· REVIEWS · ①

·综 述·

p38 mitogen-activated protein kinase plays a critical role in the control of energy metabolism and development of cardiovascular diseases

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Abstract: p38 mitogen-activated protein kinase (p38) is a member of MAP kinase family. Its wide-spectrum roles in the control of energy metabolism have been indicated in numerous studies. p38 participates in the energy metabolism in all major tissues/organs involved in the control of energy metabolism, including adipose tissue, skeletal muscles, islet cells, and liver. In white adipose tissue, p38 plays an important role in adipose differentiation and glucose uptake although it is still inconclusive whether this role of p38 is stimulatory or inhibitory. The stimulatory role of p38 in transcription of the uncoupling protein 1 (UCP1) gene in brown adipose tissue is relatively clear. A fundamental role for p38 in the differentiation of skeletal muscles and mitochondrial biogenesis in skeletal muscles is rather definitive although the role of p38 in glucose uptake of skeletal muscles remains controversial. In islet cells, p38 appears to be involved in β-cell apoptosis. p38 has been indicated in the control of preproinsulin gene transcription, but remains controversial. However, it seems clear that p38 does not play a significant role in insulin secretion. In the liver, p38 plays a central role in hepatic glucose and lipid metabolism. Activation of p38 participates in the processes to increase blood glucose levels through reducing glycogen synthesis and increasing hepatic gluconeogenesis. p38 appears to prevent fat storage by inhibiting hepatic lipogenesis and promoting fatty acid oxidation in the liver. Additionally, p38 may play a critical role in cholesterol metabolism by regulating expression of the LDLR gene and bile metabolism. p38 does not only participate in various physiological and pathophysiological processes in cardiomyocytes, but also is heavily involved in the development of atherosclerotic lessions through its influences on monocytes/macrophages, vascular endothelial cells, and vascular smooth muscle cells.

Key words: p38; obesity; diabetes; apoptosis; adipocyte; uncoupling protein 1 (UCP1); skeletal muscle; glucose uptake; glucose transporter-4 (Glut 4); insulin secretion; insulin signaling; gluconeogenesis; phosphoenolpyruvate carboxykinase (PEPCK); glucose-6-phosphatase (G6Pase); atherosclerotic cardiovascular disease (ASCVD)

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p38 丝裂原活化蛋白激酶在能量代谢控制和心血管疾病中的作用

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[摘要] p38 是丝裂原活化蛋白激酶家族中的成员之一,大量研究显示 p38 在能量代谢中具有广泛的作用。p38 参与脂肪组织、骨骼肌、胰岛细胞和肝脏等组织、器官的能量代谢,这些组织、器官都是控制能量代谢的主要组织与器官。在白色脂肪组织,p38 对脂肪细胞分化和葡萄糖摄取的重要作用是一致公认的,尽管 p38 对脂肪细胞葡萄糖摄取究竟是促进还是抑制至今尚未定论;在棕色脂肪组织,p38 对解偶联蛋白-1 基因转录起促进作用。在骨骼肌,虽然 p38 对葡萄糖摄取的作用仍有争议,但 p38 对骨骼肌细胞分化和骨骼肌线粒体生成的重要作用是非常肯定的。在胰岛细胞,p38 似乎与细胞凋亡有关;p38 还可能控制胰岛素原基因转录,但对胰岛素分泌无明显作用。在肝脏,p38 在肝脏的糖、脂代谢中起核心作用,一方面,p38 通过抑制肝脏糖原合成,增加肝脏糖异生,使血糖升高;另一方面,p38 通过抑制肝脏脂肪合成、促进脂肪酸在肝脏的氧化代谢,从而抑制脂肪在肝脏的贮存;另外,p38 还通过调节低密度脂蛋白受体基因表达和胆汁代谢对胆固醇代谢起关键作用。p38 不仅参与心肌细胞的各种生理、病理过程;也通过影响单核-巨噬细胞、血管内皮细胞和血管平滑肌细胞参与动脉粥样硬化斑块的形成。

