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Signal transductions and nonalcoholic fatty liver

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Abstract

Nonalcoholic fatty liver disease is a common liver disease, and the incidence increases year by year. The pathogenesis of nonalcoholic fatty liver disease is correlated with insulin resistance and oxidative stress, which induces varied inflammatory cytokines (tumor necrosis factor-α, interleukin-1, interleukin-6, etc). Different signal transductions, such as mitogen-activated protein kinase, nuclear factor κB, activated protein kinase, Janus kinase 2/signal transducer and activator of transcription 3, peroxisome proliferator-activated receptor, phosphatidylinositol 3-kinase/protein kinase B, toll-like receptor, were activated by the pathogenic factors to regulate correlative reactions. Thus, an in-depth study of the signal transductions will probably provide new suitable solutions for the prevention and therapy of nonalcoholic fatty liver disease.

Keywords: nonalcoholic fatty liver disease; pathogenesis; signal transduction

Introduction

Ludwing came up with the term "Nonalcoholic Fatty Liver Disease" in 1980. It is a medical condition where too much fat builds up in the liver and cells in the liver break down, even when no alcohol is consumed. [1] Non-alcoholic fatty liver disease is a group of genetic, environmental, and metabolic stress-related diseases that include simple steatosis to nonalcoholic steatohepatitis, which can progress to cirrhosis and hepatocellular carcinoma. Nonalcoholic fatty liver disease affects 10% to 24% of the general population in various countries and the prevalence has even been up to 75 percent in obese people. [2] In the United States, it translates to approximately 30.1 million obese people affected by steatosis and 8.6 million with steatohepatitis. [3] Hyperlipidemia (hypertriglyceridemia and/or hypercholesterolemia), which is frequently associated with both obesity and type 2 diabetes, has been reported in 20% to 80% of patients with nonalcoholic steatohepatitis. [4] More and more proof shows that nonalcoholic fatty liver disease is the liver part of a metabolic syndrome that includes being overweight, having high insulin levels, peripheral insulin resistance, diabetes, high triglycerides, and high blood pressure.

In recent years, with the improvement in living standards and lifestyle, especially the change in the diet structure and decrease in physical activity, the number of nonalcoholic fatty liver disease patients increased year by year, and their ages are younger, therefore, nonalcoholic fatty liver disease has become a global public health problem. So far the pathogenesis of nonalcoholic fatty liver disease has not been fully clarified, and currently, a variety of factors based on the insulin-oxidative stress injury are considered to be involved in it. Still, its intracellular signal transduction mechanisms are not clear yet. As is known that intracellular signaling transduction is an important way for numerous factors to stimulate cell changes, in other words, the relevant causative factors play a role in the signal transmission within the liver cells. Currently, many factors such as free fatty acids, reactive oxidative stress, tumor necrosis factor-α, and interleukin-6 that cause insulin resistance, hepatocyte fat accumulation, and cellular injury are involved in the pathologic processes of nonalcoholic fatty liver disease by directly activating the c-Jun N-terminal kinase. [5] Otherwise, signaling pathways related to insulin resistance, oxidative stress, and inflammation fibrosis include: nuclear factor κB, adenosine monophosphate-activated protein kinase, Janus kinase/signal transducers and activators of transcription, peroxisome proliferator-activated-receptors, phosphatidylinositol 3-kinase/protein

kinase B, Toll-like receptor. Blocking any one of the above pathways would not be effective in the prevention and treatment of nonalcoholic fatty liver disease. [6]

The pathogenesis of nonalcoholic fatty liver disease is not a simple mechanism, the most widespread and prevailing theory is the so-called “two-hit” model. The first hit is insulin resistant leading to hepatic fat accumulation; on this basis a large number of adipokines (leptin, adiponectin, resistin) regulate free fatty acids (free fatty acids) to induce reactive oxidative stress injury is to be the second hit[3]; reactive oxidative stress could activate Fas ligand/Fas system, and progress to lead to structural protein of the Fas death zone to raise the downstream caspase family members to form the protease procascade reaction and then results in cellular disorganization and apoptosis; What’s more, the apoptotic hepatocytes could form the aggregation of inflammatory cells, thereby inducing a variety of inflammatory cytokines (tumor necrosis factor-α, interleukin-1, interleukin-6, interleukin-8, interleukin-18, monocyte chemoattractant protein, etc.) directly mediate fibrosis to induce inflammation of the liver and steatohepatitis, the process above is inflammatory-necrotic circulation[7]; One more hit by fibrosis factors (such as triglycerideF-β) results in the synthesis of hepatocyte extracellular matrix is greater than the degradation, thus forming a progressive fibrosis. [8] Although a variety of factors are involved in the pathogenesis of nonalcoholic fatty liver disease, the development of fatty liver is a highly integrated process. Now it's clear that intracellular signaling transduction is an important way for a variety of factors to stimulate cell changes. Namely, the relevant causative factors play an important role in the signal transmission within the liver cells, so it will be helpful for the prevention and cure of nonalcoholic fatty liver disease by in-depth study of the signal transductions in liver cells about the pathogenesis of nonalcoholic fatty liver disease.

