Insight into the role of angiopoietin-like protein 4 in podocypopathies (Review)

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Abstract. Angiopoietin-like proteins are a group of seven proteins whose structure is different from that of angiopoietins in linkage to Tie2 or Tie1 receptors. Angiopoietin-like protein 4 (ANGPTL4), which is also known as peroxisome proliferator-activated receptor-γ (peroxisome proliferator-activated receptors-γ) angiopoietin-related or fasting-induced adipose factor, exists in two isoforms: Hyposialylated ANGPTL4 with a high-isoelectric point (high-pI), and normal sialylated ANGPTL4 with a neutral isoelectric point (neutral-pI). The present review discusses the role of ANGPTL4 in podocypopathies. Neutral-pI ANGPTL4 may also reduce proteinuria by binding β5 integrin and is secreted in various glomerulonephritis, while high-pI ANGPTL4 is upregulated in minimal change disease (MCD), modifying slight diaphragm power and increasing protein loss. In experimental animal models, high-pI ANGPTL4 is present in higher concentrations in MCD relapses than in disease remission. The administration of N-acetylmannosamine converts high-pI ANGPTL4 to neutral-pI ANGPTL4 and intraperitoneal epigallocatechin-3-gallate reduces the glomerular expression of ANGPTL4, with a reduction in albuminuria. Glomerular ANGPTL4 upregulation appears earlier in animal models, suggesting that the dysregulation of glomerular ANGPTL4 may result in foot process damage. Serum ANGPTL4 and proteinuria are likely reduced following glucocorticoid therapy. A high pI ANGPTL4/neutral pI ANGPTL4 ratios or their ratio compared to soluble urokinase-type plasminogen activator receptor could identify a marker for the differential diagnosis between early focal segmental glomerulosclerosis and MCD, in younger patients or in those who are not eligible for a kidney biopsy.

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Contents

1. Introduction

Angiopoietin-like proteins are a group of seven proteins whose structure is comparable to that of angiopoietins; however, they do not bind to Tie2 or Tie1 receptors (1). Angiopoietin-like proteins are present in the majority of the mammals' reign, apart from angiopoietin-like protein 5, which is exclusively human. Angiopoietin-like protein 8, also known as betatrophin, is another form of angiopoietin-like protein, characterized by N-terminal domains similar to angiopoietin-like protein 3, without a C-terminal fibrinogen-like domain (2).

Angiopoietin-like protein 1, or angioarrestin, is an inhibitor of vascular endothelial growth factor (VEGF), which has been demonstrated to block the STAT3 pathway and, consequently, angiogenesis in hepatocellular carcinoma (3). Angiopoietin-like protein 2 activates nuclear factor-κB (NF-κB) and plays a role in inflammatory diseases, reactive oxygen species production and carcinogenesis (4-6). Angiopoietin-like protein 3 inhibits lipoprotein lipase (LPL), similar to a angiopoietin-like protein 4 (ANGPTL4), and together with angiopoietin-like protein 8, they are involved in lipid metabolism. Moreover, both angiopoietin-like proteins 3 and 8 are more highly expressed in hepatocellular carcinoma (7).

Angiopoietin-like protein 5 and angiopoietin-like protein 7 play a role in the expansion of hematopoietic stem cells and lung cancer. While angiopoietin-like protein 7 appears to be associated with the inhibition of cancer, increased levels of angiopoietin-like protein 5 have been shown to be associated with the poor survival of patients with non-small cell lung cancer (8).

Angiopoietin-like protein 6 is expressed in keratinocytes and the liver. This protein binds to ERK1 and ERK2, regulating epidermal proliferation. It is involved in psoriasis and appears to interact with E-cadherin as a poor prognostic factor in colon cancer (9).

The present review discusses the role of ANGPTL4 in podocypopathies. For this purpose, a search was performed on the Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Ovid and google scholar databases to identify relevant articles. A search was made for articles in the English language. The following key words were used: Angiopoietin-like protein OR angiopoietin-like protein 4 OR ANGPTL OR ANGPLT4; proteinuria OR nephrotic syndrome OR minimal change disease OR mcd OR focal and segmental glomerulosclerosis (FSGS) OR focal and segmental glomerulosclerosis OR podocytopathies; Animal studies OR *in vitro* OR human studies.

2. Angiopoietin-like protein 4

ANGPLT4 is also known as peroxisome proliferator-activated receptor-γ (peroxisome proliferator-activated receptor-γ) angiopoietin-related or Fasting-induced adipose factor, and its gene is located in chromosome 19p13.3. This protein has a molecular weight of 45-65 kDa and is composed of 406 amino acids, including four cysteines responsible of sulfide linkages, three N-terminal glycosylation sites and a fibrinogen-like C-terminal domain. Following cleavage, the N-terminal fragment spreads around as an oligomeric protein, while C-terminal protein as a monomer.

ANGPLT4 is produced by several tissues, including the liver, blood plasma, placenta, small intestine, heart and adipose tissue, induced by both glucocorticoid and nuclear hormone receptors via a peroxisome proliferator-activated receptor-γ-response element located in the human ANGPLT4 gene (10). The function of ANGPLT4 is tissue-dependent; thus, it may be involved in the regulation of vascular permeability, angiogenesis, tumor metastasis and ischemia-reperfusion injury (11).

ANGPLT4 interacts with β1 and β5-integrin of the renal extracellular matrix, modifying the podocyte cytoskeleton (12,13). The inflammatory response associated with ANGPLT4 overexpression can lead to the development of podocytopathies and nephrotic syndrome, while lower glomerular levels of this protein have been shown to be associated with a reduced apoptotic rate of podocytes (14), improving their repair processes (15). However, the intravenous administration of recombinant ANGPLT4 has been found to reduce proteinuria in rat models of nephrotic syndrome due to membranous nephropathy and diabetic kidney disease (15).

