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# Pathogenesis of Nonalcoholic Steatohepatitis

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**Nonalcoholic steatohepatitis (NASH) is a necro-inflammatory response that ensues when hepatocytes are injured by lipids (lipotoxicity). NASH is a potential outcome of nonalcoholic fatty liver (NAFL), a condition that occurs when lipids accumulate in hepatocytes. NASH may be reversible, but it can also result in cirrhosis and primary liver cancer. We are beginning to learn about the mechanisms of progression of NAFL and NASH. NAFL does not inevitably lead to NASH because NAFL is a heterogeneous condition. This heterogeneity exists because different types of lipids with different cytotoxic potential accumulate in the NAFL, and individuals with NAFL differ in their ability to defend against lipotoxicity. There are no tests that reliably predict which patients with NAFL will develop lipotoxicity. However, NASH encompasses the spectrum of wound-healing responses induced by lipotoxic hepatocytes. Differences in these wound-healing responses among individuals determine whether lipotoxic livers regenerate, leading to stabilization or resolution of NASH, or develop progressive scarring, cirrhosis, and possibly liver cancer. We review concepts that are central to the pathogenesis of NASH.**

*Keywords:* Nonalcoholic Fatty Liver Disease; Lipotoxicity; Wound-Healing Response; Misrepair.

Nonalcoholic fatty liver disease comprises nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH),[1] which each progress differently. NAFL rarely results in cirrhosis or liver cancer, whereas patients with NASH are at risk for these outcomes.[2,3] The rate of hepatocyte death is greater in NASH than in NAFLD—the key factor that differentiates NASH from NAFL.[4] The toxic effects of specific lipids on hepatocytes (hepatic lipotoxicity) could cause hepatocyte death in patients with NASH.[5] However, the risk for lipotoxicity differs according to the type of lipid that accumulates, and is modified by factors that can exacerbate or defend against their effects.[6] What factors contribute to the effects of hepatic fat accumulation (steatosis)?

## Steatosis Sets the Stage

Steatosis, the accumulation of fat in hepatocytes, is present in NAFL and NASH.[7] Steatosis occurs whenever the import or synthesis of fat exceeds fat export or degradation[8] (Figure 1). Triglyceride (triacylglycerol) is the most conspicuous type of fat in fatty livers.[9] So, the extent of triglyceride accumulation has been the basis for grading the severity of steatosis in NAFLD. Triglycerides per se are not hepatotoxic,[10] so steatosis grade or severity does not predict hepatic injury, inflammation, or fibrosis.[11,12] On the other hand, some of the other types of lipids that accumulate in fatty livers (eg, fatty acids, diacylglycerol, oxysterols, cholesterol, and phospholipids)[9] can injure hepatocytes. The realization that lipotoxicity is caused by lipids other than triglyceride has spurred development of strategies to prevent or treat NASH by blocking hepatic accumulation of lipotoxic lipids.[13] Lipotoxicity therefore initiates NASH development and is a new therapeutic target.

Briefly, under conditions of chronic energy surplus, adipose tissue produces adipocytokines that prevent adipocytes from assimilating fatty acids and promote release of fatty acids from adipose depots. This results in increased delivery of fatty acids to the liver and fuels hepatocyte triglyceride synthesis.[14,15] The ability of triglyceride synthesis to compensate for increased hepatic fatty acid exposure appears to determine whether or not lipotoxicity results. For example, studies of mouse models of NASH showed that inhibiting liver triglyceride synthesis increased hepatic accumulation of free fatty acids and the severity of liver injury and fibrosis, despite reducing steatosis.[10] Other studies extended the evidence that fatty acids (rather than triglyceride) are hepatotoxic, demonstrating that lipotoxicity is affected by the specific types of fatty acid that

*Abbreviations used in this paper:* NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SHH, sonic hedgehog; SMO, smoothened, frizzled class receptor; TNF, tumor necrosis factor.