Signal transductions and nonalcoholic fatty liver disease

Mitogen-activated protein kinase and nonalcoholic fatty liver disease

Mitogen-activated protein kinase is a class of serine/threonine protein kinases that widely exist in mammalian cells and mediates signal conduction from the cell surface to the endonuclear, which includes cell-extracellular signal-regulated kinases, c-Jun amino-terminal kinase, and p38mitogen-activated protein kinase. The extracellular signal-regulated kinases play a major role in the cellular response induced by growth factor stimulation, and Jun N-terminal kinase and p38 are related to stress and inflammation. [9] Mitogen-activated protein kinase activation is involved in the regulation of cell proliferation, differentiation, transformation, and apoptosis through phosphorylation of nuclear transcription factors, cytoskeletal proteins, and enzymes, which is closely related to mechanisms of inflammation, cancer, and many other diseases. [10] In recent years, many researchers have indicated that Jun N-terminal kinase is closely related to insulin resistance; And inflammatory cytokines such as tumor necrosis factor α, free fatty acids, oxidative stress that could lead to insulin resistant, hepatocyte fat accumulation and cell injury were involved in the pathogenesis of nonalcoholic fatty liver disease rat model by activating the Jun N-terminal kinase. [5] Dynamic observation of the Jun N-terminal kinase signaling pathway protein expression in rat liver tissue and the generated impact and mechanism of insulin resistance in the process of the formation of high-fat-diet-induced nonalcoholic fatty liver disease from the first week, drawing that the high-fat-diet rat liver tissue Jun N-terminal kinase1 protein expression levels were higher compared with the control group over the same period, and Jun N-terminal kinase1 protein expression and insulin resistant level was positively correlated from the end of the second week, which indicated that high-fat- diet activated Jun N-terminal kinase1, diminished insulin signaling, thus causing insulin resistant. [11] p38 signaling pathways are involved in the cell inflammatory response and apoptosis process under stress conditions, which are related to the release of a variety of inflammatory cytokines (such as interleukin-1, tumor necrosis factor-α and interleukin-6, etc.) after activation. [12] To study the action mechanism of an antioxidant in high-fat-diet rats, Sinha-Hikim et al [13] analyzed the phosphorylation of Jun N-terminal kinase and p38 signal level in the high-fat-diet-induced nonalcoholic fatty liver disease rats, which confirmed a significant ($P<0.05$) increase in both phospho-Jun N-terminal kinase and phospho-p38mitogen-activated protein kinase levels than the normal control group and significantly reduced after antioxidants treatment, and drew that oxidative stress can promote activation of both p38mitogen-activated protein kinase and Jun N-terminal kinase, which through mitochondria-dependent intrinsic pathway signaling promotes apoptosis in various cell types. The pathogenesis of nonalcoholic fatty liver disease is related to insulin resistance and a variety of inflammatory cytokines, so it is known that the Jun N-terminal kinase and p38 signaling pathways are involved in the pathological process of nonalcoholic fatty liver disease.

Nuclear factor κB and nonalcoholic fatty liver disease

Nuclear factor-κB is a nuclear transcription factor widely present in varied cells, which could regulate a variety of cytokines involved in inflammation, adhesion molecules, and protease gene transcription in vivo, and it is closely related to inflammation. Nuclear factor κB activation can promote the expression of inflammatory cytokines, while inflammatory factors, in turn, can further enhance the activity of nuclear factor κB, to make the inflammation worse. [14] Cytokines (tumor necrosis factor-α, TNF-β, interleukin-1, etc.), growth factors (such as insulin), immune receptors, the medium, stress response (oxygenation, etc.), bacteria and products (lipopolysaccharide, etc.), viruses and the product, biological xenobiotics, environmental hazards, and other factors could induce nuclear factor κB activation [14], initiating transcription of many genes such as tumor necrosis factor-α, interleukin-1, interleukin-6, interleukin-8 after activation. These gene products regulated by nuclear factor κB are involved in inflammation of the liver, liver fibrosis, liver regeneration, and apoptosis. In addition, free fatty acids, and reactive