Two forms of ANGPLT4 are known on the basis of their sialylation state: Hyposialylated ANGPLT4, which has a high-isoelectric point (high-pI), while normal sialylated ANGPLT4 has a neutral isoelectric point (neutral-pI) (16). The second isoform is the most secreted, particularly by bone and muscle, in response to hypertriglyceridemia (17) and, unlike the hyposialylated ANGPLT4, neutral-pI ANGPLT4 may also reduce proteinuria by binding β5 integrin, as has been demonstrated in an experimental model (16). Previous studies have indicated that neutral-pI ANGPLT4 is secreted in podocytopathies and other glomerulonephritis, while high-pI ANGPLT4 is upregulated in minimal change disease (MCD) (16,17). Furthermore, ANGPLT4 can increase reactive oxygen species production, as it spurs NADPH oxidase 1 (18) and increases the levels of pro-inflammatory interleukins (such as interleukin-6), the O_2^-/H_2O_2 ratio and the synthesis of serum amyloid A protein (10).

According to the study by Clement *et al* (15), normal sialylated angiopoietin-like protein 4 can protect the glomerular endothelium, while the hyposialylated form may be a cause of injury in MCD, as the glomerular secretion of ANGPLT4 can influence the glomerular basement membrane charge, modifying its diaphragm power and increasing protein loss (16). The expression of ANGPLT4 is also increased in renal cancer cells and metastatic disease, although its role in tumor progression remains unclear (19,20).

ANGPLT4 and lipid metabolism. The oligomerization of ANGPLT4 reduces the activity of LPL in uptaking free fatty acids (FFAs) in muscle cells and adipose tissue, causing hypertriglyceridemia, as demonstrated in experimental models with high-pI titers of angiopoietin-like protein (17). Oligomerization stabilizes ANGPLT4 following cleavage (12,21) and the N-terminal interaction with lipoprotein lipase is transient; however, it causes the permanent inactivity of this enzyme, inducing its conversion from a dimeric to monomeric inactive form. Some mutations of ANGPLT4, as those regarding Cys76 and Cys80, reduce the inhibitory effects of ANGPLT4 on LPL (22). This protein carries out its role in lipid metabolism by inhibiting the fasting signal in the hypothalamus cortex, where it is expressed (12). Furthermore, some genetic mimicry of ANGPTL4 appear to be related to a reduced risk of developing coronary heart disease in patients with diabetes (23). It is known that free fatty acids increase ANGPLT4 through the activation of peroxisome proliferator-activated receptor (peroxisome proliferator-activated receptor), in particular in the case of a high FFA/albumin ratio, as occurs in proteinuric diseases such as MCD, characterized by the selective urinary loss of albumin and in analbuminemic experimental models. Moreover, according to the study by Clement *et al* (21), the transgenic expression of adipose aP2-ANGPLT4 gene increases serum ANGPLT4, but does not affect proteinuria, differently from the selective overexpression of podocyte NPHS2-ANGPLT4, which induces proteinuria and the loss of glomerular basement membrane charge, reflecting the different roles of the isoforms of ANGPLT4. Leptin appears to be directly or indirectly implicated with angiopoietin-like protein regulation, as it can inhibit ANGPLT4 mRNA transcription (10). Moreover, it has been demonstrated that ANGPLT4 overexpression is related to inflammation and hypoxia, particularly in adipose tissue, causing chronic inflammation and macrophage infiltration in white adipose tissue (24).

ANGPLT4 and MCD. MCD is a podocytopathy, representing the most frequent cause of nephrotic syndrome in children and one of the most frequent in adults. It is characterized by selective proteinuria (often without hematuria), hypertension and edema (25). The typical histological lesions are visible with electron microscopy, which reveals the effacement and fusion of podocyte foot processes in the absence of electron-dense deposits. In 1974, Shalhoub (26) suggested that T-lymphocytes play a primary role in the pathogenesis of MCD and further studies confirmed an association between MCD and atopy or an increased number of the T-helper 2 (Th2) cell subset (27,28). The disease is usually cortico-sensitive, with a remission rate of up to 90% of cases, unlike other podocytopathies, such as FSGS, in which complete remission is achieved in 30-40% of patients (29-31).

In 2004, Reiser *et al* (32) demonstrated that lipopolysaccharide (LPS) upregulates B7-1 (CD80), increasing proteinuria and in 2016, Liu (33) proposed the existence of an association between B7-1 and the modified charge of glomerular basement membrane induced by ANGPLT4, although this is not yet completely clear. A previous study using a child population, demonstrated that ANGPTL4 worsens the nephrotic syndrome, with a reduction of podocin and actin on podocyte foots (34). Similarly, recombinant ANGPTL4 animal models or treatment that reduced it, as reported in a review of 2014, seemed to be related with an improvement in the nephrotic syndrome (35). Similar results were found in another animal study at 21 weeks of follow-up (36). The observation of murine models of MCD, such as puromycin aminonucleoside-affected glomeruli, has revealed a deficiency in heparan sulfate proteoglycans compared to healthy glomeruli (37).

ANGPLT4 appears to induce the effacement of podocyte foot processes by activating signals at the podocyte-glomerular basement membrane interface binding αvβ5 integrin (38); consistently, ANGPLT4 is poorly expressed in normal glomeruli, although it is overexpressed in mouse models of MCD, both locally as confirmed by the *in situ* hybridization of capillary loop, and in serum and urine (24,39).