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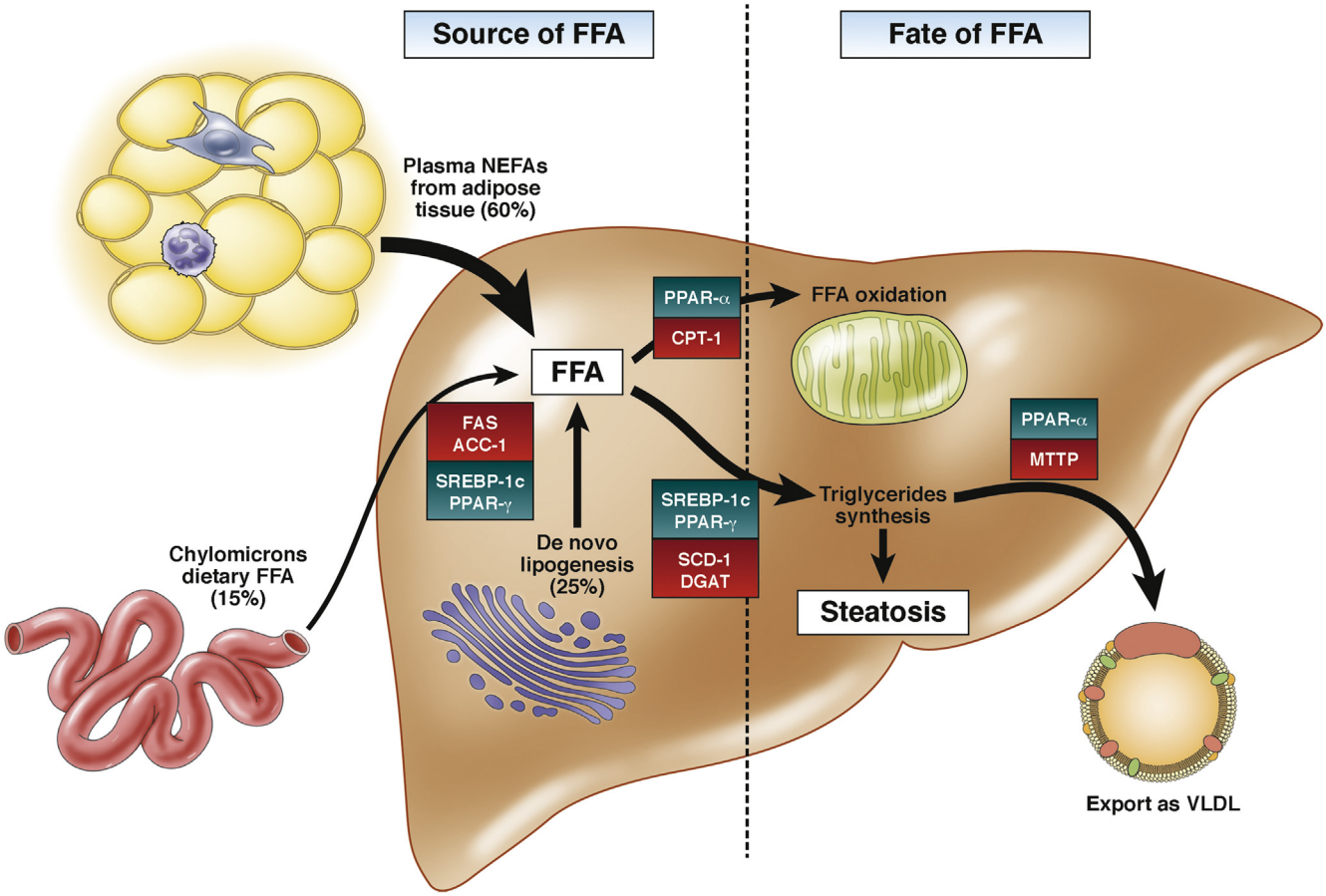


**Figure 1.** Mechanisms of hepatic steatosis. Hepatic steatosis results from increased influx of lipids to the liver or decreased lipid disposal. The main sources of fatty acid (FA) are plasma free fatty acid (FFA) (arriving mostly from the adipose tissue), de novo lipogenesis, and dietary FA. The liver discards fat by oxidation or by exporting it as very-low-density lipoprotein. Alternatively, hepatocytes can shunt excess lipids to the synthesis of triglycerides and storage in lipid droplets. *Red boxes* highlight rate-limiting enzymes that regulate the main fates of FAs in the liver: fatty acid synthase and acetyl-CoA carboxylase, which are enzymes in FA synthesis; carnitine palmitoyltransferase 1, enzyme that allows entry of acyl groups into the mitochondria by transferring an acyl group from CoA to carnitine and subsequent transport of acylcarnitine; stearoyl-CoA desaturase, an enzyme that converts saturated in monounsaturated FAs the FAs that are preferentially incorporated in triglycerides; diglyceride acyltransferase that catalyzes the synthesis of triglycerides from diacylglycerol and acylCoA; microsomal triglyceride transfer protein, which controls lipoprotein assembly. *Blue boxes* indicate transcription factors involved in lipid metabolism: sterol regulatory element-binding protein-1c and peroxisome proliferator-activated receptor-$\alpha$ and -$\gamma$. NEFA, nonesterified fatty acid.

accumulate. For example, Li et al[16] found that simply inhibiting stearoyl-CoA desaturase (an enzyme that converts saturated fatty acids into monounsaturated fatty acids) exacerbated liver injury in mouse models of NASH. The realization that the lipotoxic potential of various types of lipids differs helps to explain why the outcomes of hepatic steatosis vary. Interventions that block accumulation of lipotoxic lipids might therefore be used to prevent or treat NASH.

Lipids can cause toxicity by diverse mechanisms. For example, lipotoxicity can result from lipid metabolism. Mitochondrial and peroxisomal fatty acid oxidation generate reactive oxygen species that may be immediately toxic or that eventually deplete antioxidant reserves, rendering hepatocytes more vulnerable to other factors that generate oxidative stress.[17,18] Accumulation of fatty acids within mitochondria could also dissipate the proton-motive force that typically occurs during mitochondrial respiration.[19,20] This makes mitochondria more vulnerable to other insults that collapse the mitochondrial membrane potential, such as tumor necrosis factor (TNF)$-\alpha$, and could lead to release of mitochondrial factors that promote apoptosis.[21,22] Extreme depolarization of mitochondrial membranes causes complete cessation of mitochondrial electron transport and adenosine triphosphate synthesis, resulting in cellular necrosis.[23] Because damaged mitochondria cannot metabolize fatty acids efficiently, fatty acids accumulate.[24] In addition to its directly cytotoxic effects, fatty acid accumulation exacerbates insulin resistance and hyperinsulinemia,[25] which leads to further hepatic lipid accumulation,[26] and promotes inflammatory[27] and fibrogenic responses,[28] as well mitogenic responses that could be carcinogenic.[26]