oxidative stress initiate the activation of the transcription factor nuclear factor κB, which leads to increased pro-inflammatory cytokines (tumor necrosis factor-α, triglycerideF-β, interleukin-1β, interleukin-6, interleukin-8) production, and insulin resistance in the liver. [4] Several pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1, interleukin-6, various adipocytokines, and several transcription factors and kinases such as c-Jun N-terminal kinase and a kinase located proximal of nuclear factor-κB participate in the occurrence and development of the insulin resistant. [6] The insulin-resistant and inflammatory cytokines are related to the pathogenesis of nonalcoholic fatty liver disease. Some experiments confirmed that nonalcoholic fatty liver disease rat liver tissue nuclear factor κB expression was significantly enhanced than the normal group. [15] Therefore, the nuclear factor κB signaling pathway is probably involved in the pathological process of nonalcoholic fatty liver disease.

Activated protein kinase and nonalcoholic fatty liver disease

Adenosine monophosphate-activated protein kinase (activated protein kinase) is a heterologous trimeric protein kinase activated by adenosine monophosphate and widely exists in eukaryotic cells, which is a central regulator of cellular energy balance and plays an important role in fatty acid metabolism through the fatty acid biosynthetic pathway. Activated protein kinase is composed of α, β, and γ subunits, α is the catalytic subunit controlled by the adenosine monophosphate/adenosine triphosphate ratio, which could be activated by stress stimuli caused by any reduction in intracellular adenosine triphosphate that include metabolic product, the oxidation stress, hypoxia and low sugar [16]; when the adenosine monophosphate/adenosine triphosphate ratio increases, activated protein kinase phosphorylation activates a large number of downstream target molecule acetyl coenzyme A carboxylase, which reduce the use of adenosine triphosphate (inhibition of glycogen, fat and cholesterol synthesis) and increase adenosine triphosphate production (promotion of fatty acid oxidation and glucose transporter) [17], so that the cell catabolism increases. Sterol regulatory ele-ment-binding proteins are a family of transcription factors that control the expression of genes required for the biosynthesis of cholesterol, fatty acids, triglycerides, and phospholipids, and sterol regulatory element-binding protein-1c preferentially controls the expression of genes involved in triglyceride synthesis and accumulation, such as fatty acid synthase and acetyl coenzyme A carboxylase. [18] Therefore, activated protein kinase activation suppresses the expression of acetyl coenzyme A carboxylase and fatty acid synthase via down-regulation of sterol regulatory element-binding protein-1c. [19]. Activated protein kinase activators, metformin, have been shown to inhibit the expression of the SREPB-1c gene and to prevent the development of hepatic steatosis. [20] Adiponectin is a recently discovered hormone against diabetes insulin resistance, which comes from the fat cells, has the function of regulating energy balance, glucose, and fat metabolism, and it is closely related to insulin resistance and atherosclerosis hardening. Adiponectin is inhibited by tumor necrosis factor-α, interleukin-6, resistin, and insulin, and stimulates mitochondrial β-oxidation by activating activated protein kinase and inhibits lipogenesis by down-regulating sterol regulatory element-binding protein-1c. [16] Yamauchi et al. also believed that its signal transduction mechanisms were activating activated protein kinase function. [21] In conclusion, activated protein kinase is closely related to insulin resistance and liver lipid content. Several experimental studies also confirmed that phosphorylated activated protein kinase protein expression level in high-fat-diet-induced nonalcoholic fatty liver disease was significantly lower than the normal control group [16], which suggested that activated protein kinase was involved in the pathological process of nonalcoholic fatty liver disease.

Janus kinase 2/signal transducer and activator of transcription 3 and nonalcoholic fatty liver disease