In particular, in puromycin aminonucleoside-affected glomeruli, there is a glucocorticoid sensitive overexpression of high-pI ANGPLT4. This isoform is present at a higher concentration in the case of MCD relapses and it is not detectable during disease remission, membranous nephropathy and FSGS (16). Furthermore, increased serum levels of high-pI angiopoietin-like protein have been found in patients with MCD (17). The administration of N-acetylmannosamine (ManNAc), which converts high-pI ANGPLT4 to neutral-pI ANGPLT4, has been demonstrated to lead to a reduction in albuminuria of 40% (39).

According to Davin (40), the hyposialylated form is a mediator of proteinuria in MCD, through its binding to glomerular basement membrane and endothelial cells: Specifically, in glomeruli, it binds to endothelial alpha V beta5 integrin (at the very least) and modifies putative-podocyte feedback loops to reduce proteinuria. Furthermore, increased serum levels of high-pI angiopoietin-like protein have been found in patients with MCD (40).

In addition, according to the study by Li *et al* (41), urinary ANGPLT4 may represent an earlier biomarker of podocyte injury in a rat model of damage induced by adriamycin. Another study found that ANGPLT4 glomerular expression and urinary excretion exhibited the same trend, associated with the early stage proteinuria (42). Proteinuria then continued to increase despite the decrease in ANGPLT4 levels. Glomerular ANGPLT4 upregulation appeared significantly earlier than the changes in desmin and synaptopodin in rats with damage induced by adriamycin, suggesting that adriamycin and glomerular ANGPLT4 may result in foot process effacement and cytoskeletal damage. When rats with damage induced by adriamycin received tacrolimus administration, it resulted in preventing desmin enhanced expression and reversing the reduction in synaptopodin. Moreover, the immunosuppressive effects of tacrolimus significantly reduced angiopoietin-like protein 4 glomerular countenance and urinary release (43).

In another study on an animal model of cisplatin-induced acute kidney injury, increased levels of mRNA and neutral ANGPLT4 were observed in proximal tubules, probably associated with lipoprotein lipase damage (44).

Glucocorticoid therapy appears to reduce proteinuria, as well as serum ANGPLT4 levels within 6 days; however, it remains unclear whether it is a direct impact on ANGPLT4 expression, or whether this relation is subject to a reduction of nephrotic syndrome manifestations (proteinuria and hypoalbuminemia), which act as a stimulus for the renal synthesis of ANGPLT4 (26).

ANGPLT4 and other podocytopathies. Both in humans and experimental models, there is no modification in the expression of ANGPLT4 mRNA in collapsing type FSGS, in contrast to what occurs in MCD (36). Clement *et al* reported a significant upregulation of ANGPLT4 in experimental MCD as opposed to FSGS, and anti-Thy1.1 (mesangial proliferative) glomerulonephritis (MsPGN) (15).

Conversely, urinary ANGPLT4 is overexpressed in FSGS during relapses and appears to be associated with proteinuria in relapsing FSGS and other glomerulopathies, excluding MCD (45). Furthermore, serum ANGPLT4 levels appear to be reduced in association with LPS podocyte injury, whereas urinary and glomerular ANGPLT4 levels appear to be increased. No changes have been found in mesangial cells (46). In *in vitro* experiments, LPL and puromycin aminonucleoside-induced injury caused minimal change disease. This can explain the similar ANGPLT4 evolution (45).

When comparing patients with MCD, FSGS and membranous nephropathy, elevated circulating levels of high-pI and oligomeric neutral-pI ANGPLT4 have been detected only in relapsing MCD (24). Furthermore, the hyposialylated form is not upregulated in membranous syndrome or other glomerulopathies.

Soluble urokinase-type plasminogen activator receptor: A potential confounding factor in FSGS. MCD and FSGS are often considered as two faces of the same disease. Of note, similar mechanisms are present in these conditions, including ANGPLT4 involvement through the soluble urokinase-type plasminogen activator receptor (suPAR). Its pathogenetic role in FSGS is currently a topic of debate among scientists (47). Soluble urokinase-type plasminogen activator receptor is a glycosylphosphatidylinositol-anchored membrane glycoprotein, composed of three homologue domains termed DI, DII and DIII, and found in an insoluble form of 35-60 kDa or a soluble form 20-50 kDa, with different molecular masses depending on the site of glycosylation. Its secretion increases in an inflammatory status and its serum levels are associated with chronic kidney disease and a decline in the glomerular filtration rate (48-50). It is found in FSGS at high serum levels during disease flare, while lower levels are associated with

