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NARRATIVE REVIEW

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Autoimmunity in MASLD: Focus on autoantibodies, anti-apolipoprotein A1 IgG and G protein-coupled receptors

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Abstract

Background: The increasing prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), represents a significant public health concern, as it is closely linked to rising obesity rates and metabolic syndrome, affecting approximately 30% of the global population. In addition, MASLD, along with its more severe form, metabolic dysfunction-associated steatohepatitis (MASH), increases the risk of cardiometabolic diseases and hepatocellular carcinoma. In recent years, multiple G-protein-coupled receptors (GPCRs) have been identified as potential therapeutic targets for these disorders. Additionally, autoimmunity is believed to potentially play a role in the development of mechanisms contributing to the pathogenesis of MASLD/MASH. This narrative review examines the diverse autoantibodies associated with the disease, with a particular emphasis on antibodies targeting apolipoprotein A-1 (AAA-1) and their relationship with anti-GPCRs antibodies.

Results: Several autoantibodies have been identified in up to 30% of individuals with MASLD/MASH, both with and without concomitant autoimmune diseases. Among the anti-GPCR autoantibodies identified in MASLD to date are those targeting the angiotensin II type 1 receptor and the endothelin-1 type A receptor. While the contribution of this class of autoantibodies to MASLD/NASH remains unclear, AAA-1 appears to be pathogenic, acting as pro-steatotic and pro-inflammatory mediators. Additionally, current data suggest shared functional responses between anti-GPCR antibodies and AAA1 in cell-based assays used to detect anti-GPCR presence.

Conclusion: A better understanding of the role of humoral autoimmunity and the interactions among its various components in the metabolic dysfunction underlying MASLD/MASH has the potential to open new perspectives for early detection and therapeutic interventions.

KEYWORDS

anti-apolipoprotein A-1 antibodies, anti-GPCRs antibodies, autoimmunity, G protein-coupled receptors, MASH, MASLD

1 | INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as the most common liver disorder globally, affecting up to 30% of the population in developed countries.[1,2] Steatotic liver is characterized by abnormal lipid accumulation in hepatocytes, which can progress to inflammation, fibrosis, and ultimately cirrhosis and hepatocellular carcinoma.[3] The disease is now recognized as part of a wider spectrum of metabolic syndrome, linked to obesity, dyslipidemia, hypertension, insulin resistance and systemic inflammation. The old term NAFLD referring to liver steatosis in the context of cardiometabolic risk factors is now named MASLD, which could develop into metabolic dysfunction-associated steatohepatitis (MASH).[1] This reclassification holds considerable significance for both public health and healthcare systems.[4]

Autoimmunity is characterized by the body's immune system mistakenly attacking its tissues, which can lead to various organ dysfunctions, including the liver. Immune cells play a central role in the onset and progression of the metabolic disorder-related disease MASLD.[5–7] Additionally, crosstalk between hepatocytes and various immune and non-immune cell subsets, such as T and B cells, macrophages, neutrophils and hepatic stellate cells (HSC) contributes significantly to the initiation and progression of the pathology.[7–9] During the MASH stage, inflammation mediated by immune cells may serve as critical driver of disease advancement.[10] Understanding the role of autoimmunity in MASLD/MASH could pave the way for elucidating additional disease mechanisms and identifying novel therapeutic targets.

In this narrative review, we evaluate the current body of evidence linking autoimmunity to MASLD, with a particular focus on autoimmunity directed against G protein-coupled receptors (GPCRs), increasingly recognized as key endogenous regulators of numerous physiological processes and contributors to disease. Finally, we explore the relationship between anti-GPCR antibodies and those targeting apolipoprotein A-1 (AAA-1), which appear functionally related and have recently been implicated in the development of MASLD/MASH.

2 | PRESENCE OF AUTOANTIBODIES IN MASLD

A growing body of evidence indicates that both cellular and humoral autoimmune processes may play a role in the development of the disease, although the precise mechanism remains unclear.[11,12] To date, in MASLD patients without co-existing autoimmune conditions or specific autoimmune liver disease (AILD), various autoantibodies have been detected, with seropositivity prevalence ranging from 1.5% to 35%.[13–16] Among these, anti-nuclear antibodies (ANA) and smooth muscle antibodies (SMA), have been reported to be associated with a higher inflammatory grade and advanced fibrosis, leading some experts to recommend liver biopsy in MASLD patients tested positive for these autoantibodies.[13,14] A high prevalence (around 25%) of both ANA and/or SMA seropositivity has also been observed in paediatric MASLD cases without concurrent AILD and found to be associated with increased liver disease severity.[15,17] Along the same line, other studies reported the presence of antibodies targeting oxidative stress-derived epitopes (OSEs) in patients with MASLD.[18]

The production of antibodies in MASLD has been attributed to the accumulation of hepatic natural killer cells or to the reduction of regulatory T cells resulting from hepatocyte damage.

Knowing whether autoantibodies represent innocent byproducts in the context of sustained liver injury, or rather play an active pathogenic role in disease progression by promoting inflammation and fibrogenesis is under active scrutiny, but these data highlight the involvement of B cell-mediated immune responses in MASLD physiopathology, a well-established concept in hepatitis B for example.[19]

So far, various B cells subtypes (B1, B2 and regulatory B cells) have all been implicated in MASLD disease progression.[11] Similarly to what has been established in autoimmune diseases and atherogenesis,[20,21] B1 cells appear to have a protective role through the production of natural IgM antibodies, while B2 subtype (plasma cells) may promote disease progression by producing pro-inflammatory cytokines and pathogenic antibodies in MASLD.[11]

Early liver-resident B2 cells have been associated with elevated levels of IFN-γ, antibodies against OSE, lobular inflammation and fibrosis in humans.[18] On the other hand, mouse models indicate that microbial byproducts triggers a B cells-driven Th1 response through the toll-like receptor (TLR)-dependent production of tumour necrosis factor (TNF)-α, and IL-6 to promote MASH progression, while depletion of B2 cells ameliorates hepatic inflammation and fibrosis.[22]

