Advances in Molecular Protective Mechanisms of Goose Liver Steatosis and Fatty Goose Liver Formation: Postprint

Authors: Preface by Liu, Guo Songchang, Liu Yaowen, Qu Xiangyong

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Abstract

Foie gras, together with caviar and truffles, is acclaimed by Westerners as one of the world' s three greatest delicacies. The unsaturated fatty acids, linoleic acid, lecithin, and other nutrients it contains exert significant health benefits in softening blood vessels, reducing blood lipids, and preventing cardiovascular and cerebrovascular diseases. This review primarily summarizes the molecular protective mechanisms underlying hepatic steatosis and foie gras formation in geese, providing a theoretical foundation for molecular breeding of foie gras traits and offering an important reference for research on human non-alcoholic fatty liver disease.

Full Text

Preamble

Title: Research Progress on Molecular Protective Mechanisms of Hepatic Steatosis and Foie Gras Formation in Geese

Authors: LIU Xu[1,2], GUO Songchang[1,2], LIU Yaowen[1,2], QU Xiangyong[1,2*]

Affiliations: [1]College of Animal Science and Technology, Hunan Agricultural University, Changsha 410128, China
[2]Hunan Co-Innovation Center of Animal Production Safety, Changsha 410128, China

Abstract: Foie gras, caviar, and truffles are acclaimed by Westerners as the world' s three greatest delicacies. The unsaturated fatty acids, linoleic acid, lecithin, and other components abundant in foie gras play important health-promoting roles in softening blood vessels, reducing blood lipids, and preventing cardiovascular and cerebrovascular diseases. This paper primarily reviews the

molecular protective mechanisms of goose hepatic steatosis and foie gras formation, providing a theoretical basis for molecular breeding of foie gras traits and offering an important reference for studying non-alcoholic fatty liver disease (NAFLD) in humans.

Keywords: foie gras; hepatic steatosis; protective mechanism

*Corresponding author: Professor QU Xiangyong, E-mail: quxy99@126.com

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In natural environments, certain wild fish before migration and birds before long-distance journeys consume large quantities of food over short periods to meet energy demands for their arduous travels, causing excess fat to deposit in the liver and form fatty liver. After completing their migration, liver fat is consumed and the organ returns to normal morphology, with the entire process being reversible and without cirrhosis or necrosis [1]. As avian descendants, waterfowl such as geese and ducks also possess this characteristic, which has been widely exploited in animal husbandry for producing food-grade fatty liver (goose or duck foie gras) [2]. In recent years, diseases caused by lipid metabolism disorders in humans have risen continuously, with the high incidence of non-alcoholic fatty liver disease (NAFLD) making it one of the most serious threats to human health worldwide over the past two decades [3]. Studies have found that serum enzyme activities in force-fed geese are similar to those in humans or mammals with NAFLD, but the key difference is that goose liver does not exhibit obvious pathological symptoms even after severe steatosis, indicating that hepatic fat deposition mechanisms in geese share similarities with yet also exhibit distinct differences from those in humans and mammals [4]. Therefore, this review focuses on goose hepatic steatosis, summarizing the molecular protective mechanisms of goose liver steatosis and foie gras formation to provide a theoretical basis for genetic breeding of foie gras geese in China and an important reference for studying NAFLD in humans and mammals.

1. Mechanism of Goose Hepatic Steatosis

Current research on foie gras formation mechanisms primarily focuses on the "first hit" stage, which involves progression from excessive glucose intake to simple fatty liver formation and represents the pathogenic basis of NAFLD in mammals. The main mechanism is as follows: after geese are force-fed high-energy diets, the raw material for fatty acid synthesis (glucose) increases substantially in the liver, generating triglyceride levels that far exceed lipoprotein transport capacity while produced fatty acids vastly outnumber those degraded through -oxidation. This leads to massive fat accumulation, causing hepatocyte enlargement and proliferation, ultimately forming a fatty liver 5–10 times heavier than normal [5]. Consequently, researchers generally believe that foie gras formation results primarily from disruption of the normal physiological balance among fat synthesis, lipoprotein transport, and fatty acid -oxidation [6]. This process is

closely associated with endoplasmic reticulum stress (ERS), insulin resistance (IR), and hepatocyte growth and proliferation [7-8].