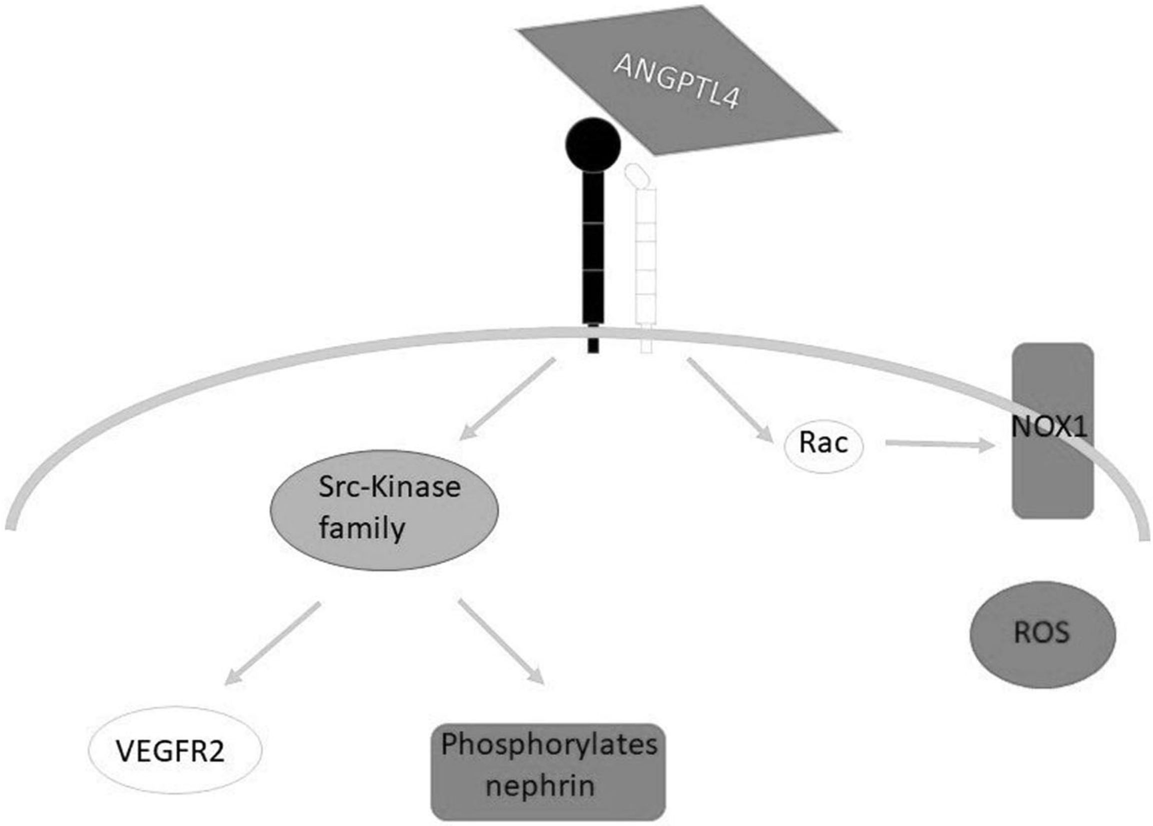

Figure 1. ANGPTL4 can link to two types of integrins: αvβ1 and αvβ5. These interactions active different pathogenetic pathways: The activation of Src-kinases (αvβ1) with the phosphorylation of nephrin and the activation of Rac (αvβ5) with the overproduction of ROS through NOX1 stimulation. ANGPTL4, angiopoietin-like protein 4; ROS, reactive oxygen species; NOX1, NADPH oxidase 1.

remission of the disease. Apart from its role in the regulation of chemotaxis, suPAR can interact with α3β1 and αvβ3 integrins which have both a structural role binding vitronectin molecules and podocyte actin-based cytoskeleton to the glomerular basement membrane, and a role in intracellular signaling. suPAR is able to induce vitronectin-dependent αvβ3-integrin activation, thus modulating the Rac1 pathway and increasing the production of contractile fibers in cultured podocytes and murine models, determining foot process effacement. Conversely, β1 integrin can modulate the Src-kinase family that phosphorylates nephrin and, consequently, regulates actin polymerization, and β5 can regulate laminin and fibronectin distribution (51) (Fig. 1).

Furthermore, nephrin expression is reduced with the increased expression of ANGPTL4 following treatment with palmitic acid, perhaps mediated by the AMP activated protein kinase/phosphor-acetyl-coA carboxylase pathway (52).

ANGPTL4 and peroxisome proliferator-activated receptors. Peroxisome proliferator-activated receptors are steroid/thyroid nuclear hormone receptors involved in metabolic homeostasis and distinct in three forms: Peroxisome proliferator-activated receptor α (NR1C1), peroxisome proliferator-activated receptor γ (NR1C3) and peroxisome proliferator-activated receptors β/δ (NR1C2). Their activation can, in turn, reduce hypertriglyceridemia (peroxisome proliferator-activated receptor α), serum glucose in type 2 diabetes, independent of the insulin-glucose effect (peroxisome proliferator-activated receptor γ), or provide benefit to steatohepatitis in metabolic syndrome, as well as reducing the regulation of the molecule NF-κB (peroxisome proliferator-activated receptors β/δ) (53). Peroxisome proliferator-activated receptor γ expression is low in the glomerular basement membrane, whereas it increases after damage. Peroxisome proliferator-activated receptors α and γ are also ANGPTL4 and leptin targets (10,53).

ANGPTL4 mRNA expression is lower in heterozygous peroxisome proliferator-activated receptor γ-mutant mice than in non-mutant mice; conversely, the leptin level is higher (49). In embryonic mouse fibroblast NIH 3t3 cells, ANGPTL4 mRNA expression is low prior to the administration of pioglitazone, although its expression multiplies 2 h after treatment (54). On the contrary, Lu *et al* demonstrated that paeoniflorin restores podocyte features and upregulates peroxisome proliferator-activated receptor γ expression, decreasing ANGPTL4 levels in the kidney, in an experimental model of nephrotic syndrome (55). In a model of puromycin aminonucleoside nephropathy, Yang (51) demonstrated that the early administration of peroxisome proliferator-activated receptor agonist reduced overall sclerosis and decreased ANGPTL4 expression (Fig. 2).