These results concur to support a causal role of B cells in the evolution from MASLD to MASH through TLR signalling. Because numerous autoantibodies have been shown to act as damage-associated molecular patterns (DAMPS) by their ability to stimulate similar TLRs to those activated by the gut microbiota derivative (TLR4 and TLR2 mostly), humoral autoimmunity is gaining momentum as an overlooked suspect in the pathogenesis of MASLD/MASH.[11]

Among the class of anti-OSE antibodies reported in MASLD,[18] Ampuero and colleagues[23] reported the presence

of antibodies directed against oxidized low-density lipoprotein (anti-oxLDL IgG) in lean-MASLD patients and the possibility to use the anti-oxLDL IgG/high-density lipoprotein cholesterol ratio as a potential biomarker associated with MASH, hepatocellular ballooning, and liver fibrosis in this specific class of patients.[23]

Such associations indicate that autoantibodies could be associated with pathogenic pathways in MASLD, but the evidence supporting a causal role in this disease is still lacking. Nevertheless, recent studies have started to dissect the role of specific autoantibodies in MASLD, as modulators of liver steatosis, inflammation and fibrosis. In addition to defining the role of humoral response in MASLD, ongoing research aims to determine whether these autoantibodies directly contribute to liver damage, serve as biomarkers of disease severity or influence therapeutic responses.

3 | AUTOIMMUNE DISEASES WITH CO-OCCURRENCE OF MASLD

More common in individuals already affected by liver autoimmune diseases such as primary biliary cholangitis and autoimmune hepatitis (AIH),[24] MASLD is also frequently observed in other autoimmune conditions. MASLD prevalence has been documented in about one-third of patients with (i) rheumatoid arthritis,[25] (ii) systemic lupus erythematosus,[26] (iii) inflammatory bowel disease (IBD),[27] (iv) celiac disease,[28] and in 20% of individuals with type 1 diabetes mellitus.[29] Despite some significant differences between cases and controls in some studies, these reported prevalences are of the same order of magnitude as those observed in the general population. It remains, therefore, unclear whether autoimmune diseases and MASLD are entirely separate entities that merely coexist, or whether the presence of one may predispose individuals to the development of the other.

4 | GPCRs AT THE CROSSROADS OF MASLD, MASH, OBESITY AND TYPE 2 DIABETES

G protein-coupled receptors (GPCRs) represent a vast superfamily of receptors found in many cell types, mediating a very wide spectrum of physiological processes, including environment sensing, inflammation, metabolism and immune responses.[30] They are the largest family of membrane proteins encoded in the human genome, with more than 1000 different members.[31,32] These proteins are crucial in physiology and disease, which makes them of high pharmaceutical interest.[33,34] Currently, over 30% of approved drugs in the market target GPCRs, while approximately the same proportion of GPCRs have no known biological function,[35] highlighting the importance of understanding GPCR functions at cellular and molecular levels.

Dysregulation of GPCR signalling is increasingly recognized as a contributing factor to autoimmune diseases, including those affecting the liver.

GPCRs are key mediators of various signalling pathways in the body, influencing metabolic processes and immune functions. The exploration of GPCRs in the context of MASLD has unveiled critical insights into the mechanisms underlying liver disease progression, potentially paving the way for novel therapeutic interventions.[36–38] More than 50 GPCRs are supposed to be expressed in the mouse liver.[39]

GPCRs have been shown to play essential roles in MASLD and underlying metabolic causes including obesity and T2D, through their function as receptors for bile acids, free fatty acids (FFARs) and hormones regulating glucose signalling.[40,41] However, the knowledge of how GPCRs regulate liver metabolism and fibrosis in the different cell types of the liver is very limited.[38] In addition, a better understanding of the possible link between GPCRs and gut microbiota is likely to foster innovations in a broad variety of diseases.[42,43]

There is currently a lack of available drugs to treat MASLD/MASH. Targeting GPCRs offers potential therapeutic applications across different stages of the disease. Up to date, several GPCRs have been reported to be associated with MASLD through their function as receptors for FFARs, bile acids, hormones, cannabinoids in regard to hepatic lipid metabolism and inflammatory responses. Nevertheless, preclinical and clinical data in humans are limited and it must be emphasized that most GPCR-mediated effects reported so far for hepatic steatosis, liver fibrosis and liver cancer have been derived from cellular and animal models.

Changes in the expression or activity of these GPCRs may exacerbate the metabolic dysregulation observed in MASLD and trigger an aberrant immune response, leading to the significant progression of liver disease, as discussed in the following paragraphs, with Table 1 summarising several GPCRs associated with MASLD/MASH.

4.1 | Free Fatty Acid Receptors (FFARs)

FFARs interact with fatty acids and regulate signalling pathways involved in hormone secretion, carbohydrate and lipid metabolism, as well as immune responses. These receptors belong to the GPCR family and include various subtypes, such as FFAR1 (GPR40), FFAR2 (GPR43),

FFAR3 (GPR41) and FFAR4 (GPR120) which are expressed in different tissues and have distinct functions.[44,45] FFAR1 and FFAR4 enhance insulin and incretin release, promote FA oxidation and reduce inflammation,[46] while FFAR2 and FFAR3 modulate glucose and lipid pathways. Additionally, FFAR4 influences intestinal and pancreatic hormone secretion. FFAR1 and FFAR4 primarily bind medium-chain fatty acids and long-chain fatty acids, while FFAR2 and FFAR3 show a preference for short-chain fatty acids (SCFAs), which are generated through the colonic fermentation of dietary fibres by gut microbiota.[44,45] Many groups have found FFAR2 to be protective against diet-induced obesity.[47] SCFAs have also been shown to stimulate leptin secretion through activation of both FFAR2 and FFAR3 in adipocytes[48] and FFAR1, FFAR2 and FFAR3 induce Glucagon-Like Peptide-1 (GLP-1) release.[49]

