REVIEW

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Basic and translational evidence supporting the role of TM6SF2 in VLDL metabolism

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Purpose of review
Transmembrane 6 superfamily member 2 (*TM6SF2*) gene was identified through exome-wide studies in 2014. A genetic variant from glutamic acid to lysine substitution at amino acid position 167 (NM_001001524.3:c.499G>A) (p.Gln167Lys/p.E167K, rs58542926) was discovered (p.E167K) to be highly associated with increased hepatic fat content and reduced levels of plasma triglycerides and LDL cholesterol. In this review, we focus on the discovery of *TM6SF2* and its role in VLDL secretion pathways. Human data suggest *TM6SF2* is linked to hepatic steatosis and cardiovascular disease (CVD), hence understanding its metabolic pathways is of high scientific interest.

Recent findings
Since its discovery, completed research studies in cell, rodent and human models have defined the role of *TM6SF2* and its links to human disease. TM6SF2 resides in the endoplasmic reticulum (ER) and the ER-Golgi interface and helps with the lipidation of nascent VLDL, the main carrier of triglycerides from the liver to the periphery. Consistent results from cells and rodents indicated that the secretion of triglycerides is reduced in carriers of the p.E167K variant or when hepatic *TM6SF2* is deleted. However, data for secretion of APOB, the main protein of VLDL particles responsible for triglycerides transport, are inconsistent.

Summary
The identification of genetic variants that are highly associated with human disease presentation should be followed by the validation and investigation into the pathways that regulate disease mechanisms. In this review, we highlight the role of *TM6SF2* and its role in processing of liver triglycerides.

Keywords
APOB100, endoplasmic reticulum stress, VLDL metabolism

INTRODUCTION

The metabolic pathways that regulate the assembly and secretion of apolipoprotein (APO) B100 lipoproteins, particularly VLDL, from the liver, continue to be studied extensively, due to the role as a carrier and regulator of triglycerides. The links between elevated plasma levels of triglycerides, VLDL and its downstream products, IDL and LDLs in the development of cardiovascular disease (CVD) has been well studied and reviewed [1,2]. Importantly, many of the key molecular pathways in the secretion of the VLDL are also critical for the maintenance of normal intrahepatic triglyceride levels. Dysfunction of one or more of those pathways can lead to accumulation of triglycerides (hepatic steatosis), which is commonly present in patients also at risk for CVD. Hepatic steatosis can occur due to increased uptake of fatty acids from the circulation, increased synthesis of fatty acids from acetylCoA, called de-novo lipogenesis (DNL), and decreased utilization of triglycerides/fatty acids in lipid droplets.

Steatotic liver disease (SLD) is typically associated with metabolic disorders such as insulin resistance, diabetes mellitus, obesity, and metabolic syndrome. The term metabolic dysfunction associated steatotic liver disease (MASLD) [3] was recently chosen to replace the longtime name, nonalcoholic liver disease (NAFLD) [4]. If an individual with MASLD consumes excess alcohol, the term is modified to MetALD (metabolic and alcohol-related/associated liver disease [4]. Importantly, these disorders are the most common causes of steatohepatitis and

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KEY POINTS

- TM6SF2 variant p.E167K is important in development of liver steatosis.
- TM6SF2 variant has been linked to myocardial infarction.
- Understanding how lipidation of VLDL particles can regulate liver disease is of clinical importance.
- Understanding the regulation of liver triglycerides processing may help to identify additional biomarkers that elucidate the crosstalk between liver and heart disease.

cirrhosis [5▪▪,6]. SLD can also be a consequence of viral infections or therapies that increase liver fat, such as antibiotic tetracycline or antiarrhythmic agent amiodarone. Particularly relevant to the present review, genetic variants that affect pathways of triglycerides synthesis and utilization, as well as VLDL assembly and secretion, interact significantly with the metabolic and environmental causes of steatosis [7,8▪▪,9].

In this review, we focus on the discovery of the transmembrane superfamily (TM6SF2) [10–12]. Hobbs and colleagues have shown that TM6SF2 is localized to the smooth endoplasmic reticulum (SER) and ER-Golgi intermediate compartment (ERGIC), but not the Golgi, in rat liver [8▪▪]. Of relevance to VLDL secretion pathways, the TM6SF2 liver and intestine tissue expression pattern mirrors that of APOB [13]. In this review, we will focus on studies in cells, rodent models, and humans that support a role of TM6SF2 in the secretion of VLDL. There is evidence of the link between TM6SF2 and CVD [14], however, that is beyond the scope of the current review.

