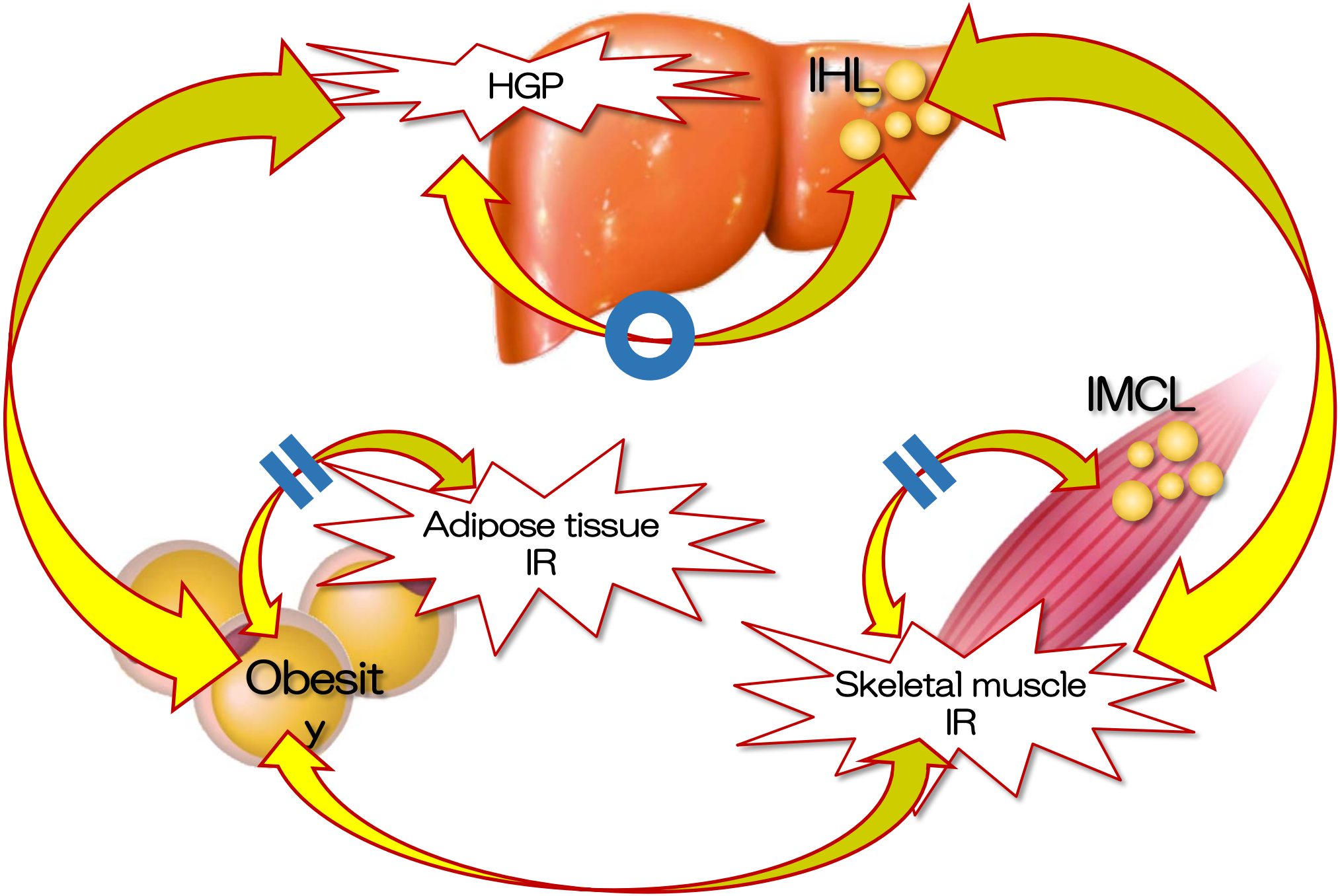
transcription factors for gluconeogenesis and lipogenesis, respectively. SREBP-1c is also activated by ER stress. Such activation of these factors occurs independently of insulin resistance, and may mimic so-called 'selective insulin resistance' in the liver with type 2 diabetes, that is, coexistence of fatty liver and enhanced gluconeogenesis. (modified from Ref. (27))