4.2 | G Protein-Coupled Bile Acid Receptors

Since bile acids regulate both lipid/glucose metabolism and inflammation, their dysregulation contributes to metabolic dysfunction, inflammation and liver injury in MASLD. G protein-coupled bile acid receptor (GP-BAR1), also known as Takeda G protein-coupled receptor 5 (TGR5), highly expressed in skeletal muscle and adipose tissue, is one of the master regulators of carbohydrate and lipid metabolism, as well as bile acid homeostasis. The activation of GP-BAR1 is associated with increased energy expenditure and glucose and lipid utilization, decreasing hepatic steatosis,[50] making it of high interest for therapeutic interventions in MASLD, MASH and in cardiometabolic disease according to in vitro, animal and human studies.[50,51] In addition, GP-BAR1 is highly expressed in intestinal and liver cells, both epithelial and non-epithelial cells, including Kupffer cells, liver sinusoidal cells, cholangiocytes and innate immune cells like monocytes, macrophages and NK cells. In macrophages, its activation induces a tolerogenic state, while its absence leads to liver and gut inflammation.[52] In cholangiocytes, it supports bile secretion and protects against cell damage. Animal studies indicated that GPBAR1 agonists show promise as therapies for modulating inflammation and fibrosis in primary sclerosing cholangitis.[53]

4.3 | Cannabinoid receptors

The endocannabinoid system (ECS) is a complex physiological signalling pathway influencing metabolism in the brain and in peripheral organs.[54] It includes cannabinoid receptors (CB1 and CB2), endocannabinoids (their endogenous ligands), and enzymes for their production and metabolism.[55] CB1 receptors are primarily found in central and peripheral neurons, where they inhibit neurotransmitter release. CB2 receptors, predominantly expressed in immune cells, regulate cellular migration and cytokine release in and outside the brain.[55] The two cannabinoid receptors, CB_1 and CB_2, are the main effective receptors of the ECS. However, the ECS includes deorphanized GPCRs like GPR3, GPR6, GPR18, GPR55, GPR119 and non-cannabinoid receptors. In addition, CB receptors can heterodimerize with other GPCRs such as serotonin, angiotensin, opioid, somatostatin, orexin, dopamine, and adenosine receptors among others.[56] The ECS is differentially affected by hepatic glucose metabolism and insulin resistance; for example, blocking CB1 can enhance glucose tolerance and reduce insulin resistance. The hepatic ECS is typically inactive in physiological conditions due to low CB receptor expression. However, under pathophysiological conditions, CB receptors expression increases, and the ECS is significantly upregulated in chronic liver disease,[57] with studies highlighting its mechanistic and therapeutic roles in liver fibrosis, particularly through its receptors CB1 and CB2, where CB2 seems to have an antifibrogenic properties.[57] CB1 receptor activation by the endogenous EC anandamide increased de novo lipogenesis through the induction of the lipogenic transcription factor sterol regulatory element-binding protein 1c and its target enzymes acetyl-CoA carboxylase1 and fatty acid synthase in diet-induced obesity (DIO) mouse model, leading to steatosis. In liver disease, the ECS is implicated in fibrotic tissue synthesis, increased intrahepatic vascular resistance and development of portal hypertension.[58]

4.4 | Glucagon-Like Peptide-1 Receptor

Glucagon-Like Peptide-1 Receptor (GLP-1R) plays a crucial role in glucose regulation and has beneficial effects on the liver, reducing hepatic steatosis and inflammation.[59] GLP-1 analogs and other incretin-based are now classic anti-diabetic drugs and become key additional therapeutic options for managing obesity.[59,60]

GLP-1 is a gut-derived hormone classified as incretin, which stimulates glucose-induced insulin secretion, suppresses glucagon production indirectly, and reduces appetite. GLP-1 receptor analogs are commonly used to treat T2DM. While the GLP-1R is extensively expressed throughout the body, its presence in the liver appears minimal, initially suggesting that its effects on the liver may be indirect. In fact, the metabolic benefits associated with GLP-1 therapy include enhanced insulin sensitivity, appetite limitation, and body weight reduction, which

TABLE 1 GPCRs associated with MASLD/MASH.

