Role of cytokines in pathogenesis and progression of nonalcoholic steatohepatitis

Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) has been considered to be the hepatic manifestation of metabolic syndrome, and may progress to Non-alcoholic steatohepatitis NASH and/or hepatocellular carcinoma (HCC), thus being associated with a high cardiovascular and carcinogenic risk. Thus, it becomes necessary to understand the underlying mechanisms involved in the genesis of NAFLD and its progression to NASH and HCC, so that a better therapeutic approach can be defined in an attempt to cease and reverse this progression.

Objective: To review main mechanisms involved in NASH, from inflammatory pathways, microbiota, cytokines and some more current theories such as the role of the extracellular trap of degranulation and neutrophil production (NETs). Methods: An integrative review was conducted with active search of articles in English using Medline, Embase, Lilacs and Pubmed data, using descriptors related to “non-alcoholic fatty liver disease”, “non-alcoholic steatohepatitis”, “pathophysiology”, “cytokines” and “molecular mechanisms” without restriction of period. Results: 182 articles were found, of which 40 were selected for this review, including original articles, clinical and experimental research, and systematic reviews.

Discussion: Non-alcoholic fatty liver disease may occur through increased absorption, fatty acid synthesis, lipogenesis, reduction of triglyceride hydrolysis and mitochondrial beta-oxidation of fatty acids, contributing to increased production of free radicals and reactive oxygen species, involving many inflammatory mediators. Cytokines may play an active role in the development and progression of NAFLD by stimulation hepatic inflammation, cell necrosis, apoptosis and induction of fibrosis. However, they are also essential for liver regeneration.

Conclusion: metabolic dysfunction leads to lipotoxicity, innate immune responses and the resulting pattern of cellular inflammation in the liver are probably also relevant for liver fibrogenesis and hepatocarcinogenesis. The most studied and described cytokines were adiponectin, leptin, TNF-α, IL-6, visfatin, A-activator and chemerin.. This knowledge becomes fundamental for new diagnostic procedures and therapeutic strategies to avoid NASH progression.

Keywords: steatosis, non-alcoholic fatty liver disease, inflammatory mediators, oxidative stress

Introduction

Nonalcoholic fatty liver disease (NAFLD) is an important obesity outcome, being recognized as the hepatic manifestation of metabolic syndrome. The process happens to children and adults, is characterized by the presence of high levels of fat storage in the liver (steatosis). With inflammation, cell death and fibrosis, the process may result into the final stage of hepatic disease, or even hepatocellular carcinoma. Nowadays, excess of liver fat is recognized as an independent marker of cardiovascular risk.1

Nonalcoholic fatty liver disease is a spectral condition and is subdivided in two main groups, according with clinical and morphological aspects: Hepatic steatosis or just fat liver and non-alcoholic steatohepatitis (NASH).2 The first stage is characterized by lipid accumulation in hepatocytes and it usually shows a non-progressive clinical course, whilst the last one is a more aggressive way of NAFLD and it may progress to cirrhosis. This heterotopic fat triggers variable degrees of necroinflammatory phenomena, which corresponds to steatohepatitis, associated condition of progressive disease.7

Nonalcoholic fatty liver disease is considered one of the most prevalent liver diseases in developed countries. Its clinical importance has grown for the last years, mainly because of obesity epidemic, sedentarism and hypercaloric diet from western countries, reflecting the rise of cardiovascular risk and endocrine-metabolic diseases. The prevalence of NAFLD varies from 2,8% to 88%, depending on population and the methods of investigation.1 The main risk factors associated to metabolic syndrome are abdominal obesity, insulin resistance, diabetes, and dyslipidemia. Curiously, NAFLD can also be describing non-obese and non-diabetic patients.8-9 However; it’s still not clear how these metabolic factors can affect the pathogenesis and progression.9

The origins of hepatocellular injury and lobular inflammation which distinguish NASH from simple steatosis have intrigued investigators, but it is now widely accepted that NASH results from...
liver lipotoxicity.\textsuperscript{7} It is believed that the mechanism varies according to the accumulated molecules and the different forms of organization.