A common point between ANGPTL4 and peroxisome proliferator-activated receptors is hypoxia. ANGPTL4 has a hypoxia-inducible factor (HIF)-1α-dependent mechanism. Hypoxia-inducible factor is a heterodimeric transcription factor with angiogenic activity. The A-subunit

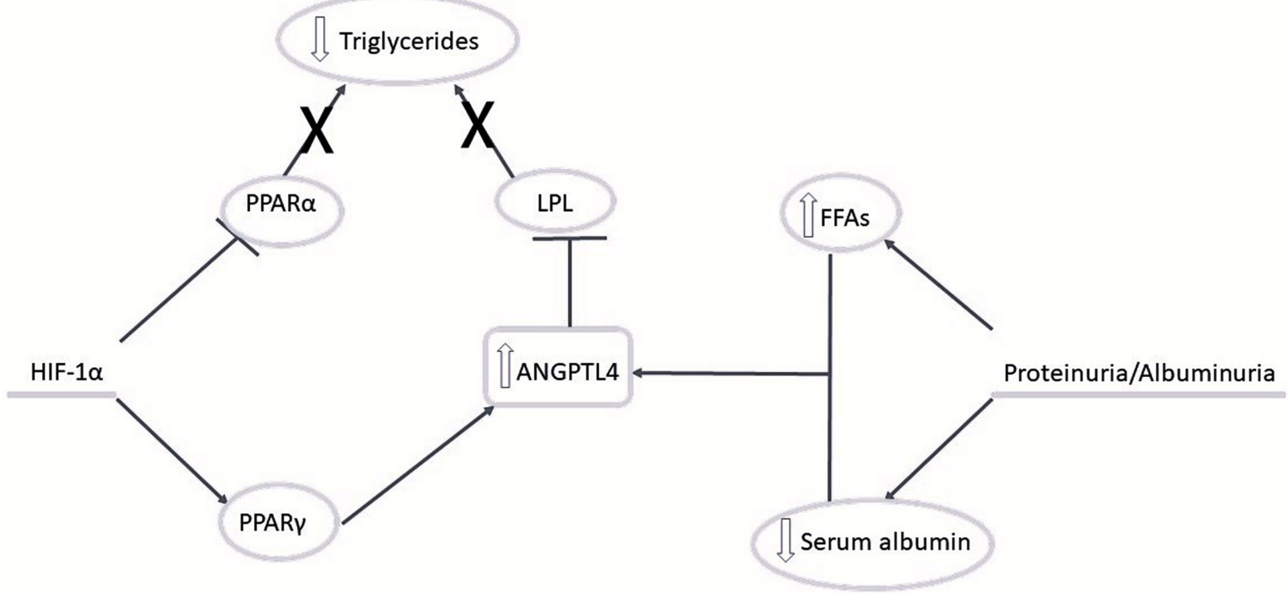

Figure 2. ANGPTL4 level is increased from HIF and proteinuria through two different pathways: HIF increases PPAR-γ and proteinuria, which reduces serum albumin and enhance FFA levels. These three consequences increase serum ANGPTL4 levels. ANGPTL4, angiopoietin-like protein 4; HIF, hypoxia-inducible factor; FFA, free fatty acid; PPAR, peroxisome proliferator-activated receptor; LPL, lipoprotein lipase.

is oxygen-sensitive and contains proline residues (residues 402 and 564). Following the hydroxylation of these residues, von Hippel-Lindau tumor suppressor protein binds HIF-1α for degradation. If oxygenation is <5%, HIF-1α binds to HIF-1β. It has been observed that the reduction of HIF-1α expression decreases ANGPTL4 mRNA expression. Conversely, peroxisome proliferator-activated receptors β/δ, in synergy with HIF-1α, upregulate ANGPTL4 mRNA expression (56,57).

Peroxisome proliferator-activated receptor γ agonists improve glomerulosclerosis in rat models administered puromycin aminonucleoside, reducing the expression of peroxisome proliferator-activated receptor γ and restoring the negative effects on glomeruli. *In vivo*, peroxisome proliferator-activated receptor γ agonists increase VEGF expression and reduce ANGPTL4 expression.

3. New treatments

In 2011, Clement *et al* (21) fed NPHS-ANGPTL4 transgenic rats ManNAc, to examine its efficacy on a model of MCD. The administration of ManNAc resulted in an increased sialylation of ANGPTL4 and a main reduction of albuminuria of ~40.6% (21).

Salvianolic acid A is a hydrosoluble substance effective against peroxidative damage in the retina and kidneys. In addition to low doses of prednisone, it has been demonstrated to reduce proteinuria and high levels of triglycerides, increase serum albumin more than steroids alone, as well as prevent the deterioration of kidney function and even revert foot processes fusion. In the same study, the authors demonstrated that salvianolic acid A increased the levels of synaptopodin and desmin *in vivo*, as well as *in vitro*, affecting the RhoA-pathway and peroxisome proliferator-activated receptor γ expression (58).

In the same year, Liu and He (59) demonstrated that the intraperitoneal administration of epigallocatechin-3-gallate in mice ameliorated sclerosis and decreased proteinuria and ANGPTL4 expression in renal tissue by suppressing the HIF1α/ANGPTL4 pathway.

In 2016, new therapeutic agents were proposed, such as recombinant mutated human ANGPTL4, which was demonstrated to significantly ameliorate proteinuria without hypertrigliceridemia, or Bis-T-23 (60). This small molecule has been investigated in several murine models of proteinuric kidney diseases and stimulates actin-dependent dynamin oligomerization and actin polymerization, reducing or even preventing proteinuria (11,49).

4. Conclusion and future perspectives

It remains unclear whether FSGS and MCD are different diseases or different manifestations of the same pathology; however, MCD may represent an early form of FSGS. CD80 lymphocytes and soluble urokinase-type plasminogen activator receptor, despite both being elevated in FSGS and MCD, have different profiles of expression in each of these podocytopathies.

The role of ANGPTL4 in podocytopathies is increasingly recognized, and may be adopted as an early predictor of MCD; however, high levels of this protein in other diseases and its impact on lipid metabolism make this hypothesis unlikely.