Leptin is the main regulator of fat in the organism. It is released from the fat tissue into blood, then dispensed into the tissues (musculoskeletal, adipose tissue, peripheral lymphoid tissue, central nervous system, gastrointestinal tract, and liver) over the body by circulation and combines with its receptors, which then interact with Janus family protein tyrosine kinase/signal transduction and activates transcription factors, mainly Janus kinase 2/signal transducer and activator of transcription 3 [22], to cause the related biological effects, and to exhibit the function of diet control, energy metabolism regulation and interfere with the role of insulin in the liver, thus decreasing triglyceride, elevating the insulin sensitivity of liver and peripheral tissues and reducing fat deposition [4]; When the receptor expression is in dysfunction, Janus kinase 2/signal transducer and activator of transcription 3 signal transduction disorder occurs, thus leptin could not play the biological effects to cause the leptin resistance. Nonalcoholic fatty liver disease patients commonly have leptin resistance [23], thereby promoting lipid synthesis in the liver and leading to the development of fatty liver. Bartek et al. found that leptin and free leptin receptors in the serum of patients with fatty liver were significantly increased, suggesting that leptin bound to its receptor may exist obstacles to cause leptin resistance. [24] The experimental results showed that leptin receptor mRNA and phosphorylation of Janus kinase 2/signal transducer and activator of transcription 3 levels in nonalcoholic fatty liver disease rat liver were lower than that in the control group. [3] To sum up, leptin Janus kinase 2/signal transducer and activator of transcription 3 signal pathway is probably involved in the pathological process of nonalcoholic fatty liver disease.

Peroxisome proliferator-activated-receptors and nonalcoholic fatty liver disease

Peroxisome proliferator-activated receptors are ligand-activated transcription factors of the nuclear receptor family that exist in three subtypes, namely α, β, and γ. Peroxisome proliferator-activated receptor alpha mainly distributes in the tissue with a high efficiency of mitochondrial fatty acid oxidation, which highly expresses in the liver, and peroxisome proliferator-activated receptor gamma highly presents in adipose tissue and the immune system.

Peroxisome proliferator-activated-receptors regulate not only the expression of genes involved in fatty acid synthesis, oxidation, and storage but also participate in the molecular mechanism of altered metabolic homeostasis, such as is found in type 2 diabetes or obesity. [25] Peroxisome proliferator-activated receptor alpha agonists and peroxisome proliferator-activated receptor gamma agonists are involved in diabetes mellitus and dyslipidemia, and they play an important role in insulin resistance. [26] Seo et al found peroxisome proliferator-activated receptor agonists, especially a peroxisome proliferator-activated receptor alpha agonist, improved the histological and biochemical parameters in the nonalcoholic fatty liver disease rat model by inducing fatty-acid metabolic enzymes. [27] Peroxisome proliferator-activated receptor alpha is considered to be the main regulator of fatty acid oxidation: peroxisome proliferator-activated receptor alpha is activated in combination with polyunsaturated fatty acids, thereby it can improve insulin resistance, reduce blood lipids, promote β-oxidation of fatty acids, inhibit lipogenesis gene expression, inhibit genes transcription related with inflammatory response, which are conducive to control nonalcoholic fatty liver disease. [28] In addition, peroxisome proliferator-activated receptor alpha is activated by adiponectin and could inhibit the NF-kB pathway. [17] Peroxisome proliferator-activated receptor gamma enhances insulin action, FFA oxidation, and adiponectin secretion, and inhibits secretion of proinflammatory cytokines [17], so peroxisome proliferator-activated receptor gamma could improve nonalcoholic fatty liver disease. However hepatic peroxisome proliferator-activated receptor gamma 2 expression is increased in high-fat-diet-fed mice due to elevated rates of lipogenesis via the upregulation of de novo lipogenic genes fatty acid synthase and acetyl coenzyme A carboxylase. [29] So it is still not conclusive as to whether the peroxisome proliferator-activated receptor gamma is beneficial or detrimental. Thus, we could know peroxisome proliferator-activated-receptors play an important role in the pathogenesis of fatty liver.

Phosphatidylinositol 3-kinase/protein kinase B and nonalcoholic fatty liver disease

The phosphatidylinositol 3-kinase pathway is one of the main signal transduction pathways of insulin action, and protein kinase B as phosphatidylinositol 3-kinase downstream kinase is the important serine/threonine kinase in this pathway which is primarily responsible for the conduction of the initial biological information by phosphatidylinositol 3-kinase. Phosphatidylinositol 3-kinase/protein kinase B signaling pathway as an insulin downstream molecular pathway, plays an important role in a variety of biological processes such as cell metabolism, cell cycle regulation, cell growth, apoptosis, glucose transporter, and it is closely related to the development of insulin resistant. [3] In addition, the p85 subunit of phosphatidylinositol 3-kinase could be combined with the insulin receptor substrate, so close to the insulin receptor and is anchored in the cell membrane, thereby activating the p110 subunit to regulate fat cells and liver cells in the uptake of glucose through a series of signal transduction. [30] Yuan J et al. found that long-term insulin-stimulated HepG2 cells could lower insulin signal transduction through the phosphatidylinositol 3-kinase signaling pathway to inhibit insulin signaling, leading to insulin resistance, meanwhile it has been confirmed that insulin signal could not pass in the direction of glucose uptake through the phosphatidylinositol 3-kinase pathway and to cause insulin resistant if the phosphatidylinositol 3-kinase expression and activity reduce. [31] Akt could suppress fatty acid oxidation gene expression, thereby regulating the process of hepatic glucose and lipid metabolism. [32] There were some study results showed that nonalcoholic fatty liver disease rat liver phosphatidylinositol 3-kinase and Akt protein were significantly lower than the normal groups. [33]