Pathophysiological mechanisms are still under investigation; nevertheless triglyceride accumulation inside the hepatocytes, result of insulin resistance, is considered the first step in pathogenic model. Oxidative stress, resulting from fatty acids mitochondrial oxidation, and inflammatory cytokines expression, has been pointed out as secondary causal factors that lead to hepatic impairment, fibrosis, and inflammation.\textsuperscript{5–10}

Intrahepatic fatty acids storage is deeply related with insulin resistance which increases hepatocyte susceptibility to aggression, as oxidative stress, mitochondrial dysfunction, overproduction and releasing of secondary proinflammatory cytokines, as well as endotoxin-mediated activation of innate immune response. The susceptibility to these factors can also explain the progression of NAFLD to NASH.\textsuperscript{5–10} Insulin resistance plays a central role in NAFLD pathogenesis. It is an inadequate answer to physiological effects of insulin circulating in specific target tissues, skeletal muscle, liver, and adipose tissue. Inflammatory cytokines activate a lot of kinases just as serine kinase IKKβ, mTOR/S6 kinase and protein kinase activated by mitogen (MAPK), as well as cytokine signaling suppressor proteins (SOCs) that meddle in the sight way and insulin action on adipocytes and hepatocytes.\textsuperscript{5–12}

Molecular changes on insulin signaling result finally in accumulation of hepatic triglycerides. In skeletal muscle, peripheral insulin resistance affects mostly a large part of the total glucose uptake.\textsuperscript{9} In adipose tissue, this resistance slows the lipogenic action of the insulin, that results in releasing of non-esterified fatty acids; in other words, insulin resistance increases the lipolysis of triglycerides and inhibits esterification of free fatty acids in adipose tissue. The result is rising serum levels of free fatty acids, which are absorbed by the liver.\textsuperscript{10} High plasma glucose and fatty acids concentrations result in higher lipids hepatic uptake. This increase in supply of fatty acids to the liver compromises the β-mitochondrial oxidation when it causes stress in the enzymatic system. As a result, these substances accumulate in the hepatocyte, determining the appearance of hepatic steatosis.\textsuperscript{11} Moreover insulin resistance also inhibits the alternative metabolism of free fatty acids (FFAs), through oxidation. Hepatic exportation of very low density lipoproteins (VLDL) can be inhibited by decreasing synthesis of apolipoprotein B (Apo B) and less conjugation to triglycerides, by the triglyceride microsomal transfer protein (MTP).\textsuperscript{12}

Summing up, fatty liver disease results from peripheral resistance to insulin and hyperinsulinemia, free fatty acids rising supply, hepatic lipogenesis increasing and reduction of hepatic exportation of triglycerides through VLDL.

**Aims**

Make a integrative review about pathophysiological mechanisms involved in NAFLD, molecular bases and signaling pathways that are determinant to progression from steatosis to non-alcoholic steatohepatitis

**Method**

An active search was carried out in Medline, Embase, Lilacs and PubMed data basis, using as descriptors: steatosis, nonalcoholic steatohepatitis, pathophysiology, cytokines, and molecular mechanisms.

**Results**

Between 1998 and 2018, 182 articles written in English, were found strictly related to the theme, from these, 40 originals articles were selected to review, involving clinical and experimental studies, as well as reviewing articles, systematic review and meta-analysis.

