



The apoM/S1P Complex—A Mediator in Kidney Biology and Disease?

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Kidney disease affects more than 10% of the population, can be both acute and chronic, and is linked to other diseases such as cardiovascular disease, diabetes, and sepsis. Despite the detrimental consequences for patients, no good treatment options directly targeting the kidney are available. Thus, a better understanding of the pathology and new treatment modalities are required. Accumulating evidence suggests that the apolipoprotein M/sphingosine-1-phosphate (apoM/S1P) axis is a likely drug target, but significant gaps in our knowledge remain. In this review, we present what has so far been elucidated about the role of apoM in normal kidney biology and describe how changes in the apoM/S1P axis are thought to affect the development of kidney disease. ApoM is primarily produced in the liver and kidneys. From the liver, apoM is secreted into circulation, where it is attached to lipoproteins (primarily HDL). Importantly, apoM is a carrier of the bioactive lipid S1P. S1P acts by binding to five different receptors. Together, apoM/S1P plays a role in several biological mechanisms, such as inflammation, endothelial cell permeability, and lipid turnover. In the kidney, apoM is primarily expressed in the proximal tubular cells. S1P can be produced locally in the kidney, and several of the five S1P receptors are present in the kidney. The functional role of kidney-derived apoM as well as plasma-derived apoM is far from elucidated and will be discussed based on both experimental and clinical studies. In summary, the current studies provide evidence that support a role for the apoM/S1P axis in kidney disease; however, additional pre-clinical and clinical studies are needed to reveal the mechanisms and target potential in the treatment of patients.

Keywords: apolipoprotein M, sphingosine-1-phosphate, kidney failure, proteinuria, chronic kidney disease, lipoproteins

INTRODUCTION

The etiology leading to the development of kidney disease is diverse, but the disease can be divided into two categories, acute or chronic kidney disease, which are both characterized by a decrease in kidney function. Chronic kidney disease is estimated to affect more than 10% of the population worldwide, and up to 5% develop acute kidney injury during hospitalization. Unless resolved, the disease will result in a progressive loss of kidney function and, eventually, the need for dialysis or kidney transplantation. Kidney disease is also linked to other diseases, such as cardiovascular diseases, diabetes, and sepsis. Despite the detrimental consequences for patients, no good treatment options directly targeting kidney function are yet available. Thus, a better understanding of the pathology and new treatment modalities are required.

Apolipoproteins (apo)s are found associated with lipoproteins and assist with the structural stability of the particles as well as the formation, secretion, and uptake of lipoproteins via receptor-mediated pathways. Furthermore, some apos are also involved in inflammation and oxidation and function as chaperones of vitamins or bioactive lipids among others (1–5). So far, apoA through R have been discovered. ApoM was discovered in 1999 by Xu and Dahlbäck, and it was later revealed that apoM acts as the principal carrier of S1P in plasma (5, 6). Since its discovery, apoM has been suggested to be involved in mechanisms such as lipoprotein turnover, especially LDL, and to have anti-inflammatory and atheroprotective effects in part via an improved HDL cholesterol efflux capacity and anti-oxidative effect (7–10). Also, the apoM/S1P complex is involved in maintaining a normal endothelial cell barrier and participates in the regulation of triglyceride metabolism (5, 11). Thus, mice that do not express apoM have increased vessel permeability, increased amounts of brown adipose tissue, and improved triglyceride turnover (5, 11). In contrast, mice overexpressing apoM have delayed triglyceride turnover (12). In addition, apoM has been linked to diabetes [recently reviewed by Christoffersen (13)] and sepsis (14, 15). In a recent study, it was also shown that low apoM levels are associated with adverse outcomes in patients with heart failure (16). Finally, accumulating evidence points toward a role for apoM in fibrosis formation both in the liver and lungs (17, 18). However, the role of apoM in kidney biology and disease has received much less attention. The increasing knowledge from other studies related to different organs or diseases suggests that apoM might also play a role in the pathology of kidney disease. This will be discussed further in this review.

APOM AND LIPOPROTEINS

Regulation of ApoM Expression

ApoM is primarily expressed in the liver and kidneys but has also been detected in the intestine, and recent studies suggest that apoM is also expressed in brain endothelial cells and adipocytes (19–22). The apoM gene is localized within the MHC class III region of the genome containing genes involved in the immune system, and it is therefore speculated that apoM might be regulated by inflammatory stimuli. This link has been supported by a study that showed that inflammation results in decreased apoM expression (23). Furthermore, several cytokines [e.g., Transforming growth factor alpha (TGF α), Transforming growth factor beta (TGF β), Epidermal growth factor (EGF), and Hepatocyte growth factor (HGF)] downregulate apoM expression in liver cells, with TGF β having the most pronounced effect (24). In contrast, Interleukin 1 alpha (IL-1 α) and tumor necrosis factor alpha (TNF α) did not affect apoM expression in HepG2 cells, whereas platelet-activating factor (PAF) stimulation increased apoM expression (25).