GPCR	Endogenous ligand	Localization	References
FFARs			
GPR40 (FFAR1)	Medium/long-chain FFAs	Pancreas, Brain, Hepatocytes, Immune cells, Small intestine.	36, 37, 38, 39, 40, 41
GPR43 (FFAR2)	Acetate, Propionate, Butyrate, Pentanoate, Hexanoate, Formate.	Immune cells, Liver, Small intestine, Adipose tissue, Colon, Spleen, Stomach, Lung, Heart, Muscle, Bone marrow, Mucosal mast cells.	36, 37, 38, 39, 40, 41
GPR41 (FFAR3)	Propionate, Butyrate, Pentoanoate, Acetate, Formate.	Adipose tissue, Small intestine, Pancreas, Spleen, Placenta, Lung, Pituitary, Brain, Liver, Stomach, Kidney, Bone marrow, Prostate, Colon, Immune cells, Pancreas.	36, 37, 38, 39, 40, 41
GPR120 (FFAR4)	Omega-3 polyunsaturated fatty acids	Liver, Adipose tissue, Pancreas, Lung, Brain, Intestine, Neuroendocrine cells.	36, 37
G protein-coupled bile acid receptor			
GP-BAR1 (TGR5) or GPR19	Bile-acids	Spleen, Placenta, Gastrointestinal tract, Liver, Endocrine tissue	42, 43
Endocannabinoid system			
CB1	Endocannabinoids: Arachidonoylethanolamide, 2-arachidonoylglycerol	Brain, Cardiovascular system, Adipose tissue, Reproductive system, Gut, liver.	44, 45, 47, 48
CB2	Tetrahydrocannabinol, 2-Arachidonoylglycerol	Immune cells, Skin, Tonsils, Spleen, Thymus, Intestine, Liver, Brain.	44, 45, 47, 48
GPR3	Orphan receptor: no confirmed endogenous ligand	Brain, Adipose tissue, Lung, Kidney, Testis, Ovary, Eye.	46
GPR6	Orphan receptor: no confirmed endogenous ligand	Brain, Adipose tissue, Lung, Kidney, Testis, Ovary, Eye.	46
GPR55 (LPIR1)	Cannabinoid	CNS, Neutrophils, Gastrointestinal tract, Adipose tissue, Liver, Skeletal muscle, Pancreas.	46
GPR119 (GPCR2)	Oleoyl-lysophosphatidylcholine, oleoylethanolamide	Pancreas, Small intestine, Stomach, Colon, Liver, Macrophages.	46
Distinct classes of GPCRs			
GLP-1R	Glucagon-like peptide 1	Pancreas, Brain, Gastrointestinal tract, Salivary gland, Breast, Testis, Muscle, Adipose tissue, Thymus, Lymphoid tissue.	49, 50, 51, 52, 53
S1PR	Sphingosine-1-phosphate	Brain, Endocrine tissue, Lung, Digestive tract, Liver, Gallbladder, Pancreas, Kidney, Testis, Male and Female tissue, Muscle, Adipose tissue, Skin, Bone marrow, Lymphoid tissue.	54, 55, 56, 57, 58, 59, 60
GPR65 (TDAG8)	Psychosine	Brain, Endocrine tissue, Lung, Digestive tract, Gastrointestinal tract, Liver, Pancreas, Kidney, Skin, Adipose tissue, Male and Female tissue, Bone marrow, Lymphoid tissue.	61, 62, 63, 64, 65
βAR	Adrenaline Noradrenaline	Brain, Endocrine tissue, Lung, Digestive tract, Gastrointestinal tract, Liver, Pancreas, Kidney, Adipose tissue, Male and Female tissue, Heart, Muscle, Bone marrow, Lymphoid tissue.	66, 67
AT1R	Angiotensin II	Brain, Endocrine tissue, Lung, Digestive tract, Gastrointestinal tract, Liver, Pancreas, Kidney, Adipose tissue, Male and Female tissue, Heart, Muscle, Adipose tissue, Skin, Bone marrow, Lymphoid tissue.	68, 69, 70

(Continues)

TABLE 1 (Continued)

GPCR	Endogenous ligand	Localization	References
ET-1R	Endothelin-1	Brain, Eye, Endocrine tissue, Lung, Digestive tract, Gastrointestinal tract, Liver, Pancreas, Kidney, Male and Female tissue, Heart, Muscle, Adipose tissue, Bone marrow, Lymphoid tissue.	71, 72, 73
Chemokine receptors			
CCR2	CCL2/MCP-1	Endocrine tissue, Lung, Gastrointestinal tract, Liver, Kidney, Male and Female tissue, Muscle, Adipose tissue, Bone marrow, Lymphoid tissue.	74, 75, 76, 77, 78
CCR5	RANTES MIP-1α MIP-1β	Brain, Endocrine tissue, Lung, Digestive tract, Liver, Gallbladder, Pancreas, Kidney, Testis, Male and Female tissue, Adipose tissue, Skin, Bone marrow, Lymphoid tissue.	74, 75, 79, 80, 81
CXCR2	CXCL8 (IL-8) CXCL1(GRO-α)	Brain, Endocrine tissue, Lung, Digestive tract, Liver, Gallbladder, Pancreas, Kidney, Testis, Male and Female tissue, Heart, Muscle, Adipose tissue, Skin, Bone marrow, Lymphoid tissue.	74, 75, 82
Cytokine receptors			
CXCR3	CXCL9 CXCL10 CXCL11	Endocrine tissue, Lung, Gastrointestinal tract, Liver, Pancreas, Muscle, Male and Female tissue, Bone marrow, Lymphoid tissue.	83, 84, 85, 86

Abbreviations: AT1R, Angiotensin II type 1 Receptor; CB, Cannabinoid Receptor; CCL2, C-C Motif Chemokine Ligand 2; CCR, C-C chemokine receptor; CXCL, C-X-C motif chemokine ligand; CXCR, CXC chemokine receptors; ET-1 R, Endothelin- 1 Receptor; FFARs, Free fatty acid receptors; GLP-1, Glucagon-like Peptide 1; GPCR, G-protein Coupled Receptor; MCP-1, Monocyte Chemoattractant Protein 1; MIP-1, Macrophage Inflammatory Protein 1; S1PR, Sphingosine-1-Phosphate Receptor; TDAG8, T cell death-associated gene 8; βAR, beta-Adrenergic Receptor.

collectively contribute to improvements in MASLD, especially for patients with MASLD and coexisting T2DM and obesity.[60] In addition, GLP-1 RAs have demonstrated surprising cardio-and nephroprotective properties since they significantly reduce major adverse cardiovascular events' (MACEs) rate and the risk of kidney disease progression in patients with T2DM.[61] To date, the U.S. Food and Drug Administration has approved seven GLP-1R agonists for managing T2DM and numerous new GLP-1 medications are currently under development, ranging from small molecules GLP-1R agonists and antibodies to innovative hybrid molecules designed to influence additional signalling pathways acting in synergy with GLP-1R agonism.[62,63]

4.5 | Sphingosine-1-Phosphate Receptors

Sphingosine-1-Phosphate Receptors (S1PRs) play a pivotal role in immune cell recruitment, and dysregulation is also involved in liver fibrosis, particularly through S1P1 and S1P2.[64]