Studies have shown that IR plays a crucial role in NAFLD development, while ERS can effectively promote IR occurrence, leading to abnormal fat deposition and fatty liver formation [9]. Geng et al. [10] investigated the mechanism of foie gras formation and found that force-feeding could induce IR. In force-fed geese, mRNA levels of ERS marker genes glucose regulated protein 78 (Grp78) and X-box binding protein 1 (Xbp1) were downregulated, while mRNA levels of fatty acid desaturase gene family members Fads1, Fads2, and Fads6 were upregulated. These findings indicate that ERS does not occur in goose liver during force-feeding, possibly due to upregulation of Fads1, Fads2, and Fads6 mRNA. However, force-feeding can still induce IR and fatty liver in an ERS-independent manner, suggesting that alternative mechanisms may exist in geese.

Mammalian fat is primarily composed of saturated fatty acids (SFA), whereas fat in goose liver consists mainly of unsaturated fatty acids (USFA). Research has shown that SFA can induce ERS and IR, while USFA can inhibit these SFA-induced effects [11]. This represents one of the key differences between geese and mammals during the "first hit" stage of hepatic fat deposition, leading to the inference that ERS suppression may play a protective role in foie gras formation [12].

The rapid liver enlargement observed in geese during short-term force-feeding demonstrates that goose hepatocytes possess strong growth and proliferation capabilities. Wei et al. [13] cultured goose primary hepatocytes with different glucose concentrations (0, 5, 25, 35 mmol/L) for 48 hours and found that glucose treatment increased DNA content, proliferative index (PI) of the cell cycle, and protein and mRNA expression levels of Cyclin D and the cyclin-dependent kinase inhibitor p21. These results suggest that glucose may promote growth and proliferation of goose primary hepatocytes by activating the Cyclin D family and p21 protein [14]. Moreover, low glucose concentrations (0 and 5 mmol/L) had no significant effect on hepatocyte proliferation, whereas high concentrations (25 and 30 mmol/L) significantly promoted it, indicating that goose primary hepatocytes exhibit strong glucose tolerance. Studies have also found that certain insulin concentrations can promote hepatocyte growth and synergize with glucose to enhance hepatocyte activity, but excessively high insulin concentrations can cause IR in hepatocytes, reducing their sensitivity to insulin and thereby inhibiting growth [15-16].

In recent years, advances in molecular biology techniques have enabled considerable progress in researching foie gras formation mechanisms through identification of genes closely related to hepatic lipid metabolism. Lu et al. [7] employed second-generation high-throughput sequencing to publish the first whole-genome data for domestic geese, preliminarily discovering that leptin (lep) gene deletion may be an important cause of foie gras formation. Zhu et al. [18] used suppression subtractive hybridization to screen differentially expressed genes in normal versus force-fed goose fatty livers, finding that stearoyl-CoA desaturase

1 (SCD1) gene expression increased significantly, possibly promoting hepatic fat synthesis through regulation by sterol regulatory element-binding protein-1c (SREBP-1c).

Osman et al. [19] force-fed 60-day-old Landes geese for 19 days and found that mitochondrial-related gene expression levels increased significantly in the livers of force-fed geese—an observation that contrasts sharply with findings in mammalian livers with NAFLD. The probable reason is that SFA increases cellular oxidative stress, apoptosis, and mitochondrial dysfunction, whereas USFA can inhibit these SFA-induced adverse effects.

To further investigate foie gras formation mechanisms, Chen et al. [20] used microRNA (miRNA) sequencing to screen for differentially expressed miRNAs in normal versus force-fed goose fatty livers, discovering that aan-miR-222 and aan-miR-203a were upregulated while aan-miR-30d, aan-miR-125b-5p, and aan-miR-146a-5p were downregulated. These miRNAs may represent key regulatory factors in foie gras formation. Zhang et al. [21] found that miR-122 is highly expressed in goose liver, but its expression decreases after force-feeding, accompanied by downregulation of aldolase B (ALDOB) and M2 isoform of pyruvate kinase (PKM2) genes. A significant regulatory relationship exists between miR-122 and both ALDOB and PKM2, suggesting that these may be target genes of miR-122.