[关键词] p38; 肥胖; 糖尿病; 凋亡; 脂肪细胞; 解偶联蛋白-1; 骨骼肌; 葡萄糖摄取; 葡萄糖转运体-4; 胰岛素分泌; 胰岛素信号; 糖异生; 磷酸丙酮酸羧化酶; 葡萄糖-6-磷酸酶; 动脉粥样硬化样心血管病
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1 INTRODUCTION

The imbalance of energy metabolism can cause a series of metabolic disorders, including obesity, metabolic syndrome, diabetes mellitus, and atherosclerotic cardiovascular disease (ASCVD), etc. Obesity is usually the prelude of many metabolic problems. With the development of modern technology providing us plenty of food and increasingly reducing physical activities, obesity has become rampant in developed countries, in particular, in the United States, and is increasingly turning into a major health problem worldwide. Although it is obvious that a majority of these problems caused by the imbalance of energy metabolism can be prevented or reverted simply by controlling food intake and increasing physical activities, it is unethical and impossible to regulate people's behavior in food intake and physical activities. (Note: Educating people about keeping a balance between food intake and energy expenditure will definitely help.) This reality has increased our responsibility to further understand the mechanisms of energy metabolism and identify new ways to modulate energy metabolism.

Energy metabolism is predominantly controlled by opposing hormones including adrenelines and insulin. Adrenelines stimulates the energy expenditure from glucose (glycogenolysis and glycolysis), fat (lipolysis and fatty acid oxidation), and amino acids (protein degradation and oxidation of amino acids). In contrast, insulin promotes energy conservation or storage by stimulating glucose uptake through Glut4 and converting glucose into glycogen through glycogen synthesis or converting glucose into fatty acids and triglyceride through lipogenesis. Insulin can also stimulate protein synthesis. A lot has been learnt about the intracellular signaling of adrenelines and insulin in the control of energy metabolism. For example, the

function of adrenelines is mainly carried out through a cAMP/PKA-dependent pathway, while the signal from insulin is transmitted by the sequential activation of PI3K, PDK1, and Akt. However, accumulating studies have suggested that other kinases like p38 mitogen-activated protein kinase (p38) can also play important roles in the control of energy metabolism.

p38 is one member of the MAP kinase family, which includes at least ERK1/2, JNK, ERK5, and p38[1]. The activation and function of p38 were originally discovered to be related to apoptosis caused by cellular stresses such as UV light exposure, hyperosmolarity, pH change, cellular injury, and ROS[1]. It is currently known that p38 can also be activated by cAMP-producing hormones[2-5], cytokines[1], glucose[6-8], and fatty acids[9-10]. There are four known p38 isoforms: p38α, p38β, p38γ, and p38δ[1]. These isoforms are differentially expressed in different tissue[1]. p38 can influence many aspects of energy metabolism in various tissues, and has been implicated in the development of many metabolic disorders.

2 ROLE OF p38 IN THE ENERGY METABOLISM IN ADIPOSE TISSUE

Adipose tissue is not only an energy storage, but is also essential for the survival and continuation of human and other animal species. Adipose tissue is exquisitely sensitive to hormone regulation, and is currently recognized as an endocrine organ that can secret various adipokines such as leptin, adiponectin, visfatin, TNF-α, IL-1β, IL-6, IL-8, IL-10, monocyte chemoattractant protein-1 (MCP-1), macrophage migration inhibitory factor, nerve growth factor, vascular endothelial growth factor, plasminogen activator inhibitor-1, haptoglobin, and resistin, etc[11-12]. These adipokines serve as messengers to communicate with surrounding cells or remote tissues/organs. For example, when the adipose depot reaches certain level, the leptin from adipose tissue will be sent to the hypothalamus to stop food intake[13].