Among the five S1P receptor types, S1P/S1PR signalling has recently been identified as a key regulator in various inflammatory diseases, including atherosclerosis, rheumatoid arthritis, multiple sclerosis and cholestasis-induced liver injury.[65,66] Increased liver S1P levels activate hepatic stellate cells to undergo fibrotic changes.[67] Hyperactive SphK1/S1P/S1PR signalling drives significant pro-inflammatory and pro-fibrotic responses, exacerbating tissue damage.[68] These findings highlight the potential of targeting S1P/S1PR signalling as a promising therapeutic approach for liver fibrosis.[69,70]

4.6 | GPR65

GPR65, also known as T Cell Death Associated Gene 8 (TDAG8), was first identified as a G protein-coupled receptor associated with activation-induced T-cell apoptosis.[71] It was subsequently recognized as a pH sensitive detector, leading to increased cAMP production when exposed to acidic conditions outside the cell.[72] The signalling networks downstream of GPR65 have been implicated in many pathophysiological processes including tumour growth, immune-related diseases, and inflammation. Transcriptomic analysis of the liver and adipose tissue in the study by Hui et al. reported GPR65 to be associated with higher triglyceride levels.[73] Additionally, it is reported that GPR65 is a major regulator that modulates the progression of liver fibrosis.[74] Thus, targeting GPR65 could be an effective therapeutic strategy for the

prevention of liver fibrosis. It is important to mention that recent findings have highlighted elevated GPR65 expression in tumours such as colorectal and hepatocellular carcinoma in patients with obesity and in animal models, suggesting that it may play a role in tumour growth across various obesity-related cancers and serve as potential therapeutic targets.[75]

4.7 | Beta-Adrenergic Receptor

Beta-adrenergic receptors (β-ARs), expressed in different organs including the liver, respond to both catecholamines epinephrine and norepinephrine released from the sympathetic nervous system, regulating liver metabolism.[76] β1-AR and β2-AR increase with age, enhancing hepatic glucose output and lipid catabolism. β-AR activation boosts glycogen phosphorylase, Pck1, G6pc, and pklr expression, while reducing glycogen levels. It also increases hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) activity, with ATGL regulating triglyceride content via Sirtuin 1 and HSL aiding triglycerides and cholesterol esters hydrolysis.[77] Overall, β-AR activation promotes hepatic glucose production and lipid breakdown.

4.8 | Angiotensin II receptor type 1

The Gq-coupled angiotensin II type I receptor (AT1R) plays a role in cardiovascular regulation[78] but also contributes to HSC activation and fibrosis by activating the janus kinase-2 (JAK2), RhoA and Rho-associated kinase 1 (ROCK1). In primary rat hepatocytes, an angiotensin II analog has been shown to enhance insulin receptor signalling and glucose metabolism.[79] Recent studies in in vivo models have demonstrated that vasoactive hormones such as angiotensin II (ANGII) not only develop endothelial dysfunction and hypertension but also cause fatty liver, increase adipose tissue, and develop a pro-steatotic environment characterised by a low-grade systemic pro-inflammatory and pro-oxidant state, with elevated blood lipid levels.[80]

4.9 | Endothelin Receptor

Endothelin-1 (ET-1), a 21-amino acid vasoconstrictor peptide, plays a role in various pathological processes, including vascular tone regulation, hormonal balance, neurotransmission, oxidative stress, inflammation and ER stress.[81] These effects are primarily mediated through two G-protein-coupled receptor subtypes: endothelin type A receptor (ETAR) and endothelin type B receptor (ETBR).

Recent findings from animal studies and clinical trials suggest that blocking ET1 signalling with endothelin receptor antagonists can alleviate diabetic pathology and its complications.[82] ETAR is a key mediator of ET-1-driven pathophysiological effects, including those linked to diabetes.[83] However, the specific impact and underlying mechanisms of inhibiting hepatic ET1/ETAR signalling in metabolic diseases remain uncertain.

4.10 | Chemokine receptors

A key feature of MASLD/MASH is hepatic inflammation, marked by higher levels of proinflammatory cytokines and acute-phase proteins. NF-kB and JNK pathways are activated, while chemokines help coordinate immune cell responses.[84,85] Signals released from injured hepatocytes, as well as circulating mediators (lipids, cytokines) can activate Kupffer cells (liver-resident macrophages), which, in turn, recruit inflammatory cells and release C-C chemokine ligand 2 (CCL2) to attract monocyte-derived macrophages (MoMF) that express the receptor CCR2. Myeloid-macrophage populations play a central role in obesity-induced inflammation, worsening hepatic insulin sensitivity. In adipose tissue, inflammation partly arises from the recruitment and activation of the CCL2/CCR2 pathway.[86] Targeting this pathway in mice reduces monocyte infiltration and monocyte-derived macrophages (MoMF) accumulation in the liver, alleviating liver fibrosis and steatohepatitis.[87,88] Additionally, CCL5 (RANTES) promotes hepatic macrophage recruitment and fibrosis.[89] CCR5, which recognizes CCL3-CCL5, is expressed on T cells and hepatic stellate cells (HSCs). In mouse models and human liver cells, CCR5 activation is linked to CD4+ and CD8+ T-cell-mediated inflammation and fibrosis. CCR5 signalling polarizes Kupffer cells and MoMFs toward a type1 pro-inflammatory state, driving HSC activation, myofibroblast differentiation, and extracellular matrix production. CCR2/CCR5 antagonists further suppress M1 macrophage activation and help prevent MASLD and liver fibrosis.[90,91]

CXCR2 serves as the receptor for several chemokines, including CXCL1 and CXCL8 (IL-8), and activates pathways such as PI3K/Akt and MAP kinases to enhance neutrophil recruitment to inflamed sites. Notably, IL-8 overexpression in high fat diet-fed mice exacerbates fibrosis-related processes, including collagen deposition and HSC activation. Overall, hepatic overexpression of human IL-8 drives neutrophil infiltration and accelerates the progression of fatty liver to MASH in HFD-fed mice.[92] Nevertheless, our understanding of the intricate interactions between CXC chemokines and their receptors

remains limited, potentially impeding the development of novel treatments for obesity, T2D and MASLD.