The high-pI ANGPTL4/neutral-pI ANGPTL4 ratio in serum and urine or between the two isoforms of ANGPTL4 and soluble urokinase-type plasminogen activator receptor should be further studied, in order to identify a marker that allows for the differential diagnosis between early FSGS and MCD. This may also lead to the development of appropriate therapeutic protocols, in particular in younger patients or those who are not eligible for a kidney biopsy.

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Authors' contributions

VCa and FGV conceptualized the study. FZ and VCe were involved in the search for relevant literature. FZ and VCa and RS were involved in the writing and preparation of the original draft of the manuscript. VCa and DS were involved in the analysis of the studies identified in the literature for inclusion in the review. FGV and FZ and RS were involved in the writing, reviewing and editing of the manuscript. VCe and FGV were involved in the processing of images. DS supervised the study. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Kadomatsu T, Tabata M and Oike Y: Angiopoietin-like proteins: Emerging targets for treatment of obesity and related metabolic diseases. FEBS J 278: 559-564, 2011.
2. Endo M: The roles of ANGPTL families in cancer progression. J UOEH 41: 317-325, 2019.
3. Yan Q, Jiang L, Liu M, Yu D, Zhang Y, Li Y, Fang S, Li Y, Zhu YH, Yuan YF and Guan XY: ANGPTL1 interacts with integrin α1β1 to suppress HCC angiogenesis and metastasis by inhibiting JAK2/STAT3 signaling. Cancer Res 77: 5831-5845, 2017.
4. Tabata M, Kadomatsu T, Fukuhara S, Miyata K, Ito Y, Endo M, Urano T, Zhu HJ, Tsukano H, Tazume H, *et al*: Angiopoietin-like protein 2 promotes chronic adipose tissue inflammation and obesity-related systemic insulin resistance. Cell Metab 10: 178-188, 2009.
5. Aoi J, Endo M, Kadomatsu T, Miyata K, Ogata A, Horiguchi H, Odagiri H, Masuda T, Fukushima S, Jinnin M, *et al*: Angiopoietin-like protein 2 accelerates carcinogenesis by activating chronic inflammation and oxidative stress. Mol Cancer Res 12: 239-249, 2014.
6. Aoi J, Endo M, Kadomatsu T, Miyata K, Nakano M, Horiguchi H, Ogata A, Odagiri H, Yano M, Araki K, *et al*: Angiopoietin-like protein 2 is an important facilitator of inflammatory carcinogenesis and metastasis. Cancer Res 71: 7502-7512, 2011.
7. Arca M, Minicocci I and Maranghi M: The angiopoietin-like protein 3: A hepatokine with expanding role in metabolism. Curr Opin Lipidol 24: 313-320, 2013.
8. Wang L, Geng T, Guo X, Liu J, Zhang P, Yang D, Li J, Yu S and Sun Y: Co-expression of immunoglobulin-like transcript 4 and angiopoietin-like proteins in human non-small cell lung cancer. Mol Med Rep 11: 2789-2796, 2015.
9. Marchiò S, Soster M, Cardaci S, Muratore A, Bartolini A, Barone V, Ribero D, Monti M, Bovino P, Sun J, *et al*: A complex of α6 integrin and E-cadherin drives liver metastasis of colorectal cancer cells through hepatic angiopoietin-like 6. EMBO Mol Med 4: 1156-1175, 2012.
10. Yoon JC, Chickering TW, Rosen ED, Dussault B, Qin Y, Soukas A, Friedman JM, Holmes WE and Spiegelman BM: Peroxisome proliferator-activated receptor gamma target gene encoding a novel angiopoietin-related protein associated with adipose differentiation. Mol Cell Biol 20: 5343-5349, 2000.
11. Guo L, Li SY, Ji FY, Zhao YF, Zhong Y, Lv XJ, Wu XL and Qian GS: Role of Angptl4 in vascular permeability and inflammation. Inflamm Res 63: 13-22, 2014.
12. Zhu P, Goh YY, Chin HFA, Kersten S and Tan NS: Angiopoietin-like 4: A decade of research. Biosci Rep 32: 211-219, 2012.
13. Peng L, Ma J, Cui R, Chen X, Wei SY, Wei QJ and Li B: The calcineurin inhibitor tacrolimus reduces proteinuria in membranous nephropathy accompanied by a decrease in angiopoietin-like-4. PLoS One 9: e106164, 2014.
14. Chugh SS, Clement LC and Macé C: New insights into human minimal change disease: Lessons from animal models. Am J Kidney Dis 59: 284-292, 2012.
15. Clement LC, Macé C, Avila-Casado C, Joles JA, Kersten S and Chugh SS: Circulating angiopoietin-like 4 links proteinuria with hypertriglyceridemia in nephrotic syndrome. Nat Med 20: 37-46, 2014.
16. Zhu P, Tan MJ, Huang RL, Tan CK, Chong HC, Pal M, Lam CRI, Boukamp P, Pan JY, Tan SH, *et al*: Angiopoietin-like 4 protein elevates the prosurvival intracellular O2(-):H2O2 ratio and confers anoikis resistance to tumors. Cancer Cell 19: 401-415, 2011.
17. Zhang T, Niu X, Liao L, Cho EA and Yang H: The contributions of HIF-target genes to tumor growth in RCC. PLoS One 8: e80544, 2013.
18. Dong D, Jia L, Zhou Y, Ren L, Li J and Zhang J: Serum level of ANGPTL4 as a potential biomarker in renal cell carcinoma. Urol Oncol 35: 279-285, 2017.
19. Ge H, Yang G, Yu X, Pourbahrami T and Li C: Oligomerization state-dependent hyperlipidemic effect of angiopoietin-like protein 4. J Lipid Res 45: 2071-2079, 2004.
20. Yin W, Romeo S, Chang S, Grishin NV, Hobbs HH and Cohen JC: Genetic variation in ANGPTL4 provides insights into protein processing and function. J Biol Chem 284: 13213-13222, 2009.
21. Clement LC, Avila-Casado C, Macé C, Soria E, Bakker WW, Kersten S and Chugh SS: Podocyte-secreted angiopoietin-like-4 mediates proteinuria in glucocorticoid-sensitive nephrotic syndrome. Nat Med 17: 117-122, 2011.
22. La Paglia L, Listì A, Caruso S, Amodeo V, Passiglia F, Bazan V and Fanale D: Potential role of ANGPTL4 in the cross talk between metabolism and cancer through PPAR signaling pathway. PPAR Res 2017: 8187235, 2017.
23. Wang Q, Oliver-Williams C, Raitakari OT, Viikari J, Lehtimäki T, Kähönen M, Järvelin MR, Salomaa V, Perola M, Danesh J, *et al*: Metabolic profiling of angiopoietin-like protein 3 and 4 inhibition: A drug-target Mendelian randomization analysis. Eur Heart J 42: 1160-1169, 2021.
24. Kubo H, Kitajima Y, Kai K, Nakamura J, Miyake S, Yanagihara K, Morito K, Tanaka T, Shida M and Noshiro H: Regulation and clinical significance of the hypoxia-induced expression of ANGPTL4 in gastric cancer. Oncol Lett 11: 1026-1034, 2016.
25. Vivarelli M, Massella L, Ruggiero B and Emma F: Minimal change disease. Clin J Am Soc Nephrol 12: 332-345, 2017.
26. Shalhoub RJ: Pathogenesis of lipoid nephrosis: A disorder of T-cell function. Lancet 2: 556-560, 1974.
27. Yokoyama H, Kida H, Tani Y, Abe T, Tomosugi N, Koshino Y and Hattori N: Immunodynamics of minimal change nephrotic syndrome in adults T and B lymphocyte subsets and serum immunoglobulin levels. Clin Exp Immunol 61: 601-607, 1985.
28. Kimata H, Fujimoto M and Furusho K: Involvement of interleukin (IL)-13, but not IL-4, in spontaneous IgE and IgG4 production in nephrotic syndrome. Eur J Immunol 25: 1497-1501, 1995.
29. Kanai T, Shiraishi H, Yamagata T, Ito T, Odaka J, Saito T, Aoyagi J and Momoi MY: Th2 cells predominate in idiopathic steroid-sensitive nephrotic syndrome. Clin Exp Nephrol 14: 578-583, 2010.