There are 2 types of adipose tissues: white adipose tissue (WAT) and brown adipose tissue (BAT)[14-15]. WAT and BAT have distinct functions in the control of energy balance. WAT mainly serves as a storage of energy while BAT mainly functions as an energy consumer through thermogenesis. WAT is the predominant adipose tissue in large mammals like humans, while the typical BAT in humans disappears soon after birth. The disappearance of BAT in humans is probably related to the capability of humans to keep warm with appropriate clothing and ambient environment, which makes the thermogenesis from BAT unnecessary. However, under certain conditions such as long-term exposure to a cold environment[16] or treatment with β3-adrenergic agonists, BAT can reappear amongst WAT[17-21].

p38 plays a critical role in the development and function of both WAT and BAT. Earlier studies showed that p38 was necessary for the differentiation of 3T3-L1 preadipocytes into white adipocytes. Specifically, the differentiation of 3T3-L1 preadipocytes was completely prevented when the activation of p38 was blocked[22-23]. In contrast, the constitutive activation of p38 in 3T3-L1 preadipocytes can promote adipose differentiation[24-25]. One of the earliest steps of adipose differentiation is the activation of transcription factor C/EBPβ[26-27]. C/EBPβ can be activated by p38 through phosphorylation[22]. The activated C/EBPβ then induces transcription of the PPARγ gene, which is a major promoter of adipogenesis[27]. Prior to the differentiation, the proliferation of preadipocytes must be arrested[26]. Since p38 is known to be a critical check point kinase[28], it is possible that p38 promotes adipose differentiation by arresting preadipocytes. Aouadi et al.[29] suggested that p38 plays an inhibitory role in adipose differentiation since the adipose differentiation of preadipocytes isolated from white fat tissue of mouse models is increased when p38 activity is suppressed. The adipose differentiation from embryonic stem (ES) cells or mouse embryonic fibroblasts (MEF) is also increased by the blockade of p38 with either a chemical inhibitor or the deletion of the p38α gene[29]. The adipose dif-

ferentiation from either ES or MEF cells resulting from p38 inhibition is probably mediated through C/EBPβ since the activity of C/EBPβ is increased in MEF cells and preadipocytes when p38 activation is blocked. Nevertheless, a possible explanation is that p38 can play either a stimulatory or an inhibitory role in adipose differentiation depending upon the status and stage of cells. p38 can promote adipose differentiation by arresting the proliferating cells[28]. On the other hand, p38 may prevent fat accumulation in differentiating cells through the inhibition of lipogenesis. In our new discovery, p38 plays an inhibitory role in hepatic lipogenesis. However, whether p38 also suppresses lipogenesis in adipocytes remains to be determined.

A series of studies have suggested an important role for p38 in insulin-induced glucose uptake in WAT. The blockade of p38 with either a chemical inhibitor or dominant-negative p38 can decrease the glucose uptake induced by insulin in differentiated 3T3-L1 adipocytes[31-35]. The mechanism is not through the translocation of glucose transporter 4 (Glut4), but through the activation of Glut4, which has already been mobilized to the plasma membrane[31-34]. Additionally, p38 is also able to regulate the insulin-independent glucose uptake in 3T3-L1 adipocytes through activating Glut4. For example, p38 can potentiate arsenite-stimulated glucose uptake in 3T3-L1 adipocytes[36]. However, some studies also in 3T3-L1 adipocytes showed that the blockade of p38 with similar chemical inhibitors (SB202190 and SB203580) does not affect glucose uptake induced either by insulin or osmotic shock[37], while others have shown the opposite role of p38 in glucose uptake, i.e., p38 activation can down-regulate insulin-induced glucose uptake via Glut4[38-39]. Another study has even shown that the p38 inhibitor SB203580 can inhibit the intrinsic activity of Glut4 independent of p38 activity[40]. Since the dominant-negative form of p38 can also reduce the insulin-induced glucose uptake[34], it is more likely that p38 indeed plays a positive role in Glut4-dependent glucose uptake in WAT. Finally, p38 may be related to the decrease of Glut4 gene transcription in type II diabetes mouse models[41].