4.11 | Cytokine receptors

CXCR3, a G-protein-coupled receptor that binds the cytokines CXCL10 (IP-10), CXCL11 (I-TAC) and CXCL9 (MIG), plays a critical role in chronic liver inflammation and HCV infection.[93] CXCR3 is expressed on various cell sub-populations within the liver, including endothelial cells, HSC, T cells, NK cells and it contributes to macrophage activation. Several studies have highlighted its involvement in diet-induced obesity and insulin resistance, linking it to the development of intrahepatic inflammation and metabolic syndrome.[94] CXCR3 plays a pivotal role in MASH development by inducing production of cytokines, macrophage infiltration, fatty acid synthesis and causing autophagy deficiency and ER stress.[95] The diverse functions of CXCR3 ligands may account for its varying roles during different stages of inflammation and fibrosis in the pathogenesis of steatohepatitis.[96]

The understanding of GPCRs in MASLD/MASH is still an evolving field. The success story of GLP1-1R agonists highlights the importance of further understanding the role of other GPCRs in the development of MASLD and other liver diseases. Identifying novel GPCRs modulating liver lipid metabolism and inflammation will be key to delineating the intricacies of GPCR signalling complexity, paving the way for the development of targeted therapies in MASLD, ultimately improving the management of these increasingly prevalent liver diseases. Table 1 summarizes the GPCRs described in the previous paragraphs.

5 | ANTI-GPCR AUTOANTIBODIES

In recent years, there has been increasing interest in the involvement of functional antibodies targeting GPCRs as part of physiological homeostatic processes whose imbalance could be involved in the pathogenesis of autoimmune, cardiovascular and other diseases.[97] Functional antibodies targeting various GPCRs in human serum have been observed to exhibit agonistic or antagonistic activity, contributing to the fine-tuning of numerous physiological processes,[97,98] mimicking the endogenous ligands of these receptors and triggering either stimulatory or inhibitory effects on associated intracellular pathways.[97,99,100] In addition to the detection of target-specific anti-GPCR antibodies through standard immunoassays, functional assays have also been employed to identify the presence of anti-GPCR antibodies in human serum.[101,102] The most common cell-based assay used for this purpose is the neonatal rat ventricular cardiomyocyte model, in which a positive chronotropic response serves as the generic functional signature of anti-GPCR antibody presence and biological activity.[101,102]

Most disease-related GPCR autoantibodies originate from B-cell activation followed by antibody maturation. The generation of high-affinity autoantibodies may occur due to cross-reactivity between self and foreign antigens (molecular mimicry), modifications of self-antigens via post-translational changes, exposure of previously hidden antigens due to tissue injury, heightened inflammatory responses or impaired self-tolerance mechanisms.[103,104]

To date, a limited body of evidence link autoantibodies targeting GPCRs in MASLD and MASH, while such kind of autoimmune signatures have been well described in other conditions, including cardiovascular diseases, neurological disorders, chronic fatigue syndrome, rheumatic disease, stroke, and both acute and post-acute COVID-19.[97,99]

A recent study by Di Vincenzo et al. is the only research associated with metabolic disorder, revealing that elevated levels of autoantibodies against the angiotensin II type 1 receptor (anti-AT1R) and the anti-endothelin 1 type A receptor (anti-ETAR1) in the serum of obese individuals are associated with glycemic profiles and are reduced following bariatric surgery.[105] These antibodies are already known for their contribution to the development of CVD.[106] In animal models, a high-fat diet leads to elevated serum levels of anti-AT1R, anti-α1-AR and anti-β1-AR, which are correlated with cardiac dysfunction.[107] Similar findings have been observed in humans, as elevated levels of anti-β1-AR and AT1R in individuals with T2DM are linked to the occurrence of left ventricular dilatation.[108]

Despite the scarce literature focusing on anti-GPCR antibodies in MASLD, it is worth mentioning that, in addition to anti-AT1R, anti-ETAR1 antibodies, other well-described anti-GPCR could potentially contribute to the development of the multifactorial and heterogeneous MASLD pathology.

The example of Systemic Sclerosis (SSc) provides insight into how autoantibodies against AT1R, ETAR/ETBR, CXCR3/4, and PAR1 (protease-activated receptor 1) amplify constitutive inflammatory responses through their signalling pathways, thereby influencing the fibrotic process,[109] a key feature in SSc.[110] This mechanism could also partially contribute to the inflammation and fibrotic processes involved in the progression of MASLD to MASH and, ultimately, to liver cirrhosis. To date, none of anti-GPCR antibodies from these classes has been studied in this context, making it an open field deserving a thorough exploration. Among the unexplored

anti-GPCRs of possible relevance in MASLD/MASH, those against CXCR3 could be of particular interest given the role CXCR3 in the pathogenesis of this disease.[94–96] While anti-CXCR3 autoantibodies have not been reported in MASLD so far, they have been reported in the general population, associated with subclinical atherosclerosis and predicting all-cause and cardiac mortality.[111] In vivo active and passive immunization against CXCR3 was found to enhance atherosclerosis burden.[111] As such these autoantibodies have the potential to mediate the established link between MASLD and CVD,[112] but additional dedicated studies are required to confirm or reject this hypothesis.