Integrating miRNAs related to foie gras formation with their target genes into a network provides a novel perspective for investigating its mechanisms. The expression of one gene is influenced by other genes while simultaneously affecting the expression of yet others, creating a complex network of mutual influence that constitutes intricate gene expression regulation. Therefore, further research on the molecular mechanisms underlying foie gras formation is warranted, which will not only benefit production of food-grade fatty liver in animal husbandry but also provide new therapeutic insights for human NAFLD.

2. Molecular Protective Mechanisms of Foie Gras Formation

During NAFLD development in mammals, oxidative stress and lipid peroxidation represent two critical factors that drive disease progression following the "second hit" or "multiple hits," constituting key steps in the transformation of simple fatty liver into nonalcoholic steatohepatitis (NASH) and even cirrhosis and hepatocellular carcinoma [22]. In contrast, goose liver shows no obvious pathological damage after the "first hit" that creates simple fatty liver, indicating that special mechanisms exist in goose liver for tolerating hepatic fat accumulation.

2.1 Protective Role of Adiponectin and Adiponectin Receptors in Foie Gras Formation

Adiponectin is a cytokine secreted by adipose tissue, and its receptors include two subtypes: adiponectin receptor 1 and 2 (Adipor1/2). Adiponectin and its receptors exert anti-inflammatory, insulin-sensitizing, and anti-apoptotic effects in hepatic tissue [23-24]. Inflammatory response is a critical step in the progression from steatosis to steatohepatitis in humans and mammals. Numerous studies have demonstrated that in humans or mammals with NAFLD, mRNA expression levels of the inflammatory marker gene tumor necrosis factor- (TNF-) increase significantly, while Adipor1/2 levels in the liver and adiponectin levels in blood and abdominal adipose tissue decrease markedly [25]. However, research on foie gras geese has revealed opposite results. Geng et al. [26] force-fed 70-day-old Landes ganders for 19 days and found that mRNA expression levels of inflammation-related genes in force-fed geese decreased significantly, while Adipor1/2 mRNA expression increased substantially, with Adipor2 mRNA expression being significantly higher than Adipor1 and Adipor2 protein content also increasing markedly. These findings are consistent with results from Ramachandran et al. [27].

Additionally, studies have found that abundant expression of Adipor1/2 in the liver can block SFA-induced inflammatory responses [28-29]. This suggests that the absence of obvious pathological damage in geese after force-feeding may be attributed to adiponectin binding to its receptors, which effectively activates ceramidase to decompose ceramide. As a pro-inflammatory sphingolipid signaling molecule, ceramide can promote secretion of anti-inflammatory factors, thereby exerting protective effects during foie gras formation. Inflammatory responses, like ERS, can promote IR development. The suppression of inflammatory responses during foie gras formation further demonstrates that geese are protected during hepatic fat deposition. Xu et al. [30] modeled with 8–10-week-old ob/ob mice and found that exogenous adiponectin reduced hepatomegaly, depleted fat accumulation, decreased hepatic TNF- mRNA expression, and lowered plasma alanine aminotransferase activity. In summary, adiponectin receptors serve as protective components during foie gras formation, effectively preventing goose liver from receiving the "second hit." Therefore, adiponectin may also play an important role in treating NAFLD in humans and mammals, representing a potential novel therapeutic approach.

2.2 Protective Role of Complement System Inhibition in Foie Gras Formation

The complement system comprises complement components, complement regulatory proteins, and complement receptors present in the serum or body fluids of humans and animals, with 80%–90% synthesized in the liver. Under normal physiological conditions, most complement components exist in inactive forms and are activated when the host mounts defense and inflammatory responses [31]. Studies in humans and mice have found that fatty liver formation leads to

significantly increased expression of complement components, while knockout or inhibition of complement gene expression can effectively suppress fatty liver development [32]. In contrast, research on foie gras geese has revealed widespread suppression of the complement system, opposite to expression patterns observed in mammalian livers with NAFLD. Liu et al. [33] force-fed 65-day-old Landes geese for 19 days and found that mRNA expression levels of complement marker genes complement 3 (C3), complement 4 (C4), and complement 5 (C5) decreased significantly in force-fed geese, showing a negative correlation with Lactobacillus populations in the intestine.