In addition to its role in the differentiation and function of WAT, p38 also appears to play a critical role in BAT. p38 plays a stimulatory role in transcription of the uncoupling protein1 (UCP1) gene[2-4,42]. UCP1 is necessary for the nonshivering thermogenesis in BAT, which in return is essential for maintaining body temperature of rodents in cold. The mice treated with a p38 inhibitor could not maintain their body temperatures in a cold environment probably due to a deficiency in expression of the UCP1 gene[3]. The stimulatory role of p38 in transcription of the UCP1 gene is likely accomplished by stimulating the expression of the PPARγ co-activator-1α (PGC-1α) gene and activation of the PGC-1α protein through phosphorylation[3]. The PPARγ-induced transcription of the UCP1 gene is also p38 dependent[43]. A recent genetic study (quantitative trait loci analysis) from Kozak's group also showed that the activation of p38 is the earliest intracellular event correlated with the transcription of the UCP1 gene in BAT[44].

3 ROLE OF p38 IN ENERGY METABOLISM OF SKELETAL MUSCLES

The role of p38 in glucose uptake in skeletal muscle cells is just as controversial as that in adipocytes described above. Some studies in skeletal muscle cell lines have shown that p38 can enhance insulin- or exercise-induced glucose uptake by activating the Glut4, which has already been mobilized to the plasma membrane[31,45,46]. However, other studies in primary human myotubes have shown that the blockade of p38 dose not alter the insulin-induced glucose uptake[47], while some in L6 myotube cell line studies have even shown an opposite effect of p38 on insulin-induced glucose uptake[38]. A recent study with isolated primary skeletal muscles showed that the activation of p38 by anisomycin could enhance insulin-induced glucose uptake[48]. Additionally, p38 may also play a positive role in exercise- or AMPK-in-

duced glucose uptake in skeletal muscles through promoting the intrinsic activity of Glut4[49-50]. The exercise-induced activation of p38 has been shown to stimulate expression of the Glut4 gene through phosphorylating MEF2 transcription factors in skeletal muscles[49-50]. Furthermore, studies in both C2C12 myotube cells and primary skeletal muscles have shown that p38 can also influence glucose uptake by desensitizing insulin signaling. Specifically, p38 mediates the serine phosphorylation of insulin receptor and IRS1 or suppression of IRS1 gene transcription induced by cytokines or chemicals[51-52]. Therefore, it appears that p38 likely plays a certain role in insulin-induced and insulin-independent glucose uptake in skeletal muscles although there is still some doubt.

The role of p38 in skeletal myogenesis is quite definitive[53]. Skeletal muscles are differentiated through several stages including myoblast, myocyte, myotube, and myofifer. The blockade of p38α and p38β by SB203580 can prevent the fusion of myoblasts into myotubes, as well as the induction of muscle-specific genes[54-57]. In contrast, the activation of p38 by epitopic expression of a constitutive activator of p38 MKK6E is sufficient to induce the expression of muscle differentiation-specific genes and the appearance of multinucleated myotubes[56,58]. The activation of muscle differentiation-specific genes is controlled by myogenic regulatory factors (MRFs) through the E-box of muscle promoters[53]. The MRF family includes Myf5, MyoD, myogenin, and MRF4. The full activation of these MRFs is also dependent on their association with members of the MEF2 family of transcription factors, MEF2A-D[53]. Additionally, the participation of the chromatin remodeling complex SWI/SNF is necessary for MRF function[53].