GENETIC VARIANTS: IDENTIFICATION OF TM6SF2 LINKS TO LIVER AND METABOLIC PATHWAYS OF DISEASE

Six genome-wide association (GWAS) studies, performed between 2008 and 2013, identified variants within chromosome 19 that were associated with plasma triglycerides and cholesterol levels, additionally the variants were associated to MASLD (previously NAFLD). The locus of the variants, termed 19p12 or NCAN-TM6SF2-SUGP1-CILP2, contained more than a dozen genes, none of which had previously been implicated to lipid metabolic pathways [15]. Using the multiancestry cohort of the Dallas Heart Study, and available liver imaging data, investigators identified a nonsynonymous single nucleotide polymorphism (SNP) in coding nucleotide 499 of the *TM6SF2* gene (rs58542926 c.449 C>T), which substitutes the glutamate at residue 167 with lysine (denoted E167K) [10,16]. The allele frequency varies by ancestry with 0.07 in Europeans, 0.04 in Hispanics, and 0.02 in African–Americans [17]; hence, the phenotypes exhibited by the variant will be higher in Europeans compared to the other ethnic groups. This variant was highly associated with hepatic triglyceride content (HTGC) and MASLD. In addition, low plasma levels of triglycerides and LDL-C, but not levels of HDL-C, in the DHS, Dallas Biobank, and Copenhagen Study cohorts were characteristic of the variant [12]. Additional studies by other groups [11,18], confirmed the previously found associations with lipid traits and suggested an inverse association with incidence of myocardial infarction, the latter highlighting another clinical impact of the variant [11]. Additional studies in humans with obesity, one by O'Hare *et al.* [19] found that individuals heterozygous for the rs58542926 variant presented with higher grade steatosis than noncarriers. Interestingly, significant associations with lower fasting levels of TC, triglycerides, and LDL-C were only found in carriers of the minor allele in the subgroup that had diagnosis of liver steatosis [19]. Additional human imaging studies in 10 individuals homozygous for this variant, which used proton magnetic spectroscopy, showed a two-fold increase in liver fat when compared to matched controls [20▪▪]. Taken together, the findings from the available studies suggest that carriage of the minor TM6SF2 allele confers increased risk for SLD but also protection from hyperlipidemia, which may be cardioprotective. The latter is of interest as most individuals with MASLD are at increased risk of CVD, whereas this relationship is dissociated in carriers of the TM6SF2 minor allele.

TM6SF2: REGULATION OF VLDL APOB AND TRIGLYCERIDE SECRETION

APOB co-translationally translocates into the ER lumen and interacts with microsomal triglyceride transfer protein (MTP) to initiate assembly of a nascent, lipid poor VLDL [21]. As in moves through the ER, the nascent VLDL interacts with many proteins critical to its maturation, including TM6SF2. Previous studies have shown that TM6SF2 deficiency results in a reduction of VLDL-TG secretion. The latter due to effects of the genetic variants that cause the faster protein degradation which leads to only half of the protein being expressed [8▪▪,22]. However, the effects of reduced TM6SF2 on VLDL-APOB secretion in studies with hepatic cell lines, rodents and humans have provided mixed results.

NON-HUMAN STUDIES OF THE ROLE OF TM6SF2 IN VLDL SECRETION *STUDIES IN RODENT MODELS*

Smagris *et al.* [22] generated whole body *Tm6sf2* knockout mice and measured the secretion of triglycerides and newly synthesized APOB in vivo. Unexpectedly, despite significant reductions in triglycerides secretion from the liver and in plasma, APOB100 secretion was not changed whereas APOB48 secretion were mildly but significantly increased in the knockout mice. Moreover, there was a significant increase in plasma APOB-48 but not APOB-100 in the knockout mice. Similar results were reported from liver specific *Tm6Sf2* knockout mice (L*Tm6sf2* KO) by Newberry *et al.* [23]. VLDL isolated from plasma by fast protein liquid chromatography (FPLC) showed a slight increase in APOB-48 and a slight decrease in APOB100, similar to the results from Smagris *et al.* [24]. Using a pulse-chase assay in primary hepatocytes investigators found significant increases in APOB -48 secretion in L*Tm6sf2* knockout [23]. In contrast to these two mouse models, knockout of *Tm6sf2* in a rat [8▪▪] did not cause any significant changes in secretion of either APOB100 or APOB48. Unexpectedly, Ehrhardt *et al.* [13] found dramatically lower levels of both plasma APOB-100 and APOB-48 in *Tm6sf2* transgenic mice. The reductions in plasma levels were mirrored by reduced levels of apoB48 and apoB100 in liver.