**Discussion**

Cytokines are soluble molecules that are involved in intracellular communication. They are produced by a wide variety of cells, including hepatic cells. They comprise diverse subfamilies, including interferon, interleukins, tumor necrosis factors (TNF), transforming growth factor (TGF), colony stimulating factors, and chemokines.\textsuperscript{13} Cytokines can mediate several fundamental biological processes, including body growth, adiposity, lactation, hematopoiesis, as well as inflammation and immunity. They are implicated in various pathologies like arthritis, atherosclerosis, rheumatoid arthritis, systemic lupus erythematosus, psoriasis and NASH.\textsuperscript{14}

Under physiological conditions, the hepatic generation of constitutive cytokines is absent or minimal in the liver; nevertheless, pathological stimuli like lipid accumulation induce hepatic cells to produce these inflammatory molecules. Cytokines may play an active role in the development and progression from NAFLD to NASH through stimulation of hepatic inflammation, cellular necrosis, apoptosis, and induction of fibrosis. However, they are essentials to hepatic regeneration as well.

Total mammalian adipose tissue is composed of two distinct functional types: white and brown adipose tissue. The first one is responsible for energy storage and is a releasing site of hormones and cytokines which modulate body metabolism and insulin resistance. Its accumulation is associated with obesity. On the other hand, the brown adipose tissue, rich in mitochondria, is important for energy expenditure in form of thermogenesis, since it can modulate the susceptibility for corporeal weight gain. Physiologically, it focuses more on children, but it can also be found on adults’ adipose tissue.\textsuperscript{15–17}

Visceral adipose tissue plays a crucial role in hepatic steatosis pathogenesis, since it participates in production of more adipocytokines, such as Tumor Necrosis Factor alpha (TNF-α), resistin, and adiponectin, which are involved in insulin resistance and varying degrees of inflammation.\textsuperscript{18} Several therapeutic approaches, such as weight loss and insulin sensitizers are indicated to decrease cytokines from adipose tissue, reducing free fatty acids supply to the liver.\textsuperscript{19}

Inflammatory markers most associated with hepatic steatosis and steatohepatitis are: tumor necrosis factor α (TNFa), interleukins-6 (IL-6), 8 (IL-8), 18 (IL-18), metalloproteinases, and ultra-sensitive C-reactive protein. Interleukin-6 levels are increased only in NAFLD, whilst the ultra-sensitive CRP was shown to be elevated in obese patients. On the other hand, IL-18 deficiency caused polyphagia, obesity and insulin resistance in laboratory rats. Fatty acids and carbohydrates saturated diet is associated to high levels of TNF-α and decreased adiponectin levels in NAFLD due to high levels of fructose content present in these foods.\textsuperscript{19,20}

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Adiponectin and leptin are the main adipocytokines synthesized by adipose tissue and implicated in the pathogenesis of NAFLD. Studies have shown a close association of hyperadipocytokinemcia in patients with NAFLD compared to healthy controls and that circulatory adiponectin is inversely correlated with hepatic steatosis and insulin resistance, but not with progressing NAFLD.\textsuperscript{19,21–26}

Adiponectin is the most abundant cytokine, synthesized only by adipose tissue.\textsuperscript{23,24} It acts by stimulating anti-inflammatory cytokines secretion, such as interleukin-10 (IL-10), for example, which blocks the activation of nuclear factor kappa B (NFkB) and inhibits TNF-α and interleukin-6.\textsuperscript{25} There is evidence that adiponectin decreases hepatic and systemic insulin resistance. It attenuates necroinflammation and hepatic fibrosis and is considered a marker of NAFLD seriousness.\textsuperscript{25,29}

Drugs that increase adiponectin levels may be considered therapeutic targets for NAFLD. The identification of molecules involved in adiponectin signaling pathways and the potential role of the resistance of their receptors in NASH have been poorly investigated and may be promising in treatment.\textsuperscript{18,22,25}

Leptin is a hormone peptide derived from adipocytes and related to food intake and energy expenditure, controlling body weight and satiety, through a hypothalamic negative feedback mechanism.\textsuperscript{18–22} Serum levels of Leptin are high in obesity,\textsuperscript{23} as a result of what has been characterized as resistance to leptin,\textsuperscript{24} phenomenon that may already be present in obese children.\textsuperscript{25}