p38 can regulate expression of muscle differentiation-specific genes through several mechanisms. First, since p38 can activate MEF2 factors through phosphorylation, p38 promotes the full activation of MRFs through MEF2[55-56,59-60]. Second, p38 can activate the obligate MyoD partner E47 through phosphorylation[61]. MyoD-E47 heterodimer formation and the subsequent binding with the E-box of muscle promoters are essential for muscle-specific gene transcription. Third, p38 participates in the recruitment of the SWI/SNF chromatin remodeling complex through activating the SWI/SNF subunits via phosphorylation[62]. The recruitment of the SWI/SNF complex is subsequently linked to the engagement of the active fraction of RNA polymerase II. Finally, p38 may play an inhibitory role in the late stage of muscle differentiation by reducing the activity of MRF4 through phosphorylation[58,63]. This inhibitory role of p38 in the late stage of myogenesis is probably linked to the role of p38 in the development of muscle atrophy caused by immobilization and certain cytokines such as TNF-1α[64].

The role of p38 in mitochondrial biogenesis in skeletal muscles is relatively clear. It is known that PGC-1α is a strong inducer of mitochondrial biogenesis[65]. Transgenic expression of the PGC-1α gene can turn white muscles into mitochondria-rich red muscles[66]. It is known that the activation of p38 participates in the transcription of the PGC-1α gene in skeletal muscles[67]. The role of p38 in the transcription of the PGC-1α gene is mediated by MEF2 and ATF-2 transcription factors[67-68]. In addition, p38 in skeletal muscle cells can also directly regulate the activity of PGC-1α protein through phosphorylation and the phosphorylation of PGC-1α by p38 can also increase the stability of the PGC-1α protein[69].

4 ROLE OF p38 IN PANCREATIC ISLETS

Many studies have been conducted to explore the role of p38 in transcription of the insulin gene, insulin secretion, and islet apoptosis. Some studies have shown that p38 plays a stimulatory role in the transcription of the insulin gene induced by glucose[70-72], while others have shown that p38 does not play a role in the glucose-induced transcription of the preproinsulin gene[73]. Some studies even have shown that p38 can inhibit the expression of the preproinsulin gene induced by glucagon-like peptide-1 (GLP-1)[74]. It is unclear what has caused the discrepan-

cy.

It appears that p38 plays an important role in the development of both types I and II diabetes. In type I diabetes, pancreatic β-cells are gradually destroyed in an inflammatory reaction termed "insulitis" triggered by an autoimmune assault. The blockade of p38 activation with a chemical inhibitor was shown to prevent the development of type I diabetes in nonobese diabetic (NOD) mice[75]. Although the blockade of p38 could not eliminate the insulitis, it did prevent the infiltration of Th1 cells into islets. As a result, p38 prevented the switch from benign to destructive insulitis. It is currently unclear whether the blockade of p38 activation can be used to prevent the development of type I diabetes in humans. Type II diabetes usually starts with insulin resistance, which is often associated with obesity, and a progressive decline in β-cell function and β-cell mass. It is now unknown whether the reduction in human β-cell mass is caused by increased β-cell apoptosis or decreased neogenesis or both[76]. However, it is reasonable to believe that β-cell apoptosis plays a critical role in the development of type II diabetes based on the results from rodent models and in cultured animal and human islet cells[77-80]. Type II diabetes is almost always accompanied by hyperlipidemia, hyperglycemia, and increased levels of cytokines[81]. Since high levels of glucose, lipids, and cytokines are all able to activate p38 in a variety of cell types including islet cells, p38 seems to play a certain role in β-cell apoptosis and the consequent development of type II diabetes[77-81]. However, some studies have shown a protective role for p38 in the survival of β-cells. For example, glucose-dependent insulinotrophic polypeptide (GIP) can stimulate the survival of β-(INS) cells through the activation of p38[82].

Many studies have been attempted to determine the role of p38 in the control of insulin secretion from β-cells. The consensus conclusion now is that p38 does not play a significant role in insulin secretion from islet β-cells[83-84].