6 | FOCUS ON ANTI-APOLIPOPROTEIN A-1 ANTIBODIES

ApoA-1 is a major component of high-density lipoprotein (HDL), playing a fundamental role in lipid metabolism and reverse cholesterol transport.[113] On top of being a key molecule relevant to atherogenesis, ApoA-1 has been shown to prevent MASLD severity in vivo by decreasing oxidative stress, inflammation, endoplasmic reticulum stress, and by inhibiting fatty acid synthesis.[114–116] The existence of autoantibodies against ApoA-1 (AAA-1) have been initially reported in patients with prothrombotic autoimmune diseases[117,118] correlating with the disease activity.[119–123]

AAA-1 are elevated in high CV risk groups (acute coronary syndrome, carotid stenosis, end stage renal disease, T2DM) and linked to poor prognosis. Found in 20% of the general population,[124] they independently predict worse CV outcomes. Elevated in obesity, AAA-1 levels correlate with coronary calcification and resistance to weight loss post-Mediterranean diet or bariatric surgery—though surgery reduces levels.[125–127] Functionally, AAA-1 promotes inflammation, thrombosis, arrhythmias and atherosclerosis via TLR2/4 and CD14, contributing to myocardial damage and mortality.[128–130]

In regards of cellular lipid metabolism, AAA-1 have also been shown to impair the anti-oxidant properties of HDL,[131] and to promote foam cell formation by a complex process involving increased LDL uptake, decreased passive cholesterol efflux, and increased the Acyl-CoA cholesterol acyltransferase (ACAT) activity.[132,133] Finally, AAA-1 were also shown to promote hepatic steatosis through triglycerides pathway disruption, a key step in hepatic steatosis and MASLD.[134] In addition, passive immunization of apoE−/− mice with AAA-1 induces not only a worsening of atherosclerosis, but also fatty liver disease.[129,134] Recent evidence, using a transcriptomic approach in a MASLD mouse model specifically, the Choline-Deficient, L-Amino Acid-Defined, High-Fat Diet (CDAHFD) model, indicates that AAA-1 could contribute to the pathogenesis of MASH by promoting systemic and hepatic inflammation and upregulating several pro-fibrotic mRNAs.[135]

Because systemic AAA-1 levels are quantifiable[120–124,126,129,136–139] and target apolipoprotein A-1, a key protective molecule in MASLD[114–116] which limits both hepatic cellular lipid accumulation, inflammation, and fibrogenesis, they represent an ideal therapeutic target against MASLD/MASH.

Finally, it has been recently demonstrated that the AAA-1-related 10-year CV risk in the general population was influenced by the fatty liver index status, suggesting that the link between AAA-1 and cardiovascular disease risk could be mediated by underlying hepatic steatosis.[134]

Figure 1 highlights the main pleiotropic effects of AAA-1 in human, animal and in vitro studies.

7 | AAA-1 AS A POTENTIAL ANTI-GPCR CLASS ANTIBODY?

As AAA-1 has been shown to fulfil the functional requirements to qualify as a an anti-GPCR antibody acting as a positive chronotropic agent in vitro through L-type calcium channel activation,[139–141] and to display similar associations with overall and cardiac mortality as anti-CXCR3 antibodies, it could be hypothesised that AAA-1 could represent a new class of anti-GPCR, or at least be functionally related to this class.

Further link can be evoked by the fact that AAA-1 have been shown in the context of MASLD/MASH to upregulate hepatic GPCR65 mRNA,[135] a receptor previously described as involved in the progression of liver fibrosis and hepatic tumour growth.[74,75]

Further work is required to determine if AAA1 do belong to anti-GPCR antibodies and how they are functionally related to them and how they interact with homeostatic processes in relation with MASLD/MASH and CVD, as depicted in Figure 1.

8 | CURRENT RESEARCH AND FUTURE DIRECTIONS

The intersection of autoimmunity and MASLD is a rapidly evolving field, and current research is focused on elucidating the intricacies of these relationships. Large-scale studies are needed to validate the findings regarding AAA-1 and their impact on MASLD and disease progression, and to assess their potential role as biomarkers for diagnostic and therapeutic purposes.