30. Nachman PH, Jennette JC and Falk R: Primary glomerular disease. In: The Kidney. Brenner BM (ed). 8th edition. Elsevier, Philadelphia, PA, pp987-1066, 2008.
31. Pei Y, Cattran D, Delmore T, Katz A, Lang A and Rance P: Evidence suggesting under-treatment in adults with idiopathic focal segmental glomerulosclerosis. Regional glomerulonephritis registry study. Am J Med 82: 938-944, 1987.
32. Reiser J, von Gersdorff G, Loos M, Oh J, Asanuma K, Giardino L, Rastaldi MP, Calvaresi N, Watanabe H, Schwarz K, *et al*: Induction of B7-1 in podocytes is associated with nephrotic syndrome. J Clin Invest 113: 1390-1397, 2004.
33. Liu S and Chen J: New insight in pathogenesis of podocyte disfunction in minimal change disease. Zhejiang Da Xue Xue Bao Yi Xue Ban 45: 214-218, 2016 (In Chinese).
34. Kaneko K, Tsuji S, Kimata T, Kitao T, Yamanouchi S and Kato S: Pathogenesis of childhood idiopathic nephrotic syndrome: A paradigm shift from T-cells to podocytes. World J Pediatr 11: 21-28, 2015.
35. Chugh SS, Macé C, Clement LC, Del Nogal Avila M and Marshall CB: Angiopoietin-like 4 based therapeutics for proteinuria and kidney disease. Front Pharmacol 5: 23, 2014.
36. Li Y, Xu Z, Deng H, Liu M, Lin X, Zhang M, Li G, Yue S and Gao X: ANGPTL4 promotes nephrotic syndrome by downregulating podocyte expression of ACTN4 and podocin. Biochem Biophys Res Commun 639: 176-182, 2023.
37. McCarthy KJ and Wassenhove-McCarthy DJ: The glomerular basement membrane as a model system to study the bioactivity of heparan sulfate glycosaminoglycans. Microsc Microanal 18: 3-21, 2012.
38. Jia S, Peng X, Liang L, Zhang Y, Li M, Zhou Q, Shen X, Wang Y, Wang C, Feng S, *et al*: The study of Angptl4-modulated podocyte injury in IgA nephropathy. Front Physiol 11: 575722, 2021.
39. Zuo Y, He Z, Chen Y and Dai L: Dual role of ANGPTL4 in inflammation. Inflamm Res 72: 1303-1313, 2023.
40. Davin JC: The glomerular permeability factors in idiopathic nephrotic syndrome. Pediatr Nephrol 31: 207-215, 2016.
41. Li Y, Gong W, Liu J, Chen X, Suo Y, Yang H and Gao X: Angiopoietin-like protein 4 promotes hyperlipidemia-induced renal injury by down-regulating the expression of ACTN4. Biochem Biophys Res Commun 595: 69-75, 2022.
42. Bertelli R, Bonanni A, Caridi G, Canepa A and Ghiggeri GM: Molecular and cellular mechanisms for proteinuria in minimal change disease. Front Med (Lausanne) 5: 170, 2018.
43. Li JS, Chen X, Peng L, Wei SY, Zhao SL, Diao TT, He YX, Liu F, Wei QJ, Zhang QF and Li B: Angiopoietin-like-4, a potential target of tacrolimus, predicts earlier podocyte injury in minimal change disease. PLoS One 10: e0137049, 2015.
44. Li S, Nagothu K, Ranganathan G, Ali SM, Shank B, Gokden N, Ayyadevara S, Megyesi J, Olivecrona G, Chugh SS, *et al*: Reduced kidney lipoprotein lipase and renal tubule triglyceride accumulation in cisplatin-mediated acute kidney injury. Am J Physiol Renal Physiol 303: F437-F448, 2012.
45. Avila-Casado Mdel C, Perez-Torres I, Auron A, Soto V, Fortoul TI and Herrera-Acosta J: Proteinuria in rats induced by serum from patients with collapsing glomerulopathy. Kidney Int 66: 133-143, 2004.
46. Shen X, Weng C, Wang Y, Wang C, Feng S, Li X, Li H, Jiang H, Wang H and Chen J: Lipopolysaccharide-induced podocyte injury is regulated by calcineurin/NFAT and TLR4/MyD88/NF-κB signaling pathways through angiopoietin-like protein 4. Genes Dis 9: 443-455, 2020.