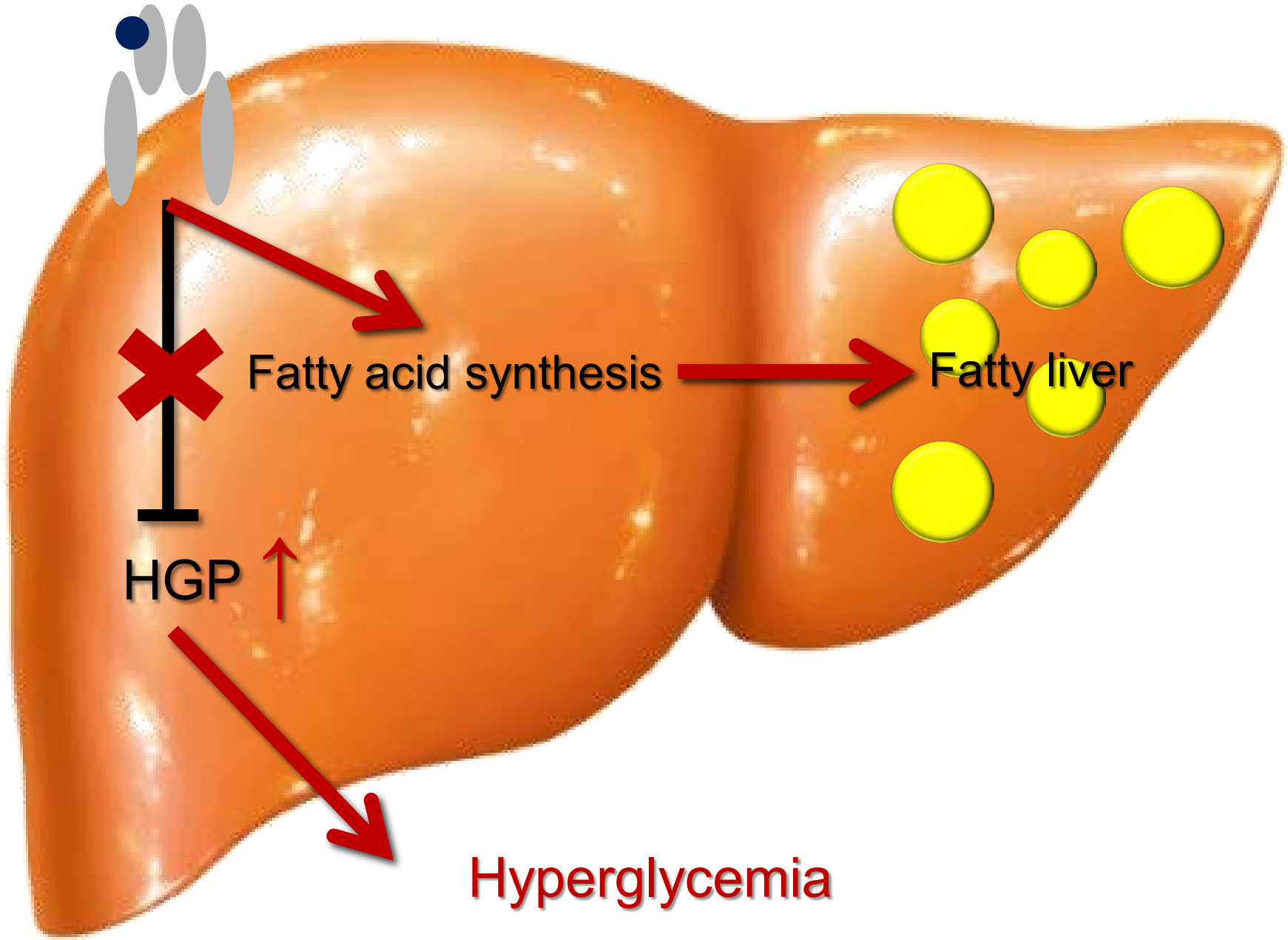
Figure 4. Selenoprotein P causes insulin resistance in the liver and skeletal muscle. *SEPP1* is upregulated through FoxOs. Insulin downregulates *SEPP1* by inactivating FoxO1, whereas antidiabetic metformin activates AMPK, inactivates FoxO3a, and thereby downregulates *SEPP1* in hepatocytes. Selenoprotein P causes hepatic insulin resistance at least partly by inactivating AMPK. (modified from Ref. (48))