5 ROLE OF p38 IN ENERGY METABOLISM IN THE LIVER

Liver is the processing center of glucose and lipids. Hepatic glycogen synthesis, glycogenolysis, and gluconeogenesis are essential for maintaining blood glucose level. Hepatic lipogenesis, lipoprotein packaging and processing, lipid transport, fatty acid oxidation, and bile metabolism are all necessary for maintaining the energy homeostasis. A role for p38 has been indicated in many of these hepatic functions.

p38 may play a regulatory role in hepatic glycogen synthesis (GS). p38β has been shown to interact with GS both in cells and in binding assays in vitro. This interaction results in phosphorylation of GS at residues Ser^{644}, Ser^{652}, Thr^{718}, and Ser^{724}. Phosphorylation at these sites are prerequisite for the further phosphorylation of GS by GS kinase 3 (GSK3). As a result of GS phosphorylation by p38, the activity of GS is partially inhibited[85], i. e., the activation of p38 should increase plasma glucose levels by blocking the conversion of glucose into glycogen. In addition, p38 may increase plasma glucose levels through promoting hepatic glucose production via gluconeogenesis. We and Qiao et al. have recently shown that p38 plays a stimulatory role in hepatic gluconeogenesis and may contribute to the unrestrained hepatic gluconeogenesis in both types I and II diabetes[5,10,86-87]. p38 promotes hepatic gluconeogenesis through several mechanisms. First, p38 stimulates the transcription of key gluconeogenic genes phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphate (G6Pase) through the expression of the PGC-1α gene and the activation of the PGC-1α protein[5,10,69]. Second, p38 promotes the transcription of PEPCK, G6Pase, and PGC-1α genes through CREB[5,10,88], which is an indirect substrate for p38[5,10]. Third, p38 activates the transcription of the PEPCK gene through phosphorylation of the C/EBP(protein[86]. The stimulatory role of p38 in hepatic gluconeogenesis is consistent with previous report that p38 mediates acidosis-induced transcription of the PEPCK gene in renal cells[89]. Hepatic gluconeogene-

sis is increased, while hepatic glycogen synthesis is decreased during fasting and in diabetes. Coincidently, the levels of plasma glucagon and free fatty acids (FFA) are also increased during fasting and in diabetes. Our studies show that the most likely activators of p38 in the liver are glucagon and FFA[5,10]. Therefore, p38 appears to be a critical player in the regulation of hepatic glucose production.

In addition to its role in hepatic glucose metabolism, p38 plays a critical role in the lipid metabolism in the liver. We have recently observed that p38 plays an inhibitory role in hepatic lipogenesis[30]. Specifically, the levels of plasma triglyceride (TG) and hepatic lipid content were dramatically increased when the activation of 38 was blocked. The blockade of p38 activity was accompanied by an increase in transcription of the central lipogenic gene sterol regulatory element binding protein-1c (SREBP-1c). The expression of the SREBP-1c coactivator PGC-1α gene was also increased upon the inhibition of p38. These results together indicated that p38 can inhibit hepatic lipogenesis. The inhibitory role of p38 is perfectly in line with the stimulatory role of p38 in glucose production. Since glucose production from the liver is essential to maintain plasma glucose levels during fasting, the inhibitory role of p38 in lipogenesis will protect the substrate supply for the glucose production. The inhibitory role of p38 in hepatic lipogenesis probably also contributes to the weight (fat) loss in frank diabetes.

In contrast to its inhibitory role in hepatic lipogenesis, p38 can promote β-oxidation of fatty acid in the liver. Previously, it was shown that p38 could promote fatty acid oxidation in cardiomyocytes through p38 phosphorylation of PPARα[90]. Recently, it was shown that the activation of p38 in the liver by knocking out the MAP kinase phospgotase-1 (MKP-1) gene prevented fat accumulation in the liver under high fat diet[87]. The activation of p38 in the liver promoted fatty acid oxidation through increasing PPARα activity via phosphorylation[87].