47. Hayek SS, Sever S, Ko YA, Trachtman H, Awad M, Wadhwani S, Altintas MM, Wei C, Hotton AL, French AL, *et al*: Soluble urokinase receptor and chronic kidney disease. N Engl J Med 373: 1916-1925, 2015.
48. Schulz CA, Persson M, Christensson A, Hindy G, Almgren P, Nilsson PM, Melander O, Engström G and Orho-Melander M: Soluble urokinase-type plasminogen activator receptor (suPAR) and impaired kidney function in the population-based Malmö diet and cancer study. Kidney Int Rep 2: 239-247, 2017.
49. Siligato R, Cernaro V, Nardi C, De Gregorio F, Gembillo G, Costantino G, Conti G, Buemi M and Santoro D: Emerging therapeutic strategies for minimal change disease and focal and segmental glomerulosclerosis. Expert Opin Investig Drugs 27: 839-879, 2018.
50. Botta M, Audano M, Sahebkar A, Sirtori CR, Mitro N and Ruscica M: PPAR agonists and metabolic syndrome: An established role? Int J Mol Sci 19: 1197, 2018.
51. Yang HC, Ma LJ, Ma J and Fogo AB: Peroxisome proliferator-activated receptor-gamma agonist is protective in podocyte injury-associated sclerosis. Kidney Int 69: 1756-1764, 2006.
52. Qiu W, Huang L, Li Y, Liu Q and Lv Y: Dysregulation of angiopoietin-like-4 associated with hyperlipidemia-induced renal injury by AMPK/ACC pathway. Curr Pharm Des 29: 300-309, 2023.
53. Kersten S, Mandard S, Tan NS, Escher P, Metzger D, Chambon P, Gonzalez FJ, Desvergne B and Wahli W: Characterization of the fasting-induced adipose factor FIAF, a novel peroxisome proliferator-activated receptor target gene. J Biol Chem 275: 28488-28493, 2000.
54. Chen S, McLean S, Carter DE and Leask A: The gene expression profile induced by Wnt 3a in NIH 3T3 fibroblasts. J Cell Commun Signal 1: 175-183, 2007.
55. Lu R, Zhou J, Liu B, Liang N, He Y, Bai L, Zhang P, Zhong Y, Zhou Y and Zhou J: Paeoniflorin ameliorates adriamycin-induced nephrotic syndrome through the PPARγ/ANGPTL4 pathway in vivo and vitro. Biomed Pharmacother 96: 137-147, 2017.
56. Xin X, Rodrigues M, Umapathi M, Kashiwabuchi F, Ma T, Babapoor-Farrokhran S, Wang S, Hu J, Bhutto I, Welsbie DS, *et al*: Hypoxic retinal Muller cells promote vascular permeability by HIF-1-dependent up-regulation of angiopoietin-like 4. Proc Natl Acad Sci USA 110: E3425-E3434, 2013.
57. Hu K, Babapoor-Farrokhran S, Rodrigues M, Deshpande M, Puchner B, Kashiwabuchi F, Hassan SJ, Asnaghi L, Handa JT, Merbs S, *et al*: Hypoxia-inducible factor 1 upregulation of both VEGF and ANGPTL4 is required to promote the angiogenic phenotype in uveal melanoma. Oncotarget 7: 7816-7828, 2016.
58. Wang X, Qi D, Fu F, Li X, Liu Y, Ji K, Gao Z, Kong L, Yu C, Xie H, *et al*: Therapeutic and antiproteinuric effects of salvianolic acid A in combined with low-dose prednisone in minimal change disease rats: Involvement of PPARγ/Angptl4 and Nrf2/HO-1 pathways. Eur J Pharmacol 858: 172342, 2019.
59. Liu G and He L: Epigallocatechin-3-gallate attenuates adriamycin-induced focal segmental glomerulosclerosis via suppression of oxidant stress and apoptosis by targeting hypoxia-inducible factor-1α/angiopoietin-like 4 pathway. Pharmacology 103: 303-314, 2019.
60. Del Nogal-Avila M, Donoro-Blazquez H, Saha MK, Marshall CB, Clement LC, Macé CE and Chugh SS: Novel therapeutic approaches for chronic kidney disease due to glomerular disorders. Am J Physiol Renal Physiol 311: F63-F65, 2016.