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EDITORIAL

Understanding the pathophysiological mechanisms in the pediatric non-alcoholic fatty liver disease: The role of genetics

Pierluigi Marzuillo, Anna Grandone, Laura Perrone, Emanuele Miraglia del Giudice

Pierluigi Marzuillo, Anna Grandone, Laura Perrone, Emanuele Miraglia del Giudice, Department of Women and Children and General and Specialized Surgery, Seconda Università degli Studi di Napoli, 80138 Naples, Italy

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Correspondence to: Pierluigi Marzuillo, MD, Department of Women and Children and General and Specialized Surgery, Seconda Università degli Studi di Napoli, Via L. De Crecchio 2, 80138 Naples, Italy. pierluigi.marzuillo@gmail.com
Telephone: +39-333-4848764
Fax: +39-081-5665427

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Abstract

Classically, the non-alcoholic fatty liver disease (NAFLD) physiopathology and progression has been summarized in the two hits hypothesis. The first hit is represented by the action of hyperinsulinemia and insulin resistance, accompanying obesity, that leads to liver steatosis increasing the absolute non esterified fatty acids uptake in the liver and the esterification to form triacylglycerol. The oxidative stress is involved in the second hit leading to the progression to nonalcoholic steatohepatitis (NASH) because of its harmful action on steatosic hepatocytes. However, at the present time, the two hits hypothesis needs to be updated because of the discover of genetic polymorphisms involved both in the liver fat accumulation and progression to NASH that make more intriguing understanding the NAFLD pathophysiological mechanisms. In this editorial, we want to underline the role of *PNPLA3* I148M, *GPR120* R270H and *TM6SF2* E167K in the pediatric NAFLD development because they add new pieces to the comprehension of the NAFLD pathophysiological puzzle. The *PNPLA3* I148M polymorphism encodes for an abnormal protein which predisposes to intrahepatic triglycerides accumulation both for a loss-of-function of its triglyceride hydrolase activity and for a gain-of-function of its lipogenic activity. Therefore, it is involved in the first hit, such as *TM6SF2* E167K polymorphisms that lead to intrahepatic fat accumulation through a reduced very low density lipoprotein secretion. On the other hand, the *GPR120* R270H variant, reducing the anti-inflammatory action of the GPR120 receptor expressed by Kuppfer cells, is involved in the second hit leading to the liver injury.

Key words: Pediatric non-alcoholic fatty liver disease; *GPR120*; *PNPLA3*; *TM6SF2*; Alanine transaminase

Core tip: At the present time, the two hits hypothesis needs to be updated because of the discovery of new genetic polymorphisms involved both in the liver fat accumulation and progression to nonalcoholic steatohepatitis that make more intriguing understanding

the non-alcoholic fatty liver disease (NAFLD) pathophysiological mechanisms. In this editorial, that is not to consider as a comprehensive review, we want to underline the role of three polymorphisms, one older (*PNPLA3* I148M) but very important and two recently discovered (*GPR120* R270H and *TM6SF2* E167K) that add new pieces to the comprehension of the NAFLD pathophysiological puzzle.

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INTRODUCTION

In the last years, the pediatric obesity prevalence has shown a constant increase[1]. The raised pediatric obesity prevalence has determined an increased prevalence of obesity complications and the non-alcoholic fatty liver disease (NAFLD) has become the most common form of liver disease in childhood. In fact, its prevalence has more than doubled over the past years. It currently involves between 3% and 11% of the pediatric population and affects about the 46% of overweight and obese children and adolescents[2]. NAFLD comprehends an extensive range of conditions, including from fatty liver or steatohepatitis with or without fibrosis, to cirrhosis and its complications (*e.g.*, hepatocellular carcinoma and portal hypertension)[3,4]. The NAFLD is defined by hepatic fat infiltration involving > 5% hepatocytes in the absence of excessive alcohol intake or other demonstrable liver diseases[3].

Classically, the NAFLD pathophysiology and progression has been summarized in the two hits hypothesis. Obesity related hyperinsulinemia and insulin resistance represent the first hit. They lead to liver steatosis increasing the absolute non esterified fatty acids uptake in the liver and the esterification to form triacylglycerol[5,6]. The oxidative stress is involved in the second hit leading to the progression to NASH because of its harmful action on steatosic hepatocytes. The reactive oxygen species (ROS), in fact, lead to hepatocellular damage inhibiting the mitochondrial respiratory chain enzymes, and inactivating both the glyceraldehyde-3-phosphate dehydrogenase and the membrane sodium channels. ROS further cause lipid peroxidation, cytokine production, and induce Fas Ligand, contributing to hepatocellular injury and fibrosis[7].