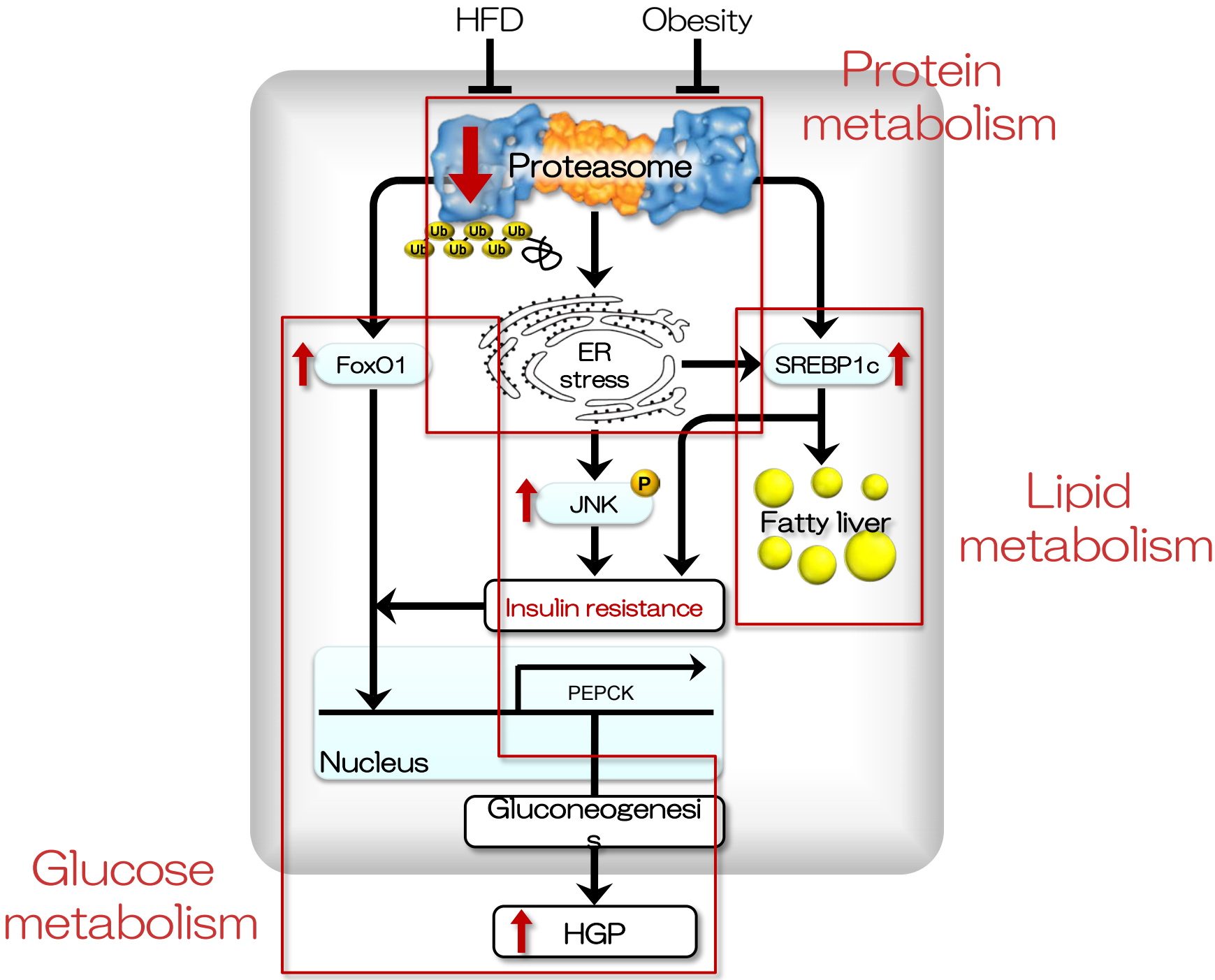
Figure 5. A satiety-associated LECT2 causes skeletal muscle insulin resistance. LECT2 is a satiety-associated hepatokine that is induced by inactivating AMPK in the liver. Overproduction of LECT2 contributes to the development of muscle insulin resistance and obesity by activating JNK and by impairing myogenesis, respectively. (modified from Ref. (50))