ApoM expression in the liver is also regulated by transcription factors and hormones [reviewed in detail by Ren (26)]. Stimulation of HepG2 cells with propofol, a commonly used anesthetic, resulted in a ~3-fold upregulation of apoM expression. This increase is seen concomitantly with an increase

in the transcription factors HNF-1 α and FOXA2, suggesting that they are both involved in regulating apoM expression (27, 28). A role for HNF-1 α is further supported by the finding that HNF-1 α deficient mice have decreased apoM expression (29), while Wolfrum et al. have shown that inactivation of FOXA2 leads to lower apoM levels (30). In contrast, stimulation of the transcription factor LXR with the artificial ligand T0901317 results in decreased apoM expression in the liver both *in vivo* and *in vitro* (31, 32), although the same LXR activation leads to increased apoM expression in the intestine (20).

Leptin and insulin seem to be the two most important hormones in the regulation of apoM expression. In humans with hyperinsulinemia, plasma apoM is reduced by ~10% (33, 34), while experimental models with hyperinsulinemia display a reduction in apoM levels of ~50% (35). In addition, Xu et al. demonstrated that insulin stimulation of HepG2 cells leads to a dose- and time-dependent downregulation of apoM (36). It is plausible that this is mediated by insulin-regulated FOXA2 activation (30, 37). Leptin plays an important role in fat metabolism and appetite regulation, and mice with leptin deficiency develop experimental metabolic syndrome and insulin resistance. These mice also have markedly lower apoM levels compared to controls, which is normalized by leptin replenishment (38). In contrast, leptin stimulation of HepG2 cells *in vitro* decreases apoM expression (39). The reason for this apparent discrepancy between the *in vivo* and *in vitro* roles of leptin is unclear and requires further investigation. However, it could at least to some extent, reflect the fact that leptin is a multifunctional hormone that affects many different metabolic pathways *in vivo*, which indirectly modulates apoM expression.

The current knowledge on the regulation of apoM expression suggests the existence of a rather complex system with interactions between transcription factors and hormones. How the different modulators affect each other needs to be further assessed, as well as the potential differences between liver and kidney-derived apoM. To date, no knowledge is available on the specific regulatory mechanisms of apoM expression in the kidney.

ApoM and Triglyceride Rich Lipoproteins

ApoM is 25 kDa, a member of the lipocalin protein superfamily, and is characterized by an antiparallel β -barrel structure that forms a binding pocket for small hydrophobic molecules (40, 41). In addition, the first 20 amino acids of the apoM protein form a hydrophobic α -helix containing a signal peptide (41). The signal peptide anchors the apoM protein into the phospholipid layer of lipoproteins (42, 43). In 2011, Christoffersen et al. showed that apoM can bind and act as a transporter of S1P (4, 5). ApoM can also bind retinoic acid and retinol in the hydrophobic binding pocket, but the physiological relevance of this is still unexplored (4).

The liver is the primary source of plasma apoM, while the contribution of plasma apoM from the kidneys and other cell types is small, if present. Importantly, apoM is one of the few apolipoproteins, where the hydrophobic signal peptide is not cleaved off during protein maturation. This means that apoM is not present in its free form in the circulation but is instead

associated with lipoproteins via its retained signal peptide (42, 43). Thus, 95% of plasma apoM is associated with HDL, but apoM is also present in LDL, VLDL, and chylomicron particles. The relatively low concentration of apoM in plasma ($\sim 0.9 \mu\text{M}$) means that only $\sim 5\%$ of the HDL particles carry an apoM molecule, while $\sim 2\%$ of LDL particles carry them (44). ApoM is a promiscuous protein that exchanges between lipoproteins in the blood (7, 45). This contrasts with most apolipoproteins that are normally associated with exclusive lipoprotein class (es). The precise mechanism for the exchange of apoM is not clear, but seems to be driven by the availability of different lipoprotein subtypes (7, 45).

Plasma apoM is positively associated not only with the concentration of cholesterol in HDL particles but also with the cholesterol concentration of LDL particles in humans (34). In mouse studies, overexpression of apoM leads to an increased plasma cholesterol concentration, whereas the absence of apoM results in decreased cholesterol concentration (8). At the same time, LDL receptor knockout mice have increased plasma concentrations of apoM, which is also the case in patients carrying single nucleotide polymorphisms in the LDL receptor or apoB (7, 45). Thus, although only a minor portion of apoM is associated with LDL particles, apoM-containing lipoproteins are dependent on the LDL receptor for clearance. Such a link was supported by data reported by our group, who showed that the turnover of apoM-enriched HDL particles injected into LDL receptor knockout mice is slower than that in WT mice (7). In contrast, apoM-containing VLDL/LDL particles had reduced turnover compared to apoM-free VLDL/LDL particles in LDL-receptor-deficient mice, suggesting that apoM may regulate clearance of VLDL/LDL via pathways other than LDL-receptor-mediated uptake.