Resistin is a cytokine secreted by adipose tissue and macrophages, which probably acts as an insulin antagonist, contributing to glucose intolerance development in obese individuals. Evidence suggests the proinflammatory action of this cytokine by stimulating TNF-α and Interleukin-12 (IL-12) in macrophages, through NFkB. In humans, their levels are elevated and may serve to distinguish steatosis from steatohepatitis.\textsuperscript{17,20}

TNF-α is produced by B and T lymphocytes (Natural Killer), macrophages and fibroblasts and plays a central role in evolution from NAFLD to NASH. This denomination refers to its biological property of inducing hemorrhagic necrosis in certain tumors. Synthetically inactivated, it becomes toxic in tissues, inducing necrosis and angiogenesis. At low concentrations, TNF-α stimulates cell growth. On the other hand, in high concentrations, it inhibits the cellular development induced by other cytokines, which are associated to obesity and insulin resistance in animal and human models.\textsuperscript{25} This cytokine has a lipogenic and fibrogenic effect, mediated by paracrine mechanism involving the activation of Kupffer cell, secretion of soluble mediators that stimulate tto cell activation into myofibroblast, which in turn is responsible for synthesizing extracellular matrix components that can be used in diagnosing NASH fibrosis.\textsuperscript{26}

Activin-A is reported to induce follicle-stimulating hormone or FSH and to regulate the menstrual cycle; however, during the last few years activin-A has been found participate in a number of crucial cellular functions, including regulatory of cell cycle and differentiation, apoptosis, metabolism and homeostasis regulation, tumorigenesis, immune responses, wound healing, and fibrosis. Activin-A belongs to transforming-beta growth factor (TGFβ) cytokine superfamily and is a dimer of two identical β subunits. Activin-A, exerts its effects through two types of serine/threonine kinase receptors. Activin-A binds first to type II receptors phosphorylate and activate type I receptors. Receptor type I, then initiate a number of intracellular cascades via smad2/3 phosphorylation. There are 3 activin receptors type I and 2 type II (ACVR1A, B & C and ACVR2A & B). A number of intra- and extracellular inhibitors, including follistatin and follistatin-related proteins that bind and disable activin-A, coordinate its effects.\textsuperscript{31–35}

One well established effects of activin-A is it’s role in the wound cure and fracture consolidation. Deregulation of this process is related to pathological collagen accumulation. Studies in animal models and small series of patients suggest that activin-A system can participate in inflammation and liver fibrosis.\textsuperscript{20,31–34}

Oxidative stress is also responsible for production of proinflammatory cytokines, among which stand out: TNF-α, transforming growth factor alpha and beta (TGF-α and TGF-β), interleukin-6 (IL-6), interleukin-8 (IL-8), NFkB and adiponectin. These cytokines are produced by lymphocytes and Kupffer cells, mediated by free radicals and it may act by changing the mitochondrial membrane permeability and inhibiting the respiratory chain.\textsuperscript{35}

Although TNF-α inhibition in NAFLD animal models has encouraged therapeutic perspectives in humans, the role of this cytokine remains under investigation. In humans TNF-α levels were higher in obese than in lean individuals, and were correlated with insulin resistance. Besides, a positive correlation was demonstrated between liver fibrosis and TNF-α circulating levels in patients with NASH. Genetic polymorphism has been described in patients with NAFLD and NASH. Rats genetically deficient for the TNF-α receptor were resistant to develop NASH.\textsuperscript{34,26,36}