Studies in hepatoma cell-lines

Mahdessian *et al.* [12] were the first to demonstrate that *TM6SF2* knockdown induced a modest, but significant reduction in the secretion of triglycerides and APOB secretion in two human-derived hepatoma cell-lines, Huh7 and HepG2, although the reduction in triglycerides secretion was greater than that of apoB. Ehrhardt *et al.* [13] reported *TM6SF2* overexpression resulted in marked reductions in APOB secretion in both HepG2 and Huh7 cells, which further confirmed the data from this same group for Tm6sf2 transgenic mice. Longo *et al.* [25] confirmed that APOB secretion was significantly decreased in HepG2 cells with TM6SF2 full knockout generated using CRISPR/Cas9. Our own very recent studies demonstrated that shRNA knockdown of *TM6SF2* in HepG2 cells resulted in significantly increase secretion of APOB [26]. When we extended these studies rat hepatoma McA-RH7777 (McA) cells with CRISPR/Cas9-mediated knockout of *Tm6sf2*, we found that that secretion of newly synthesized APOB-100 and APOB-48 were significantly elevated Reyes-Soffer and Liu [26]. Similar to the studies by Ehrhardt *et al.* [13], when we overexpressed *TM6SF2* and used [^{35}S] methionine to label APOB in HepG2 cells, synthesis of newly synthesized APOB was dramatically decreased whereas no differences were found in albumin secretion between *TM6Sf2* overexpressing cells and control cells [26].

MOLECULAR INTERACTIONS BETWEEN APOB AND TM6SF2

To understand the conflicting data on APOB secretion between TM6SF2 knockout or overexpression, it is necessary to further explore the interaction between TM6SF2 and APOB. TM6SF2 is a transmembrane protein localized at the ER membrane and APOB is a large protein (4536 amino acid) where it is lipidated, presumably in a stepwise fashion that transforms a nascent lipid-poor VLDL to a mature lipid-rich VLDL. Importantly, early, co-translocational lipidation of newly translated apoB prevents it from degradation [27]. However, whether late lipidation also protects apoB from degration within the ER or in the post-ER pathway is less well characterized [28]. Li *et al.* [29] used tandem affinity purification technology coupled with mass spectrometry and determined that TM6SF2 physically interacted with APOB in McA cells. They further demonstrated that expression of TM6SF2 with the E167K mutation and knockdown of TM6SF2 in these cells both increased APOB48 degradation. Additionally, they concluded that TM6SF2 is physically bound to APOB48 and stabilized APOB via two luminal loops in Huh7 cells with APOB48 expression. Lastly, the authors described the role of the ER lipid raft protein (ERLIN) 1 and 2 as a mediator of this stabilization. They concluded that 'defective APOB stabilization, as a result of ERLINs, TM6SF2 deficiency or E167K mutation, was a key factor that contributed to NAFLD'.

Luo *et al.* [8▪▪] observed that the N-terminal of APOB was the most abundant protein physically interacting with TM6SF2. They further confirmed that TM6SF2 physically bound APOB-48 in mouse liver by a pull-down assay. The interaction of APOB with TM6SF2 is consistent with the model that TM6SF2 is important in the second step lipidation of nascent VLDL, but could also explain the finding that overexpression of TM6SF2 would inhibit trafficking of APOB in the ER, leading to ER stress and degradation, possibly by an autophagic process. Ehrhardt *et al.* [13] employed confocal microscopy to demonstrate more APOB co-localized with ER marker in Hu7 h cells overexpressing TM6SF2, suggesting that an excess of this protein might block the trafficking of APOB out of the ER. Interestingly, Longo *et al.* [25] noticed that TM6SF2 deficiency induced abnormal ultrastructure of ER in HepG2 cells, including remarkably dilated ER lumen and disorganized fragmented tubules. They further found that disruptive ER morphology resulted in ER stress, as demonstrated