To date, the role of apoM in triglyceride-rich lipoprotein metabolism in organs other than the liver has not gained much attention. However, apoM is expressed in the intestine and may play a role in triglyceride and chylomicron processing (12, 20). Furthermore, the kidney expresses other apolipoproteins such as apoB100, an apolipoprotein important for LDL and VLDL formation (46). At this point, it is unknown whether apoM expressed in the kidney is similarly involved in the processing of triglycerides containing lipoproteins from the kidney and requires further investigation.

ApoM and HDL Particles

Due to the hydrophobic nature of the signal peptide, apoM most likely needs a close association with some form of phospholipid layer to be secreted, but the mechanism for this is still unclear. Studies in HEK293 cells and primary hepatocytes overexpressing apoM showed that the signal peptide retains apoM in the intracellular compartment, while cleavage of the signal peptide results in a higher secretion rate of apoM (47, 48). Furthermore, incubation of HEK293 cells overexpressing apoM with serum or HDL stimulates native apoM that are found localized in HDL particles in the medium (47). A similar mechanism was recently found in a study of brain endothelial cells (21). This suggests that apoM can be secreted from cells to lipoprotein particles already present in the plasma. However, how apoM

is transported through different intracellular organelles and via the cell membrane to HDL particles, and whether stimulants other than HDL can mediate the secretion, are currently not clear.

While HDL seems to stimulate the secretion of apoM, conversely, apoM also affects HDL biology. However, the data published so far are somewhat contradictory. In brief, nascent HDL particles are primarily formed in the liver in a process where apoAI, the principal apolipoprotein constituent of HDL particles, forms a scaffold at which phospholipids and minor amounts of cholesterol can be associated. This results in the formation of a sub-population of HDL particles called pre- β -HDL (49), which are then secreted from the liver for further maturation in the circulation. These mature HDL particles differ in apoAI content, particle size, and electrophoretic mobility. A study by Wolfrum et al. showed that downregulation of apoM in the liver results in decreased apoAI levels and a lack of pre- β -HDL formation, while there is an accumulation of large HDL particles (10). A similar pattern was seen in HNF-1 α deficient mice. These mice have no apoM expression and large buoyant HDL particles (29, 50). In contrast, a subsequent study by our group did not find any obvious difference in HDL particle size in either apoM knockout or apoM transgenic mice (8). In support of this, Mulya et al. have shown that apoM is not necessary for pre- β -HDL formation but is needed to form larger sized particles (51), while Liu et al. showed that the signal peptide is involved in the formation of larger HDL particles (48). Finally, overexpression of apoM in primary hepatocytes induces the formation of larger apoM-enriched HDL particles (52).

In summary, the mechanisms leading to apoM secretion are still poorly understood, but seem to be at least partially induced by HDL particles. At the same time, the predominant data available suggest that apoM plays a role in the formation of larger HDL particles; however, further studies are needed to clarify the mechanism. Finally, how these observations influence and modulate the release of apoM from the kidney remains unknown.

S1P EXPRESSION, SECRETION AND SIGNALING

S1P is synthesized from ceramide using sphingosine as an intermediate molecule. The final step of the synthesis is controlled by one of two sphingosine kinases (SPHK1 and 2), both of which are widely expressed in the body. Most cell types can produce S1P, but the S1P concentration is generally low in tissues except the blood. The plasma concentration of S1P ranges from 0.1 to 0.8 μM (53) and is primarily derived from the red blood cells but also from endothelial cells, thrombocytes, mast cells, macrophages, and thrombocytes (54–56). The secretion of S1P from red blood cells is facilitated mainly by the major facilitator superfamily transporter 2b (Mfsd2b). Plasma S1P levels are reduced by 50% in Mfsd2b knockout mice, while the S1P content in red blood cells is markedly increased (57). In addition, several other transporters, including spinster 2, PLTP, and several ABC transporters, have been shown to mediate the secretion of S1P [extensive reviewed by Thuy (58)].

In plasma, several candidates have been suggested as acceptors of S1P, such as apoM, apoAIV, and albumin. Thus, S1P is primarily associated with apoM (65%), and 30% is associated with albumin (5, 59, 60). A more recent study suggested that apoAIV can act as an S1P carrier in the absence of apoM and albumin (61). A study by Sutter et al. showed that apoM-enriched HDL particles enhance the S1P efflux from erythrocytes, while the efflux was comparable when stimulating the release of S1P by, respectively, HDL from apoM knockout mice and WT mice (62). Similar results were obtained by Christensen et al., showing that HDL is more potent than albumin in stimulating S1P release from erythrocytes, and this is enhanced when HDL contains apoM (63). Notably, apoM expression in tissues also seems to enhance S1P expression and secretion. Thus, overexpression of apoM in the liver leads to a higher S1P concentration in both liver tissue and plasma, without affecting the S1P levels in red blood cells, suggesting that S1P can be secreted with apoM from tissues expressing apoM (52, 64). This is supported by studies in HepG2, HeLa, and Raw264.7 cell lines where overexpression of apoM increased the intracellular content of S1P in all three cell types, while secretion was only induced in HepG2 and HeLa cells (64). Furthermore, introduction of a cleavage site for the signal peptide in apoM does not affect S1P expression in hepatocytes, but the secretion of the apoM/S1P complex is increased in cells expressing apoM with the cleavage site (48). Whether other apoM-independent mechanisms mediate S1P release from tissues, such as hepatocytes, remains undetermined. However, pharmacological inhibition of ceramide synthesis leading to increased S1P levels in hepatocytes results in the accumulation of S1P in the cells, suggesting that apoM is rate-limiting for S1P secretion, at least in hepatocytes (48, 52). However, additional studies are needed to reveal the precise mechanism of apoM-induced S1P expression and secretion.