p38 may also play a role in the transport of TG. Previously, it was shown in HepG2 heptoma cells that p38 could stimulate the expression of microsomal TG transfer protein (MTTP)[91-92]. MTTP is rate-limiting for the export of TG from hepatocytes and the assembly and secretion of apolipoprotein B-containing lipoproteins. The transcription of the MTTP gene is normally suppressed by insulin through ERK1/2 MAP kinases. However the suppressive role of ERK1/2 can be neutralized by the activation of p38[91]. We have also observed in the liver of mouse models and isolated primary hepatocytes that the expression of the MTTP gene is decreased when p38 activation is blocked (unpublished data).

p38 can influence plasma lipid, in particular cholesterol, profiles through the expression of low-density lipoprotein receptor (LDLR). The major role of LDLR in the liver is to facilitate the uptake LDL cholesterol from plasma. The cholesterol taken by hepatocytes will be further turned into bile and subsequently discharged through intestines and colon. Interestingly, p38 has been shown to play a critical role in the expression of LDLR and bile transport in hepatocytes. Specifically, the blockade of p38 can induce while the activation of p38 inhibits the expression of the LDLR gene in hepatoma cells. The blockade of p38 can also prevent activation and translocation of the bile salt export pump[95-96]. Furthermore, activation of p38 can stimulate the excretion of bile from hepatocytes[97].

6 ROLE OF p38 IN ATHEROSCLEROTIC CARDIOVASCULAR DISORDERS

p38 does not only play physiological and pathophysiological roles in cardiomyocytes, but also contributes significantly to the development of ASCVD. When the p38α gene was specifically knocked out from cardiomyocytes, adult mammalian cardiomyocytes can regain their capability of proliferation, suggesting that p38 normally suppresses the reproduction of cardiomyocytes[98]. This suppression may be important to maintain the normal size and function of the heart, but also limits the capability of the heart to repair the damage caused by infarction through the reproduction of cardiomyocytes[98]. Additionally, p38 also plays an important role in the development of cardiac hypertrophy and fi-

brosis. In cultured cardiomyocytes, p38 appears to promote hypertrophy[99-100]. However, results from intact mouse models showed a totally opposite role for p38 in cardiac hypertrophy. The transgenic mice with cardiac-specific expression of MKK3E or MKK6E, constitutive activators of p38, did not have cardiac hypertrophy, but did have cardiac fibrosis[101]. In contrast, transgenic mice with cardiac-specific expression of dominant-negative forms of p38α or p38β developed cardiac hypertrophy but were resistant to cardiac fibrosis in response to pressure overload[102].

p38 can regulate glucose uptake of cardiomyocytes through stimulating the expression of the Glut4 gene. For example, p38 is required for IGF-1-mediated transcription of the Glut 4 gene in adult rat cardiomyocytes[103]. Additionally, p38 may play a very important role in hypoxic/ischemic myocardial injuries because the blockade of p38 can significantly reduce cardiac injuries caused by reperfusion[104-107]. The blockade of p38 reduces cardiac injuries probably by preventing the accumulation of polymorphonuclear leukocytes in ischemic-reperfused myocardial tissue[106]. However, studies have also shown that the activation of p38 before cardiac reperfusion, i.e. preconditioning, can actually reduce the size of cardiac infarction caused by cardiac ischemia. Based on many studies, p38 is believed to be a trigger for preconditioning of cardiomyocytes[108-118]. The protective role of p38 in preconditioning is probably mediated by an increase of NO production via iNOS[112]. The harmful and beneficial effects of p38 in cardiac reperfusion is probably dependent on the timing of p38 activation, the isoform of p38 (p38α or p38β), and species of animals[110,119-121]. The role of p38 in human myocardial infarction remains currently undetermined.