To further explore the relationship between Lactobacillus and complement components, goose primary hepatocytes were treated with 5 and 8 mmol/L lactic acid. The results showed that C5 mRNA and protein expression levels decreased significantly in lactic acid-treated hepatocytes, accompanied by reduced expression of the related inflammatory factor TNF- mRNA. Therefore, lactic acid, a Lactobacillus metabolite, exerts protective effects during foie gras formation by inhibiting C5 expression and consequently suppressing complement system expression. Similar protective effects of Lactobacillus have been reported in mammalian NAFLD [34-35].

Liu et al. [36] force-fed 70-day-old Landes ganders for 19 days and found that complement receptor 1 (CR1) mRNA expression levels increased significantly in force-fed geese, representing the only upregulated complement gene identified among all differentially expressed complement genes in foie gras to date. To verify this result, goose primary hepatocytes were treated with different concentrations of glucose (25, 50, 100 mmol/L), insulin (25, 50, 100 mmol/L), palmitic acid (0.25, 0.50 mmol/L), and oleic acid (0.125, 0.250, 0.500 mmol/L). The results showed that oleic acid and 25 mmol/L glucose could significantly induce CR1 expression, while insulin treatment had no significant effect and 0.50 mmol/L palmitic acid treatment even exhibited inhibitory effects. Therefore, upregulation of complement receptor gene CR1 during foie gras formation may be caused by elevated oleic acid and glucose levels. Currently, research on the role and mechanisms of the complement system in foie gras formation remains limited, and further investigation could provide new therapeutic approaches for mammalian NAFLD.

2.3 Protective Role of Gut Microbiota in Foie Gras Formation

The liver and gastrointestinal tract are anatomically and functionally closely connected, jointly comprising the integrated digestive system. Since Marshall proposed the "gut-liver axis" hypothesis in 1998, the interplay between liver and gut has become a research hotspot in disease studies [37]. Humans and animals harbor large microbial populations in their intestines, and studies have found that mammalian NAFLD development is closely related to gut microbiota [38-39]. Yang et al. [40] investigated gut microbiota in NASH patients and found that while microbial species diversity showed no significant changes, Bifidobacterium and Lactobacillus populations decreased markedly whereas Enterobacter

and Enterococcus populations increased significantly. These findings align with results from Nielsen et al. [41] and Cotillard et al. [42], suggesting that gut microbiota imbalance and reduction of beneficial bacteria may be primary causes of NAFLD.

As a special model of NAFLD, foie gras can enlarge 5–10 fold without developing obvious pathological symptoms. Recent studies have confirmed that gut microbiota exerts protective effects during foie gras formation. Liu et al. [43] force-fed 70-day-old Landes geese for 19 days and found that compared with the control group, the force-fed group showed significantly increased microbial abundance in jejunum and cecum at the genus level, along with significantly increased Lactobacillus content. Guo et al. [44] found that Lactobacillus fermentation products can inhibit cholesterol synthesis enzymes to some extent, thereby suppressing blood cholesterol levels. Additionally, beneficial gut bacteria can promote cholesterol excretion in feces by interfering with bile salt circulation [45], which may inhibit NASH development from another perspective.

Short-chain fatty acids (SCFA) are the main metabolites of gut microbiota. In the serum of force-fed geese, SCFA consist primarily of butyric acid, with butyric acid content significantly higher than in the control group [33]. Therefore, it is preliminarily inferred that butyric acid may be a protective component during foie gras formation.

3. Summary and Outlook

Foie gras is rich in USFA, linoleic acid, lecithin, and other components that confer important health benefits in reducing blood lipids, softening blood vessels, delaying aging, and preventing cardiovascular and cerebrovascular diseases. Currently, with continuous development of biological technologies, research on foie gras formation mechanisms has advanced from the physiological level to the genomic and transcriptomic levels, achieving considerable progress. However, since foie gras formation is a relatively complex process, research on interactions among key genes remains largely unexplored, and thus the molecular mechanisms of hepatic steatosis require further in-depth investigation. In recent years, with continuously improving living standards and changing lifestyles and dietary structures, the incidence of human NAFLD has risen significantly, becoming one of the three major liver diseases threatening human health. Foie gras formation shares both similarities and unique characteristics with mammalian NAFLD development, making it a novel animal model for studying the mechanisms and preventive measures of non-alcoholic fatty liver disease, thereby providing important references and insights for treating NAFLD in humans and mammals.

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