S1P acts as both an intracellular and an extracellular signaling molecule. While the precise mechanism and signaling pathway of intracellular signaling are still only ambiguously described, extracellular signaling is mediated by binding to one of 5 G protein-coupled S1P receptors [sphingosine-1-phosphate receptor 1–5 (S1PR1–5)]. S1P is involved in multiple functions in the body, such as vascular maturation, lymphocyte trafficking, endothelial barrier functions, cell proliferation, and survival. This complexity is mainly thought to arise from the unique expression pattern of S1PRs in different organs and the G α subunits they activate. Thus, S1PR1 acts via G α_i , S1PR2, and 3 via G α_i , G α_q , or G12/13, while binding to S1P4–5 activates G α_i or G12/13. In general, S1PR1 and 3 are believed to mediate similar responses, S1P2 counteracts S1PR1 signaling, while less is known about S1P4 and 5.

Notably, accumulating data suggest that the cellular response to S1P differs depending on whether S1P is bound to apoM or albumin (65). S1P bound to apoM promote a more sustained effect on barrier function compared to S1P bound to albumin, due to a reduction in S1P1 degradation (66). Further, only apoM bound S1P seems to attenuate the endothelial inflammatory response to tumor necrosis factor α , and while albumin bound S1P promote lymphocyte egress, apoM bound S1P inhibits this process (67, 68). The complexity is further highlighted by a

study showing that while physiological concentrations of S1P preserve endothelial function, excess levels of S1P results in a dysfunctional endothelial barrier via activation of S1PR2 (69).

KIDNEY DERIVED APOM—A MEDIATOR OF S1P SEQUESTERING OR A MEDIATOR OF S1P SIGNALING IN THE KIDNEY?

In 2003, Zhang et al. showed that apoM is highly expressed in proximal tubular epithelial cells in kidneys (19). Despite this, the functional role of apoM in kidney biology remains unclear. However, it is hypothesized that apoM can be secreted from proximal tubular cells to the pre-urine. In the pre-urine, apoM may bind otherwise excreted molecules such as S1P and sequester them from excretion by re-uptake into the proximal tubular cells via binding to the megalin receptor (*Lrp2*). This hypothesis is supported by studies showing that apoM can bind to the megalin receptor (70) and that apoM is present in the urine of mice with proximal tubular-specific megalin receptor deficiency, but not in that of WT mice (62, 70). The importance of megalin as a central mediator of apoM uptake in the proximal tubular cells is further supported by a study showing that lack of either the chloride channel *Clc-5* (*Clcn5*) or cystinosis (*Ctns*), which leads to aberrant megalin receptor function, results in excretion of apoM into the urine (62).

What happens to apoM and the molecules that have been sequestered after re-uptake into the proximal tubular cells is even less studied. Likely, molecules such as S1P, which are sequestered in the pre-urine, are released into the peritubular capillaries and thereby returned into the circulation. Whether apoM follows the same route into the circulation or is degraded upon re-uptake or re-shuffled to the pre-urine is unknown. Megalin deficiency in proximal tubular cells and, thereby, loss of apoM to the urine does not affect plasma apoM levels (62), suggesting that apoM is not secreted to the basolateral site of the proximal tubular cells facing the peritubular capillaries. However, these data are only based on western blotting, and could, thus, also reflect that the amounts secreted are below what is possible to detect with such techniques.

Due to the hydrophobic signal peptide, secretion of apoM from the proximal tubular cells would require that apoM is either intracellularly lipidated or that it associates with an intra- or extracellular soluble carrier protein. Faber et al. reported that apoM in the urine of megalin-deficient mice is found in particles that are larger than apoM alone but smaller than HDL particles and devoid of apoAI (70). However, what this particle consists of remains to be determined. Notably, apoM secreted from the liver is already present in the plasma. Thus, the apoM detected in urine from mice with aberrant megalin function could originate from apoM filtered from plasma via the glomeruli. Further supporting this hypothesis, ApoAI and pre- β HDL can be filtered by glomerular capillaries (71). However, apoM was not found to be associated with pre- β HDL in plasma but instead bound to larger HDL particles that likely do not pass the filtration barrier (8, 51, 72). In addition, apoM-containing particles in the urine from megalin-deficient mice do not contain apoAI, further

indicating that apoM detected in urine does not originate from plasma but likely from the proximal tubular cells or other cells in the nephron.