However, at the present time, the two hits hypothesis needs to be updated because of the discover of 3 genes whose polymorphisms are involved both in the liver fat accumulation and progression to non-alcoholic steatohepatitis (NASH) making intriguing understanding the NAFLD pathophysiological mechanisms. In this editorial, that is not to consider as a comprehensive review, we want to underline the role of three polymorphisms, one older but very important and two recently discovered that added new pieces to the comprehension of the NAFLD pathophysiological puzzle.

PATATIN LIKE PHOSPHOLIPASE CONTAINING DOMAIN 3 GENE

The patatin like phospholipase containing domain 3 gene (*PNPLA3*) is the most important gene involved in hepatic steatosis developing. It encodes for the adiponutrin, an enzyme present in the liver and adipose tissue. Feeding and insulin resistance induce the adiponutrin[8] that shows lipolytic activity on triglycerides[9]. The *PNPLA3* rs738409 (*PNPLA3* I148M) single nucleotide polymorphism is a non-synonymous variant and it is characterized by a cytosine to guanosine substitution leading to an isoleucine to methionine substitution at the amino acid position 148 (I148M). This aminoacid substitution affects the enzyme function probably reducing the substrates access to the enzyme and then leading to the development of microvesicular steatosis[9]. On the other hand, the adiponutrin could present a gain of lipogenic function, which could further lead to the hepatic fatty acids accumulation[9]. In literature there is strong evidence of association between the *PNPLA3* 148M allele and NAFLD both in adults[10] and children[11,12].

The *PNPLA3* 148M allele plays a central role in NAFLD developing interacting with environmental NAFLD risk factors, such as obesity (and in particular visceral fat)[11] and alcohol consumption[13], and then increasing the risk of fatty liver development. In fact, these stressors seem to reveal the association between the *PNPLA3* 148M allele and hepatic damage in populations in whom it is otherwise hidden[14]. Interestingly, the obesity-driven effect of this polymorphism on liver damage[11] can be reduced by weight loss (expressed as reduction of the waist/height ratio) in obese children and adolescents[15]. Among environmental factors involved in NAFLD development and interacting with *PNPLA3* 148M allele some nutrients appear. Indeed, the total carbohydrate[16] and high omega (n) 6 to n-3 polyunsaturated fatty acids (PUFA) ratio[17] can enhance the association between steatosis and the *PNPLA3* variant.

G-PROTEIN-COUPLED-RECEPTOR 120

G-protein-coupled-receptor 120 *(GPR120)* is a receptor for PUFAs and it is expressed by adipocytes, Kupffer cells and, at low level, in hepatocytes[18]. PUFAs could play a role in inflammatory response modulation[19]. In fact, it has been shown that, in the adipose tissue, the interaction between PUFAs and macrophagic *GPR120* switch off inflammation blocking nuclear factor-kappa-B activity[20]. In particular docosahexaenoic acid (DHA), an n-3 PUFA of the fish oil, has recently shown a potential

role in treatment of liver fat accumulation and of metabolic and hepatic complications of NAFLD[21]. The 270H allele inhibits the *GPR120* signalling activity[19] and then it reduce its anti-inflammatory activity[20]. Recently, this variant has been studied in obese children and adolescents and it has been shown that the subject carrying the rare *GPR120* 270H allele presented higher alanine transaminase (ALT) levels ($P = 0.01$) and higher ferritin (marker of inflammation) levels ($P < 0.003$) than wild type subjects[22]. The carriers of the 270H allele showed an odds ratio (OR) to have pathologic ALT of 3.2[22]. Moreover, *PNPLA3* 148M allele demonstrated an interaction with *GPR120* 270H allele determining a significant effect on ALT levels ($P = 0.00001$) suggesting a driving effect of the *PNPLA3* 148M allele on liver injury in obese children carrying this variant[22]. This is in accord with the findings of Santoro *et al*[17] demonstrating that the *PNPLA3* I148M variant predispose to liver damage in patients with a lower intake of n-3 fatty acids. Therefore, GPR120 R270H variant appear to have an important role in determining liver injury expressed as ALT elevation and the *PNPLA3* 148M allele showed an important capacity to promote the GPR120 270H allele mediated liver damage. This evidence is in accord with the studies showing that DHA supplementation, activating the GPR120 receptor and then exerting potent anti-inflammatory and insulin-sensitizing activities[20], can reduced liver damage in pediatric NAFLD[23].