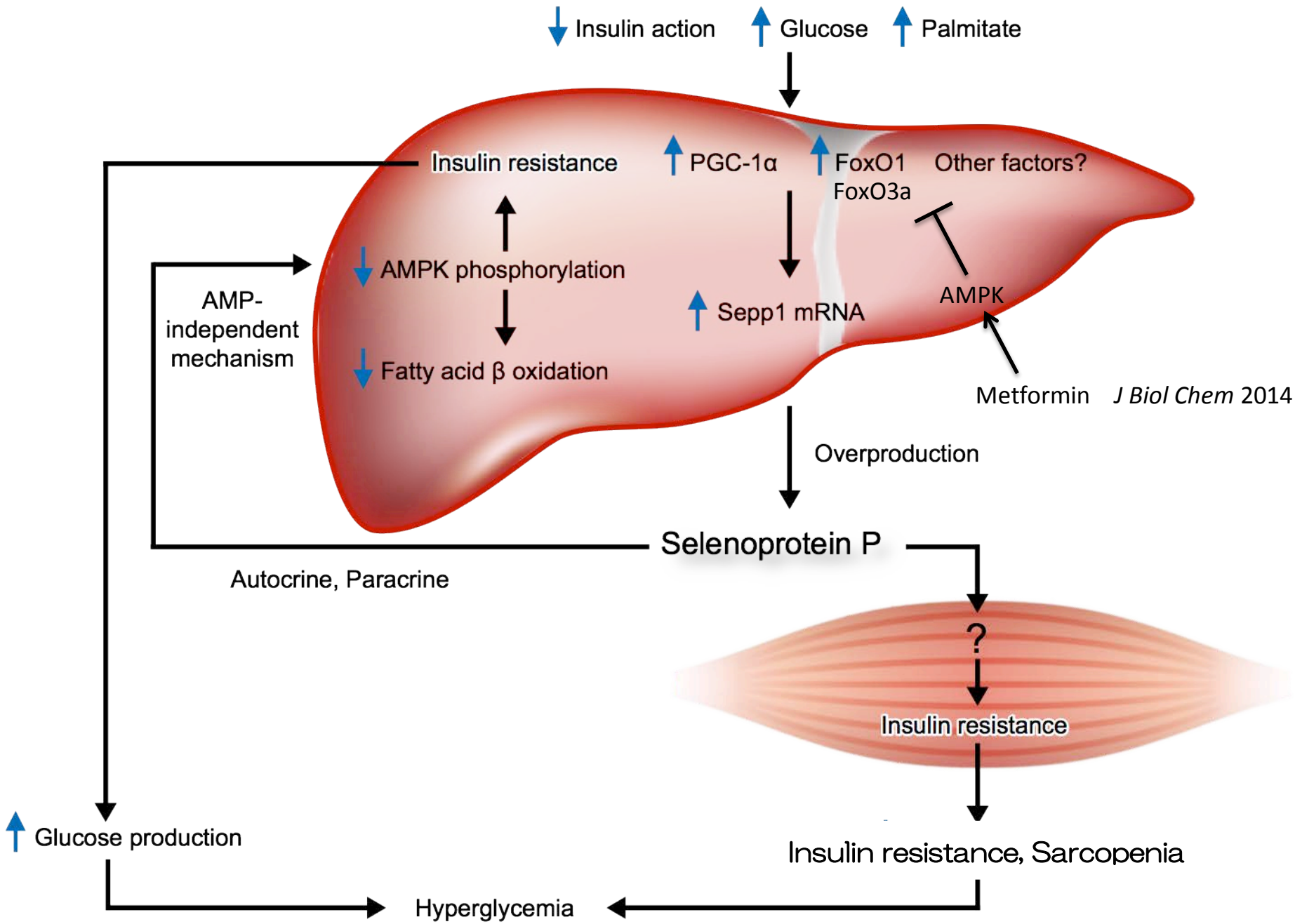



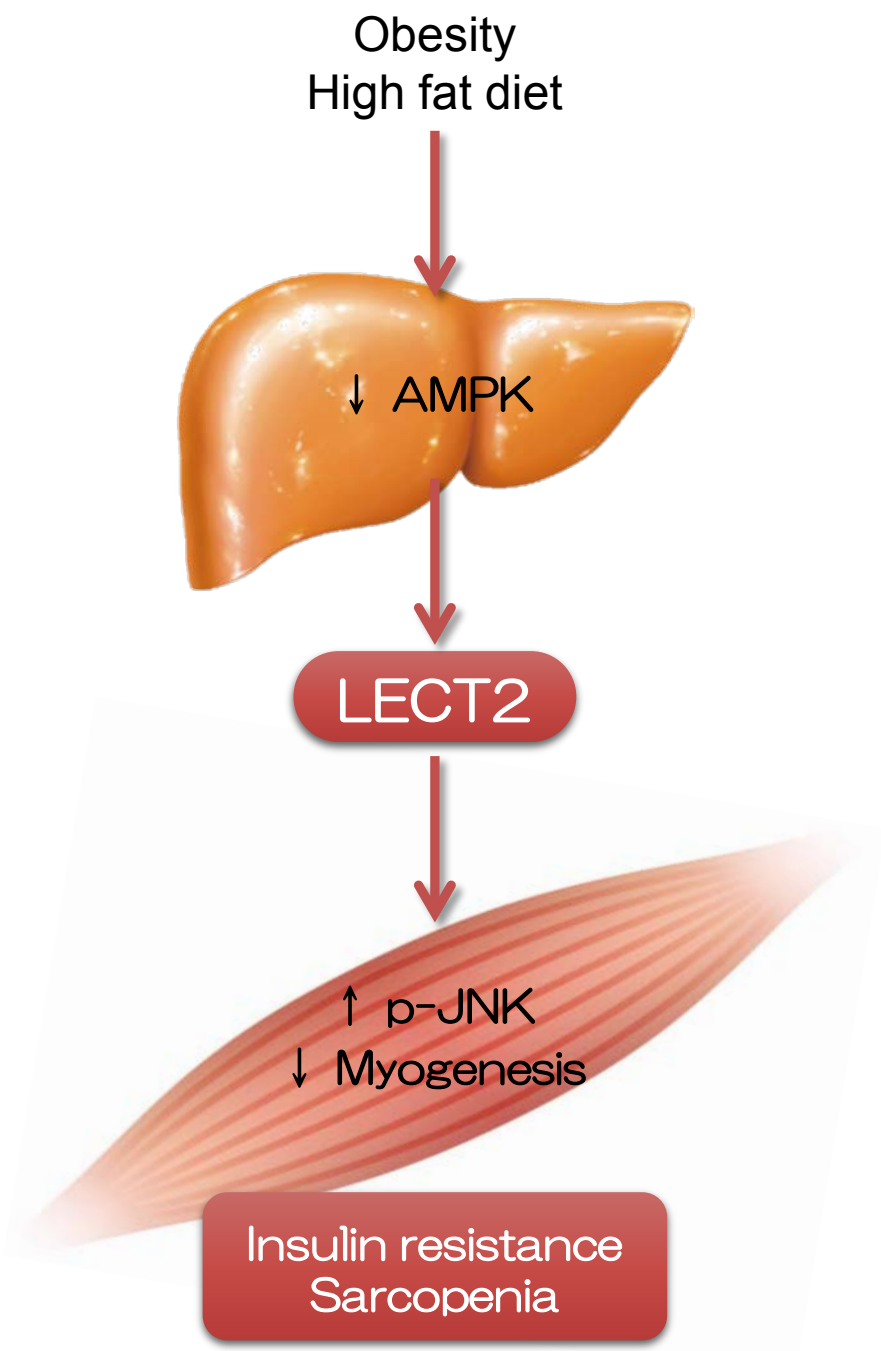
	HGP × FPI		%HGP		Rd		Rd/SSPI		%FFA	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Steatosis	0.401**	0.001	-0.161	0.187	-0.495***	<0.001	-0.460***	<0.001	-0.086	0.483
Grade	0.397**	0.001	-0.151	0.214	-0.359**	0.002	-0.361**	0.003	-0.061	0.616
Stage	0.227	0.060	-0.109	0.371	-0.300*	0.012	-0.248*	0.042	-0.001	0.991
IHL	0.245	0.089	-0.114	0.436	-0.315*	0.028	-0.271	0.062	-0.135	0.356
IMCL	0.250	0.065	-0.215	0.115	-0.156	0.256	-0.183	0.185	-0.060	0.662
Fat-free mass	0.031	0.801	-0.117	0.347	-0.216	0.079	-0.211	0.090	-0.433***	<0.001
Total fat mass	0.495***	<0.001	-0.147	0.235	-0.594***	<0.001	-0.536***	<0.001	-0.205	0.096
Body fat percentage	0.481***	<0.001	-0.115	0.355	-0.518***	<0.001	-0.478***	<0.001	-0.001	0.994
VO_2	-0.129	0.342	0.191	0.158	0.418**	0.001	0.405**	0.002	0.115	0.397


HGP
IHL
IMCL
Adipose tissue
IR
Obesit
y
Skeletal muscle
IR


Fatty acid synthesis
Fatty liver
HGP ↑
Hyperglycemia


HFD
Obesity
Protein metabolism
Proteasome
Ub
ER stress
FoxO1
SREBP1c
JNK
P
Fatty liver
Lipid metabolism
Insulin resistance
PEPCK
Nucleus
Gluconeogenesis
HGP
Glucose metabolism


Insulin action
Glucose
Palmitate
Insulin resistance
PGC-1α
FoxO1
FoxO3a
Other factors?
AMPK phosphorylation
AMP-independent mechanism
Sepp1 mRNA
AMPK
Fatty acid β oxidation
Metformin
J Biol Chem 2014
Overproduction
Selenoprotein P
Autocrine, Paracrine
?
Insulin resistance
Glucose production
Insulin resistance, Sarcopenia
Hyperglycemia


Obesity
High fat diet
↓ AMPK
LECT2
↑ p-JNK
↓ Myogenesis
Insulin resistance
Sarcopenia