The role of kidney-derived apoM as a scavenger of hydrophobic molecules is the only hypothesis put forward for kidney-derived apoM, but other functions may also exist. The accumulation of lipids in non-adipose tissue can be detrimental. This is also the case for the kidney, where lipid accumulation may lead to kidney injury and disease (73). ApoB, the primary apolipoprotein in LDL particles, is expressed in the kidney by proximal tubular epithelial cells, and Krystanek et al. showed that the kidney is able to produce lipoprotein-like apoB-containing particles with a density similar to that of LDL (46). Importantly, knockout of apoB expression leads to the accumulation of triglycerides in the kidney cortex. As apoM is expressed in the same cells as apoB and play a role in metabolism of intestinal derived apoB- and triglyceride-rich lipoproteins (12), an obvious hypothesis is that apoM plays a role in the formation and/or secretion of these particles. If so, apoM could be an important player in regulating lipid metabolism in the kidney, and downregulation could lead to lipid accumulation in kidney cells. However, this is purely speculative and needs to be addressed.

In line with the elusive biological role of apoM in the kidney, several basic features of apoM expression and regulation are still unknown. Thus, whether apoM is expressed in other cell types in the kidney in addition to the expression in the proximal tubular cells have not yet been determined. One study reported that apoM is expressed by mesangial cells (74), but further studies are needed to confirm this finding and determine the level of expression as well as to evaluate its function. In addition, a systematic analysis of the possible expression of apoM in different kidney cells is required. Moreover, no studies have addressed whether the expression of apoM in the kidney is regulated by the same mechanisms as in the liver. The HNF1 α transcription factor is expressed in the proximal tubular epithelial cells, as well as LXR, whereas FOXA2 is not expressed in the adult mouse kidney (75–77). This suggests that the regulation differs, at least to some degree, but this is purely speculative and needs to be investigated.

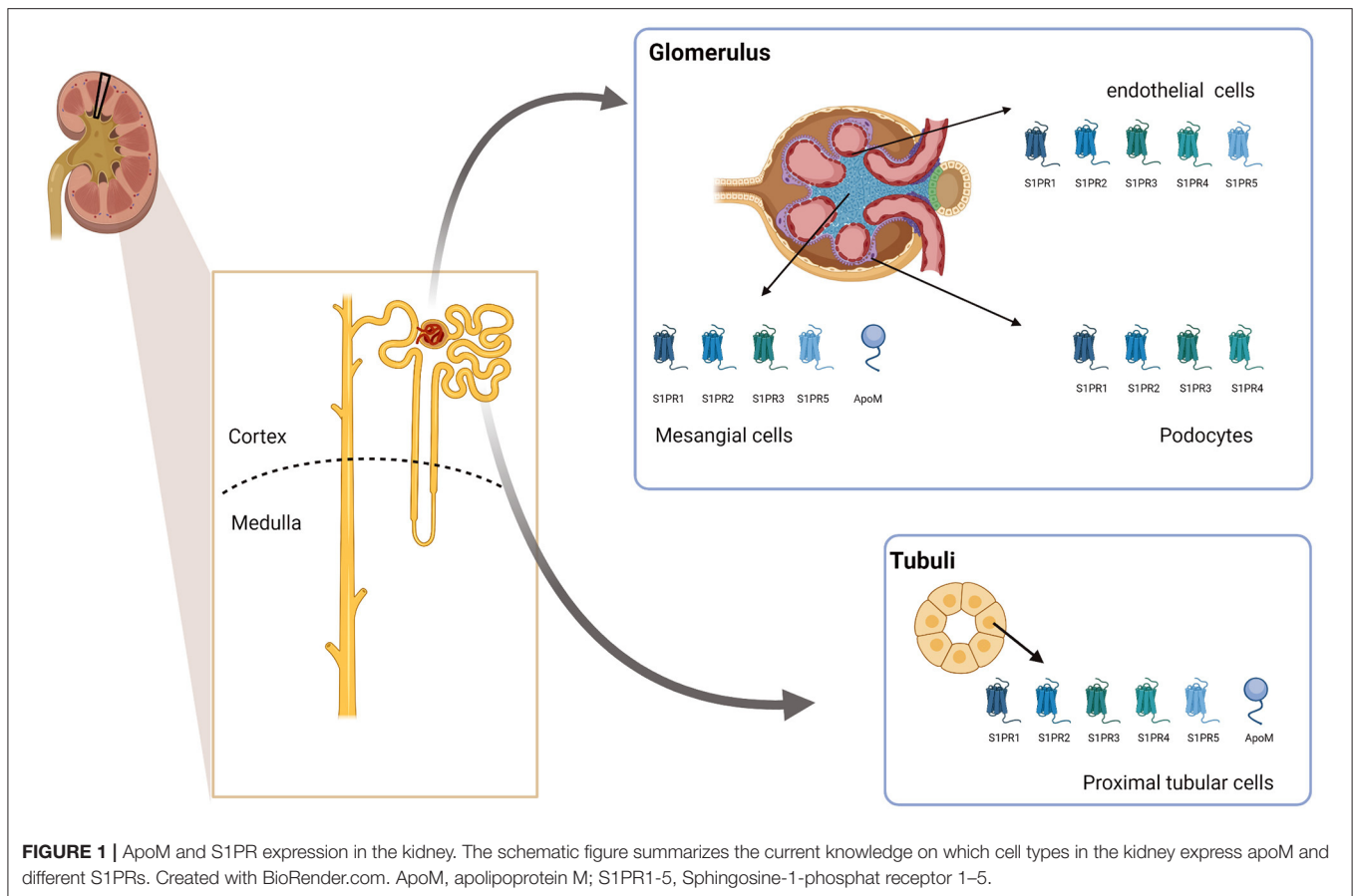
S1PR1–S1PR4 is expressed in the kidney, with 1 and 3 having the highest expression, followed by receptor 2, while 4 had the lowest expression level. Divergent data exist for receptor 5, with some studies finding it expressed while other studies do not (78, 79). As the kidney is a complex organ with many different cell types, structures, and functions, the location of the expression might be highly relevant for the functional role of S1P. So far, no systematic analysis of the expression pattern of the different receptors in the kidney and their relative expression has been published. However, *in vitro* studies have shown that S1PR1, S1PR2, S1PR3, and S1PR5 are expressed in glomerular mesangial cells (80, 81). All five S1PRs are expressed in glomerular endothelial cells (82) and proximal tubular cells (83, 84), while S1PR1 to S1PR4 are detected in immortalized mouse podocytes (85). Thus, while the expression of apoM seems to be cell-specific, S1PR1–S1PR3 is expressed in both the renal cortex as well as in the inner and outer medulla (summarized in **Figure 1**). Therefore, it could be speculated that if apoM carrying