TRANSMEMBRANE 6 SUPERFAMILY MEMBER 2 GENE

Recently, a new gene variant playing a role in the NAFLD physiopathology has been discovered in the transmembrane 6 superfamily member 2 (*TM6SF2*) gene[24]. This variant (rs58542926) is characterized by an adenine-to-guanine substitution in the nucleotide 499 which replaces glutamate at residue 167 with lysine (c.499A > G; p.Glu167Lys)[24]. The *TM6SF2* minor allele carriage has been causally related to a previously reported chromosome 19 GWAS signal that was ascribed to the gene *NCAN*[25]. This *TM6SF2* variant has been associated with higher hepatic triglyceride content (HTGC), with higher serum levels of ALT and lower plasma levels of liver-derived triglyceride-rich lipoproteins in 3 independent populations[24].

Small intestine, liver and kidney highly express the *TM6SF2* gene, but, in the other tissues, *TM6SF2* is present at low levels[24]. Recent evidence suggests that TM6SF2 is a polytopic membrane protein and that the Glu167Lys variant form is misfolded and undergoes accelerated intracellular degradation[24]. Actually, the hypothesized TM6SF2 protein function appears to be the promotion of very low density lipoprotein (VLDL) secretion and, probably, the increased HTGC result from a reduction in TM6SF2 protein function[24,26]. Therefore, the role of the *TM6SF2* 167K allele in the NAFLD physiopathology could be represented by a reduced VLDL secretion that could explain the higher HTGC, in turn resulting in higher ALT levels and in lower serum low density lipoprotein cholesterol (LDL-C) and triglycerides levels. In addition, low cholesterol levels in the carrier of the *TM6SF2* 167K allele have also been demonstrated in an adult population presenting, at the same time, reduced risk of myocardial infarction[27]. Accordingly, very recent data showed an effect of this polymorphism on reducing carotid atherosclerosis risk in adults[28]. Moreover, Liu *et al*[25] confirmed, using two histologically characterized cohorts (1074 adults) encompassing steatosis, steatohepatitis, fibrosis and cirrhosis, the *TM6SF2* minor allele association with NAFLD and, moreover, with advanced hepatic fibrosis/cirrhosis. The effect of this polymorphism on ALT and cholesterol levels has been confirmed also in obese children and adolescents[29]. Grandone *et al*[29], in fact, demonstrated, in a cohort of 1010 obese children and adolescents, that the *TM6SF2* 167K allele is associated with steatosis ($P < 0.0001$), higher ALT levels ($P < 0.001$) and lower total cholesterol (< 0.00001), LDL-C ($P < 0.0001$), triglycerides ($P = 0.02$) and non-high density lipoprotein cholesterol levels ($P < 0.000001$)[29]. Interestingly, the subjects homozygous for the *PNPLA3* 148M allele carrying the rare variant of *TM6SF2* showed an OR of 12.2 to present hypertransaminasemia compared to the remaining patients[29]. Therefore, the effect of *PNPLA3* and *TM6SF2* rare alleles appears additive in determining pediatric NAFLD[29].

OLD AND NEW CONCEPTS, AN INTEGRATED OVERVIEW

NAFLD occurs in overweight and obese children deriving from intrahepatic accumulation of triglycerides. The triglycerides accumulated in the liver mostly derive from the adipose tissue lipolysis (60%) and hepatic *de novo* lipogenesis (26%) whereas only in a little part from the diet as chylomicron remnants (14%)[30]. This fat accumulation, as indicated in the "two hits" hypothesis (Figure 1), is stimulated by obesity-related peripheral insulin resistance and hyperinsulinemia. In fact they stimulate the free-fatty-acids (FFA) uptake in the liver, the esterification of hepatic FFAs to form triglycerides, the FFA synthesis from cytosolic substrates, and the decreased apolipoprotein B-100 synthesis. Then, the export of FFA and triglycerides decreases, while the beta-oxidation of mitochondrial long-chain fatty acids increases[2]. In the last years, the knowledge of NAFLD pathophysiology is constantly increasing[8] with the discovery of new genetic polymorphisms that could promote the NAFLD development and then the progression to the NASH. Each polymorphism plays a role in a different hit and, therefore, in future, the pathophysiology could be described by a "multiple hit hypothesis". *PNPLA3* I148M polymorphism plays an important role in the NAFLD development. In fact, it