Obesity is an inflammation state characterized by pro-inflammatory cytokines increased levels as TNFα and interleukin-1 beta (IL-1β). In this regard, exists a lack of studies in hepatic tissue about the role of TNFα receptor 1 (TNFR1) in the context of obesity and insulin resistance during NAFLD progression. Mechanisms involved in HFD-derived IL-1β release and impairment of insulin signaling are still unknown. The IL-1β effects on liver insulin sensitivity and apoptosis through TNFR1-dependent pathways was studied. It was shown that knocking-out TNFR1 induces an enhanced IL-1β plasmatic release upon HFD feed. This was correlated to higher hepatic and epididymal white adipose tissue (eWAT) mRNA levels. In vivo and in vitro assays confirmed an impairment in hepatic insulin signaling, in part due to IL-1β-induced decrease of AKT activation and diminution of IRS1 levels, followed by an increase in inflammation, macrophage (resident and recruited) accumulation, hepatocyte apoptotic process and finally hepatic damage. Additionally, TNFR1 KO mice displayed higher levels of pro-fibrogenic markers. TNFR1 signaling disruption upon a HFD leads to an accelerated progression from simple steatosis towards a more severe phenotype with many NASH features, pointing out a key role of TNFR1 in NAFLD progression.\textsuperscript{33,35–36}

Ghrelin is a peptide hormone that was discovered in 1999, and acts as a growth hormone receptor binder (GHS-R) with a single post-translational modification of the residue Ser, it’s produced in stomach, pancreas and large intestine. Grelin has part in stimulating appetite and controlling body mass. Grelin O-acetyl transferase (GOAT) is the enzyme that acylates the ghrelin peptide to form acyl-ghrelin (AG). Recent studies have shown that des-acyl ghrelin (DAG) is no longer regarded as an inert product of AG. Ghrelin stimulates gluconeogenesis in the liver and prevents the suppression of glucose production by insulin; however, DAG inhibits the production of glucose in the liver.\textsuperscript{37}

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Chemerin is a protein identified as the natural linker ChemR (chemerinR), an orphaned G protein receptor coupled, expressed in immature dendritic cells and macrophages. Both adipose tissue and liver were identified as a source of this adipokine. It was observed that systemic levels of this cytokine decreases after successful bariatric surgery and this was paralleled by a significant reduction of hsCRP levels. This fits into several studies proving that the severity of NAFLD correlates with increased levels of chemerin. This adipokine protects from HCC and is reduced in human HCC. Hepatocellular carcinoma (HCC) not only develops in the cirrhotic liver but can also arise in the noncirrhotic liver in NASH. Chemerin is highly expressed in the liver and modulates insulin response and tumor growth, and may thus have a role therein. Interestingly, a low level of chemerin in HCC tissues of patients has been associated with worse outcomes. The relationship between the increase of chemerin and the degree of apoptosis suggests an association between this cytokine and the post-titration of altered cellular immune response.

Irisine is a recently discovered myocin capable of increasing energy expenditure related to thermogenesis and to improve metabolism. Serum irisin levels differ between obese and non-obese patients with NAFLD. Despite the similar levels of circulating irisin between the steatosis and steatohepatitis groups, irisine may be independently and positively associated with the presence of portal inflammation. Future experimental and clinical studies are needed to confirm and extend this information.

An unbalanced profile of adipokines in obesity contributes consecutively to metabolic inflammation in NAFLD, which is associated with a substantial risk of developing hepatocellular carcinoma (HCC) also in the non-cirrhotic phase NASH. Both adiponectin and leptin were related to hepatic tumorigenesis, especially in preclinical models.

**Conclusion**

Pathogenesis of NAFLD is multifactorial and progression to NASH represents a complex process that is not fully understood. It has been suggested that occurs in multiple parallel stages. The most widely described and studied cytokines in the pathogenesis of non-alcoholic steatohepatitis are adiponectin, leptin, ghrelin, TNF-α, activin-A, chemerin and resistin. Inflammatory mediators are of fundamental importance to develop new diagnostic modalities and therapeutic targets. The pathogenesis of NAFLD is multivariate; however, current studies have highlighted the role of increased proinflammatory cytokines accelerating progression from simple steatosis towards a more severe phenotype.

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**Conflicts of interest**

No conflicts of interest, subsidies or other financial support to declare.

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