Toll-like receptor and nonalcoholic fatty liver disease

Toll-like receptor family members are characterized by highly evolutionarily conserved Tinsulin resistant domain (Toll/interleukin-1R domain) in the intracellular region, which could recognize various pathogen-associated molecular patterns (Padenosine monophosphate) by the leucine repeat (leucine-rich repeat LRR) Ribbon in the extracellular region. Various toll-like receptors could induce a series of gene activations through the same or a different signal transduction pathway in pathogen invasion minutes, resulting in cell secretion of pro-inflammatory cytokines and chemokines, upregulation of co-stimulatory factor, increase of antigen-presenting ability, which cause systemic inflammatory response and the occurrence of innate immune response. [34] Knockout rats results showed that toll-like receptor 4 and toll-like receptor9 promoted the development of nonalcoholic fatty liver disease. [35] Toll-like receptor4 is the lipopolysaccharides receptor, and lipopolysaccharides elevation in most animal models of nonalcoholic fatty liver disease causes liver steatosis, hepatic insulin resistance, and increased liver weight, so the toll-like receptor4-lipopolysaccharides is the key pathway to promote nonalcoholic fatty liver disease development. [36] In addition, free fatty acids could also activate toll-like receptor4. [35] Toll-like receptor9 signal is related to the development of nonalcoholic steatohepatitis, toll-like receptor9 missing rats present less steatohepatitis, insulin resistance, and fiber reaction. [37] MyD88 is an adapter protein of all toll-like receptors except toll-like receptor3, which is related to the expression of a variety of inflammatory cytokines and inflammatory chemokines, and the toll-like receptor-MyD88 signaling pathway could also activate Jun N-terminal kinase and nuclear factor κB signaling [35], while Jun N-terminal kinase and nuclear factor κB signals are involved in the pathogenesis of nonalcoholic fatty liver disease. Toll-like receptor signal mediates the occurrence of steatosis, inflammation, and fibrosis, which is closely related to the incidence of nonalcoholic fatty liver disease.

Conclusions

Nonalcoholic fatty liver disease is increasingly common in the crowd, the "two-hit" theory based on insulin resistance and oxidative stress is the main theoretical basis to explain its pathogenesis. Based on the pathogenesis of nonalcoholic fatty liver disease, it could be found that mitogen-activated protein kinase, nuclear factor κB,

activated protein kinase, Janus kinase 2/signal transducer and activator of transcription 3, peroxisome proliferator-activated-receptors, phosphatidylinositol 3-kinase/protein kinase B, toll-like receptor signaling pathways are closely related with the incidence of nonalcoholic fatty liver disease. In the nonalcoholic fatty liver disease pathogenesis, the same kind of stimulation could activate different signal pathways, whereas different stimuli could activate a signal pathway: Inflammatory cytokines (tumor necrosis factor-α, triglycerideF-β, interleukin-1, interleukin-6, etc.) could activate Jun N-terminal kinase, p38 and nuclear factor κB signaling pathways, in turn, the activation of these signaling pathways could increase the expression of inflammatory cytokines; adiponectin could reduce fatty acid synthesis and enhance fatty acid β-oxidation via activation of adenosine monophosphate kinase, and then resist steatosis and increase insulin sensitivity, but also could activate peroxisome proliferator-activated receptor alpha and inhibit NF-kB pathway; Resistin could inhibit activated protein kinase activity in liver and skeletal muscle, impede insulin signaling phosphatidylinositol 3-kinase/protein kinase B pathway and induce nuclear factor κB nuclear tran-scription; leptin plays biological effects through Janus kinase 2/signal transducer and activator of transcription 3, may also stimulate activated protein kinase to increase in β-oxidation. These signaling pathways are interconnected to form a network of signaling pathways, so blocking any one of the pathways could not be effective in preventing and treating nonalcoholic fatty liver disease. Therefore, an in-depth study of liver cell signaling in the nonalcoholic fatty liver disease pathogenesis process will contribute to the prevention and treatment of nonalcoholic fatty liver disease.

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