by up-regulated expressions of ATF4, ATF6, XBP1, and GRP78. In contrast, Fan *et al.* [30] found hepatic levels of both IRE1a mRNA and the phosphorylated protein were significantly decreased in male *Tm6sf2* E167K knock-in mice fed with HFD, while spliced XBP1 mRNA was significantly decreased too. They also demonstrated that IRE1α was directly bound to TM6SF2 in Huh7 cells using co-immunoprecipitation assay, and that the TM6SF2 E167K mutation attenuated the interaction between IRE1a and TM6SF2 under lipid overload conditions. Zhu *et al.* [31] reported that GRP 78, *Xbp1*, and NF-κB gene expression levels were all downregulated in bone marrow derived macrophages (BMDMs) from myeloid cell specific *Tm6sf2* knockout mice. They confirmed their results in the THP-1-derived macrophages in which they induced ER stress by oxidized LDL: knockdown of *TM6SF2* resulted in reduced expression of BIP, IRE1α, JNK, ASK1, and XBP1, whereas *TM6SF2* overexpression upregulated these gene expressions. We recently confirmed that the protein levels of several ER stress proteins and expression of ER stress-associated genes were reduced in McA cells with full *Tm6sf2* knockout [26].

HUMAN STUDIES OF THE ROLE OF TM6SF2 IN VLDL SECRETION

A human study from Kim *et al.* [32] that included 6929 Finnish individuals found a significant association between rs58542926-T and APOB-100 particles, even after controlling for cofounders. This same study validated this association in a smaller subset of 2196 Finnish individuals from the FINRISK study ($\beta_{replication} = -0.029$, $P_{replication} = 0.029$). They further found that *TM6SF2* E167K homozygous carriers had significant reductions in plasma APOB concentrations, VLDL particle number, and the mean diameter of VLDL particles. Boren *et al.* [20▪▪] used stable-isotopes to label APOB and investigated the kinetics of VLDL-APOB metabolism in 10 homozygous *TM6SF2* E167K carriers and 10 controls. They found that VLDL1-(large triglycerides rich particles) APOB100 production rates were markedly reduced in homozygous *TM6SF2* E167K carriers versus control, whereas production rates for VLDL2-APOB-100 was similar between two groups. These studies supported impaired APOB secretion in individuals with the *TM6SF2* variant, a conclusion that was supported by a human *in vitro* 3D spheroids model established by Prill *et al.* [33]. In the latter studies, isolated primary human hepatocytes were utilized to generate human 3D spheroids from 3 wild type and 2 *TM6SF2* E167K heterozygous carriers; 3D spheroids from *TM6SF2* E167K heterozygous carriers had reduced APOB secretion as compared with spheroids consisting of wild-type hepatocytes. They concluded that decreased APOB secretion was not caused by lower *APOB* expression in the spheroid from *TM6SF2* E167K compared to spheroids from wild type hepatocytes. However, a recent study completed by Reyes-Soffer et al. using stable isotope studies, in 10 volunteers from the Lancaster Old Order Amish population (five homozygous *TM6SF2* E167K carriers and five sibling controls), showed increased secretion of VLDL APOB with no change in triglycerides secretion in p.E167K homozygous [26].

CONCLUSION

Advances in genetic sequencing technology have driven the growth and expansion of large-scale human studies. The observed effects of gene variants on human lipoprotein levels and links to disease states, have generated a wide range of studies in cells, rodent models, and humans. The latter identify the mechanisms that are driving disease incidence and can lead to therapeutic target identification. However, the results of these research efforts are often mixed or less robust than expected. TM6SF2 is one example of the inherent difficulties that exist when trying to clearly identify the mechanism that drive a human phenotype, in this case presence of hepatic steatosis and reduced levels of plasma triglycerides and LDL cholesterol. In this review, we present data from different models that complement one another yet at times contradictory data has been found. Reduced levels of TM6SF2 protein are associated with accumulation of hepatic triglycerides and reduced secretion of VLDL TG. However, the secretion of APOB100, the signature protein on a VLDL particle, has been reported as unchanged, reduced, or even increased in models of reduced TM6SF2. The reason for this heterogeneity is not clear but may be related to the complex interaction of APOB100 and TM6SF2 in the ER. TM6SF2 seems to play a critical role in adding triglycerides to nascent, lipid-poor VLDL to generate mature VLDL. Why reduced lipidation of nascent VLDL might lead to no change in secretion of the mature lipoprotein or either reduced or even increased secretion is, to say the least, puzzling. Hopefully, with continued interest and the use of more carefully defined human experimental conditions, the answer will emerge.

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Conflicts of interest

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