S1P is secreted locally in the kidney from the proximal tubular cells, it may have local effects in the kidney, even if the secretion is too low to affect the overall plasma concentration of apoM/S1P. However, further studies are required to clarify whether this is biologically relevant. Interestingly, increasing number of scRNAseq data on single cells are available in different databases such as the Kidney Interactive Transcriptomics initiative. These databases can provide new insight into which cell types express which of the S1P receptors as well as apoM and potentially also new biological understandings.

In summary, apoM is expressed in proximal tubular epithelial cells, where it is likely secreted to the pre-urine to sequester small lipophilic molecules such as S1P from excretion. However, the nature of such molecules and their faith, as well as the faith of apoM, remain unknown. Furthermore, it is unclear whether kidney-derived apoM plays a role in other physiological pathways. S1PRs are expressed throughout the kidney. Thus, it could be speculated that sequestered S1P in a complex with apoM has local effects on the kidney.

ASSOCIATION OF APOM AND S1P LEVELS WITH KIDNEY FUNCTION IN KIDNEY DISEASE

The plasma concentration of apoM is affected by different conditions and diseases. Thus, BMI and T2D are inversely associated with apoM levels, while familial hypercholesterolemia with an isolated increase in LDL-C level is associated with an increase in plasma levels of apoM (7, 13). The literature on apoM levels in patients with CKD is heterogeneous and is presented in **Table 1**. Patients with IgAV-induced nephritis have increased apoM and S1P levels compared to healthy controls but lower levels than those without nephritis (86). These results are supported by an animal study performed in HIGA mice (an experimental model of IgA nephropathy) that found that HIGA mice have increased apoM plasma levels compared to those in control mice (91). In contrast, apoM levels in patients with CKD of mixed etiology are negatively associated with CKD severity (87), while plasma apoM levels in patients with end-stage renal disease are lower than those in controls (88). In patients with primary nephrotic syndrome, plasma apoM is reduced, as well as in patients with hyperlipidemia (90). Furthermore, apoM levels were positively associated with albuminuria in patients with primary nephrotic syndrome (90), while no difference in apoM levels was found when comparing patients with micro-, normo-, and macroalbuminuria in a diabetic cohort (89). The discrepancies found for the association of apoM and kidney function in the different studies may, to some extent, reflect that the underlying etiology for developing CKD is very diverse and that conditions other than kidney disease itself are more important for determining apoM levels. Thus, diabetes is today one of the most common diseases leading to CKD, and patients with T2D have decreased apoM levels, which might at least partially explain the low apoM levels seen in patients with CKD. In line with this, Sorensen et al. found that plasma apoM levels are lower in patients with CKD combined with T2D