The role of p38 in the development of ASCVD is complicated and involves several types of cells including at least monocytes/macrophages, vascular endothelial cells, and vascular smooth muscle cells. One of the key early events in atherosclerosis development is increased interaction of monocytes and endothelial cells in the vessel wall[122-124]. Monocytes are recruited to activated endothelial cells through monocyte chemotactic protein-1 (MCP-1), and rolled along the vascular endothelium, where they are activated by MCP-1 and IL-8[125]. Subsequently, monocytes will adhere firmly to the endothelium and transmigrate through the endothelial cell monolayer[124]. These monocytes will eventually become foam cells, which together with proliferated arterial vascular smooth muscle cells (VSMC) are a major component of atherosclerotic lesions[123]. MCP-1 is secreted by the activated monocytes, endothelial cells, and VSMC, while IL-8 is secreted by the activated endothelial cells and monocytes[126-129]. p38 plays a critical role in the secretion of both MCP-1 and IL-8 from these cells because the blockade of p38 can prevent the secretion of MCP-1 and IL-8[1,6,130-135]. Furthermore, p38 is a intracellular component of MCP-1-dependent transendothelial migration, integrin activation, and chemotaxis[136-139]. p38 can promote the differentiation of human monocytes into macrophages[140], inhibit proliferation and induce apoptosis of endothelial cells[7,141-142], stimulate endothelial migration[142], mediate insulin resistance in endothelial cells[9,143], downregulate endothelial progenitor cells[144], and accelerate endothelial progenitor cell senescence[8]. The activation of p38 is also involved in vascular remodeling[145-148]. p38 can be activated in monocytes/macrophages, vascular endothelial cells, and vascular smooth muscle cells by a variety of stimulants including reactive oxygen species (ROS)[132,141], high level of glucose[6-8], chylomicron remnants[133], free fatty acid[9], cholesterol[149], proinflammatory cytokines such as TNF-α[150], and growth factors such as PDGF[145-148].

p38 has also been shown to play a pivotal role in the development of hypertension in mouse models induced by salt/fat diet. Specifically, the salt/fat diet can activate p38 in vascular endothelial cells and induce hypertension in mouse models[151]. The blockade of p38 can completely prevent both the activation of p38 in endothelial cells and the development of hypertension induced by the salt/fat diet[151]. In addition, cholesterol can potentiate the vasoconstrictive action of endothelin-1 (ET-1). However, this potentiation effect of cholesterol is abolished by the blockade of p38[152]. Studies have also shown that p38 is a necessary compo-

nent of noradrenaline-induced contraction of small arteries[153-156].

7 CONCLUSIONS

p38 is widely involved in the energy metabolism in almost every important tissue/organ system such as adipose tissue, skeletal muscles, pancreatic islet, and liver. The wide range of p38 function is probably related two key aspects about p38. First, as described above, p38 can be activated by various stimulators including physiological reagents such as growth factors and hormones and pathophysiological reagents such as high levels of plasma glucose, fatty acids, and cytokines. Basically, any significantly changes surrounding a cell, including physical (UV lights, injuries), chemical (ROS, pH, and osmolarity), and biological (infections, cytokines, and hormones) variations, can activate p38. Second, p38 can activate many substrates through direct or indirect phosphorylation. Some of these substrates such as ATF-2, CREB, C/EBPs, and MEFs are very generic transcription factors, and are widely involved in the transcription of many genes. Due to the wide spectrum of p38 function, extra caution is needed in considering blocking or activating p38 activity for the treatment of certain disorders.

From this review, readers should get another consensus impression about p38: Many results about p38 in the control of energy metabolism are controversial or conflicting. Some p38 functions described even in the same tissue or same cell line are inconsistent. This is probably caused the fact that some of the p38 substrates can be activated by many other kinases. For example, CREB can be activated by several different kinases including at least PKA, p38, and ERK1/2, while ATF-2 can be activated by either p38 or JNK. Therefore, the final outcome of certain treatment will dependent upon not only p38, but also other kinases. Finally, as discussed above, some reports have cast significant doubt about the specificity of the commonly used chemical inhibitors such as SB203580. These chemicals may possess some intrinsic effects on some important proteins such as Glut4 independent of p38 activity.

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