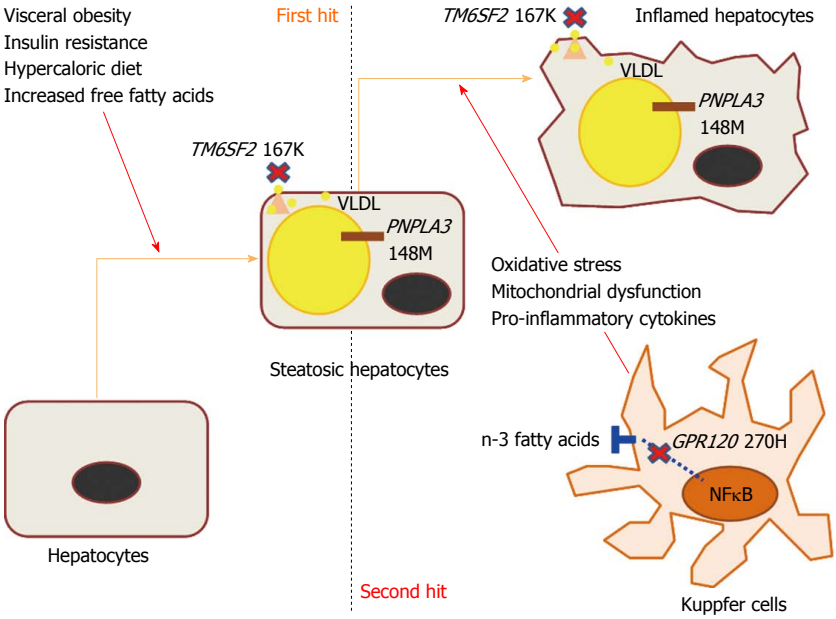

Figure 1 The updated "two hits hypothesis". The hyperinsulinemia and insulin resistance, accompanying obesity, lead to liver steatosis increasing the absolute non esterified fatty acids uptake in the liver and the esterification to form triacylglycerol. The *PNPLA3* 148M allele encodes for an abnormal protein and predisposes to intrahepatic triglycerides accumulation by both a reduced effect on triglycerides hydrolysis and an enhanced lipogenetic effect. Therefore, it is involved in the first hit. Also the *TM6SF2* E167K polymorphism plays a role in the first hit, in fact, it lead to intrahepatic fat accumulation through a reduced VLDL secretion. The oxidative stress is involved in the second hit leading to the progression to NASH because of its harmful action on steatosic hepatocytes. Reactive oxygen species can induce hepatocellular injury and then fibrosis through the inhibition of the mitochondrial respiratory chain enzymes, lipid peroxidation, cytokine production, Fas Ligand induction. The *GPR120* 270H allele, reducing the anti-inflammatory action of the GPR120 receptor expressed by Kuppfer cells, is involved in the second hit promoting the oxidative stress, mitochondrial dysfunction and pro-inflammatory cytokines release. *PNPLA3*: Patatin like phospholipase containing domain 3 gene; NASH: Nonalcoholic steatohepatitis; *GPR120*: G-protein-coupled-receptor 120; *TM6SF2*: Transmembrane 6 superfamily member 2 gene; NFκB: Nuclear factor-kappa-B; VLDL: Very low density lipoprotein.

encodes for an abnormal protein which predisposes to intrahepatic triglycerides accumulation[9,12] both for a loss-of-function of its triglyceride hydrolase activity and for a gain-of-function of its lipogenic activity[12]. Therefore, the *PNPLA3* I148M polymorphism plays a role in predisposing to the first hit (Figure 1). Another polymorphism acting on the first hit is the *TM6SF2* E167K polymorphism. In fact, it encodes for an abnormal TM6SF2 protein that predisposes to intrahepatic fat accumulation thorough reduced VLDL secretion[24,26] (Figure 1). On the other hand, the reduced VLDL secretion lead to a reduced cardiovascular risk[27,28]. The *GPR120* R270H variant promotes the second hit determining liver injury (evaluable as high ALT levels)[22]. In fact, the lack of *GPR120* anti-inflammatory activity promotes oxidative stress, mitochondrial dysfunction, overproduction and release of pro-inflammatory cytokines (second hit) (Figure 1). This hypothesis appears further supported by the evidence that the *GPR120* mutated allele needs the co-presence of the *PNPLA3* 148M allele to lead pathological ALT levels[22].

Therefore, the *PNPLA3* 148M allele can play an important role in the first hit determining hepatic steatosis and can drive the effect of the *GPR120* rare allele on the second hit leading to liver damage.

CONCLUSION

In the last years many polymorphisms playing a role in the NAFLD physiopathology have been identified[8], therefore our knowledge in this area has been constantly increased. Starting from the genetic association studies we can understand new pathophysiological mechanisms that are firstly implicated in the intrahepatic fat accumulation and then, in the progression to the NASH (Figure 1). This editorial wants to underline how these new genetic findings have improved our comprehension of pediatric NAFLD pathophysiology.

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