than in patients with CKD without diabetes (87). Furthermore, induction of mild kidney disease by 5/6-nephrectomy in mice resulted in a somewhat surprising increase in plasma apoM levels. However, the study was conducted in apoE-deficient mice, which are known to have aberrant lipoprotein metabolism and elevated plasma cholesterol levels. Elevated plasma cholesterol levels are as described earlier associated with an increase in apoM levels. Thus, the apoM levels observed in this study may be explained by the cholesterol levels and not the kidney disease, again supporting the idea that circumstances other than kidney disease itself determine apoM levels in patients with CKD (92). This is further supported by the observation that patients with CKD in contrast to the apoE-deficient 5/6-nephrectomized mice normally do not have elevated cholesterol levels (if anything it decreases with decreasing kidney function) and have decreased apoM levels. In addition, streptozotocin-induced type 1 diabetes resulted in increased apoM levels, which were reversed by insulin treatment, while age induced a decrease in apoM levels in mice (93). Together, this highlights the complexity of establishing the underlying cause for a change in plasma apoM levels. Of note, apoM is normally not detectable in the urine, but Svarrer et al. reported that apoM can be detected in urine from pediatric patients with acute kidney injury post heart surgery (94). This is believed to be caused by a direct injury to the proximal tubular cells that are then not able to re-uptake apoM secreted to the

urinary site. The study did not measure plasma apoM levels, but it cannot be excluded that pathological changes in the kidney, can induce loss of apoM in the urine and potentially contribute to changes in plasma apoM levels. Further studies are however needed to clarify this.

Only a few studies have explored the association between S1P levels and kidney function in patients with CKD. One study has shown that plasma S1P levels in patients with type 2 diabetes decrease concomitantly with kidney function (89). In addition, S1P levels in HDL particles show a tendency to decrease with decreasing kidney function in patients with CKD (87), while S1P plasma levels in pediatric patients with CKD are higher than those in controls (95, 96). In streptozotocin-induced diabetic mice, plasma S1P levels are elevated globally (93) whereas (4 days) diabetic rats have elevated S1P levels locally in glomerular cells (97). Furthermore, berberine treatment of diabetic mice leads to less kidney injury, which is associated with decreased S1P signaling (98). Interestingly, patients with systemic lupus erythematosus had decreased S1P levels compared to controls, but the decrease did not correlate with the plasma albumin levels, suggesting that the dysregulation of S1P is mediated via changes in the apoM/HDL-bound S1P fraction and not the albumin fraction (99). In line with this, S1P decreased more in the HDL fraction than in the albumin fraction in the earlier stages of CKD (87).

TABLE 1 | Studies of patients or animals with kidney disease and effects on apoM levels.

Patient group	Number of participants	Method for apoM assessment	Plasma apoM	Lipid profile	Confounders	Albuminuria/proteinuria	References
IgAV	185 (76)	Commercial elisa	↑	↑ TC ↑ LDL-C → HDL-C ↓ TG		+	(86)
CKD stage 1-5	409	In-house elisa	↓	↓ LDL-C ↓ HDL-C ↑ TG	Diabetes CVD	NA	(87)
ESRD	40 (20)	In-house elisa	↓	↓ TC ↓ LDL-C ↓ HDL-C ↑ TG	CVD	NA	(88)
T2D*	90	Commercial elisa	→	→ TC → LDL-C → HDL-C → TG	Diabetes CVD	+	(89)
PNS	205 (110)	Commercial elisa	↓	↑ TC ↑ LDL-C ↓ HDL-C ↑ TG		+	(90)
Old mice	–	Commercial elisa	↓	NA	–	NA	(18)
HIGA mice	–	Western blot	↑	NA	–	+	(91)
5/6 NX, mice	–	In-house elisa	↑	↑ TC	–	NA	(92)

ESRD, end-stage renal disease; IgAV, immunoglobulin A-associated vasculitis; CKD, chronic kidney disease; T2D, type 2 diabetes; PNS, primary nephrotic syndrome; 5/6 Nx, 5/6 nephrectomy; TC, total cholesterol; C, cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides. Plasma apoM is increased (↑), decreased (↓) or unchanged (→) compared to control groups. Number of participants are reported as total participants with the number of included healthy controls shown in ().

Changes in plasma S1P levels could be a result of excess loss via the urine. In support of this idea, results from a study in patients with T2D showed an inverse association between urinary albumin excretion and plasma S1P levels (89). In another study, albuminuria in patients with IgA nephropathy was found to have a positive correlation with both serum S1P and urinary S1P levels (100).

Altogether, the data available points toward a complex biology where the association of both apoM and S1P with kidney disease varies, likely depending on the underlying etiology of the disease. This highlights the complexity of kidney diseases in general and the possible role of apoM and S1P in the development of kidney disease and needs to be included in the interpretation of apoM and/or S1P as biomarkers for kidney disease in future studies. Further, measuring the total plasma S1P might not provide a full picture. Instead, more focus should be given on measuring S1P in albumin and apoM/HDL fractions, respectively.

THE APOM/S1P AXIS—A MEDIATOR OF KIDNEY DISEASE?

While the association between S1P and kidney function has been poorly studied, the mechanistic role of S1P signaling in kidney disease has been extensively addressed in animal models, recently reviewed in detail by Drexler et al. (65). Thus, in the present review, only a brief summary of the overall trends is provided. Solid evidence points toward a protective effect of S1P

signaling in acute kidney disease. In experimental models of ischemia reperfusion (IR) injury, both S1P treatment, an agonist for S1PR in general (FTY720), or specifically, S1PR1 (SEW2871), reduces kidney injury (78, 84, 101–103). Furthermore, SEW2871 stimulation of proximal tubular epithelial cells *in vitro* protected the cells from IR-induced apoptosis, while mice with a proximal tubular specific knockout of S1PR1 have a greater decline in kidney function after IR injury (83, 84). Similarly, mice with a proximal tubular specific knockout of S1PR1 develop more kidney injury after cisplatin injury, which could not be rescued by FTY720 treatment, indicating that local S1P stimuli of the proximal tubular cells are essential for the protective effect (104). In addition, S1P signaling in endothelial cells appears to be important in the development of acute kidney disease as selective deletion of S1PR1 in endothelial cells exacerbates kidney injury upon IR (105).

Only a few studies have examined the role of receptors other than S1PR1, but it has been suggested that S1PR3 signaling aggravates kidney injury after IR (106). In addition, in contrast to the findings for S1PR1, inhibition of S1PR2 signaling is protective against IR injury (107).

Similar to what has been found for acute kidney disease, the literature in general supports a protective role for S1P signaling in chronic kidney disease, although fewer studies are available. In a chronic model of IR injury, mice with an endothelial knockout of S1PR1 develop a more severe injury than WT mice (108). In addition, FTY720 treatment alleviates kidney injury in a rat model of polycystic kidney disease (109), and

in a model of early stage diabetic nephropathy, both FTY720 and an S1PR1 specific agonist attenuates kidney injury (85). In contrast, suppression of S1PR2 signaling protects against experimental diabetic nephropathy (110). The protective role of S1PR1 signaling seems to be relevant both in the prevention of injury and in the recovery phase. Thus, knockout of endothelial S1PR1 expression before injury leads to exacerbation of kidney injury after IR, while knockout after IR results in increased tissue fibrosis and impaired healing (108). In humans, sphingosine-1-phosphate lyase (SGPL1) deficiency has been linked to nephrotic syndrome. SGLP1 mediates the degradation of S1P, meaning that deficiency results in accumulation of S1P and increased plasma levels, which further supports a causal role for S1P in kidney disease (111–113).

Little is known about the role of apoM in kidney diseases. However, accumulating data suggest that apoM is not only affected by kidney disease, but also has a causal role. In a recent study by Ding et al., reduced apoM levels resulted in increased kidney injury (18). Similarly, adenovirus-induced overexpression of apoM results in less kidney injury in HIGA mice and reduced expression of classical markers of fibrosis (incl. TGF β and FN-1), while siRNA-induced apoM deletion results in accelerated injury compared to control animals (91). The mechanisms underlying the effect of apoM on the kidney are not clear; however, S1P bound to albumin results in increased proliferation of mesangial cells and increased expression of pro-fibrotic genes in the proximal epithelial cells; these effects were not observed when the cells were stimulated with S1P bound to apoM. To this point, only one study has addressed the role of kidney-derived apoM in kidney disease. This study suggests that silencing of apoM expression in mesangial cells leads to mitochondrial damage and apoptosis (74). However, apoM is mainly expressed in the proximal tubular cells. Therefore, it would be of great importance to unravel whether apoM derived from these cells has any role locally in the kidney during kidney injury.

Taken together, these data suggest that local S1P signaling in the kidney is of high importance for protecting the kidney against injury. What role both plasma and kidney-derived apoM play in connection to this, however, still needs to be addressed in future studies. Though highly speculative the data so far available could suggest that the apoM/S1P-complex act in two separate ways

in the kidney—(1) being a systemic effect of circulating HDL-apoM/S1P or albumin-apoM/S1P on endothelial cells in the kidney and (2) a direct effect of kidney derived apoM on tubular cells. This is important to keep in mind as these two pathways might not have the same effect and regulation, which could influence how potential drug candidates targeting the apoM/S1P axis act in different diseases.

CONCLUSION

As this review suggests and highlights, significant gaps in our knowledge still need to be elucidated before we understand the role and function of kidney-produced apoM and S1P, but also whether the plasma lipoproteins containing apoM and S1P play a role in biological processes that affect kidney function and pathologies. Drugs targeting the S1P-receptor pathways are evolving as well as apoM-modulating drugs with a focus on cardiovascular diseases and inflammation; however, only a few of these studies have also reported data that are relevant to kidney biology. For example, pharmacological targeting of S1PR1 can improve renal microcirculation during sepsis in mice (114). Acute kidney failure or organ failure is a well-known consequence of severe sepsis. Likewise, treating animals with an artificial apoM-FC component can attenuate hypertension and IR injury (115). Whether any of these drugs will reach a level of clinical use will be very interesting to follow the years ahead. Hopefully, and in parallel, the community will gain further information from upcoming pre-clinical studies on potential side effects of such drugs related to, for example, lipid accumulation or compromised inflammatory response, both harmful to the kidney.

AUTHOR CONTRIBUTIONS

LB and CC designed and wrote this manuscript. All authors contributed to the article and approved the submitted version.

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