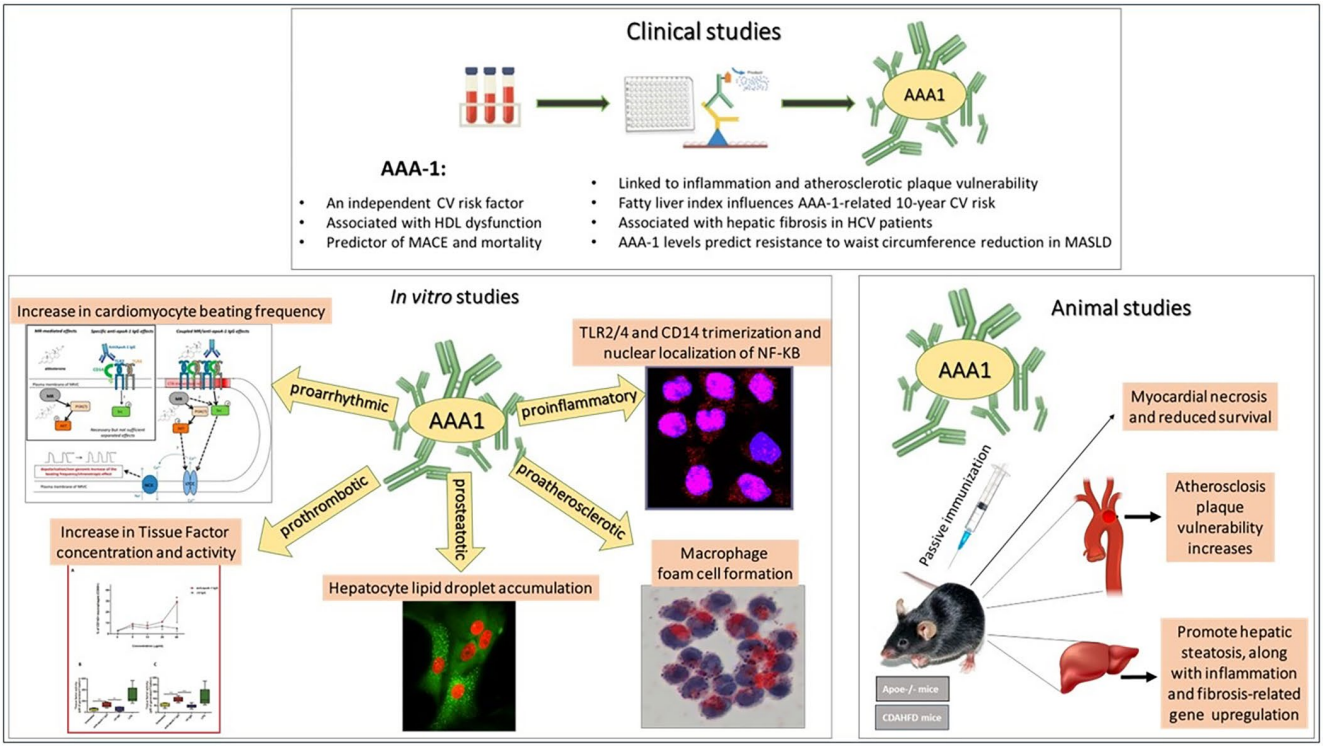

FIGURE 1 Summary of the pleiotropic effects of AAA-1 in clinical, in vitro and animal studies. Adapted from references [119–141].

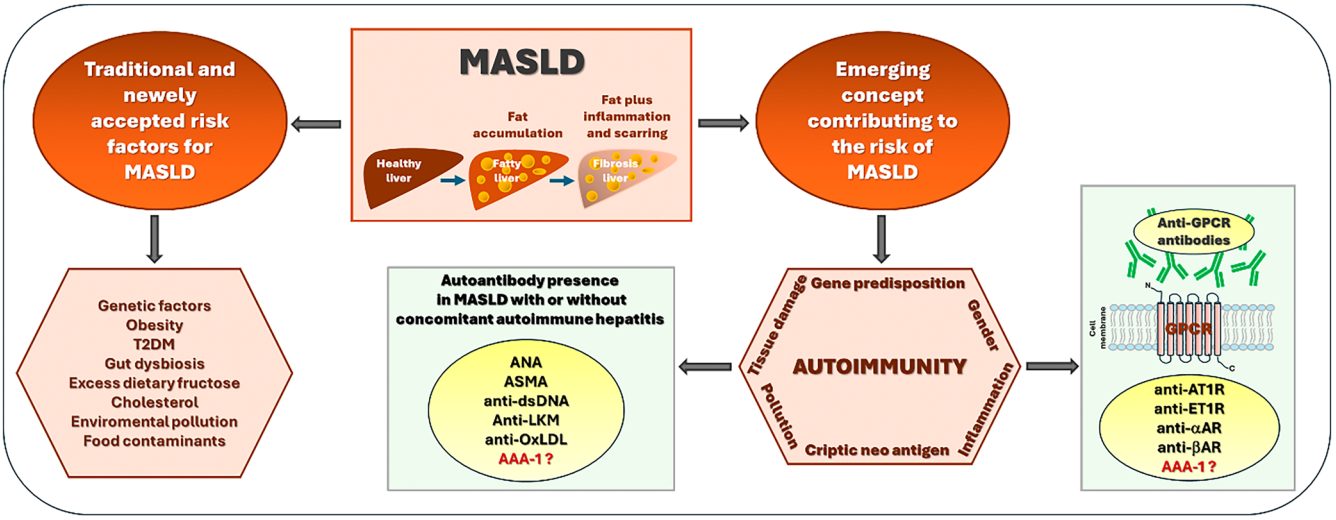

FIGURE 2 Traditional and emerging new risk factors in MASLD. MASLD is characterized by intrahepatic accumulation of triglycerides exceeding 5% and progresses along a complex spectrum of disease, including liver inflammation and scarring leading to MASH. Genetic factors and metabolic dysfunctions such as obesity and T2DM are well-established risk factors, while additional factors are increasingly recognized, as shown in the figure. An emerging concept in MASLD pathogenesis is the potential role of autoimmunity. Several autoantibodies have been identified in MASLD patients, with or without concomitant autoimmune hepatitis, though their significance as risk or diagnostic markers remains unclear. Among these, antibodies against GPCR warrant further investigation, as limited evidence suggests their presence in MASLD, although they are well known for their pathogenic role in a variety of diseases. Some anti-GPCR antibodies have also been reported in T2DM. AAA-1, identified as an emerging cardiovascular risk factor with a pro-steatotic and pro-fibrotic properties in vitro and in animal studies, is hypothesized to belong to the anti-GPCR antibody class. Its potential contribution to the broad spectrum of MASLD requires further investigation.

Research efforts should also explore the therapeutic implications of targeting GPCRs in the context of MASLD. This could involve the development of novel pharmacological agents aimed at modulating GPCR activity to restore normal metabolic and immune functions in the liver. Additionally, further investigation into the relationship between environmental and lifestyle factors, such as pollutants, diet and physical activity, and their effects on autoimmunity in MASLD may reveal important preventive strategies.

Finally, exploring the genetic and epigenetic factors that may predispose to autoimmunity in MASLD will be critical. Identifying at-risk populations and understanding the underlying mechanisms can lead to more personalised approaches to treatment and management of this condition.

9 | CONCLUSION

MASLD is a complex, multifactorial disease, with well-established risk factors including genetic predisposition and metabolic dysfunctions such as obesity and T2DM as shown in Figure 2. Moreover, the role of autoimmunity in the pathogenesis of MASLD is gaining recognition, with various autoantibodies, particularly AAA-1, playing pivotal roles in inflammation and disease severity, as illustrated in Figures 1 and 2. GPCRs and antibodies targeting these receptors also emerge as significant players in this complex interplay, influencing both metabolic and immune responses within the liver and in other organs leading to metabolic abnormalities, Figure 2. Continued research is essential to unravel the underlying mechanisms and develop targeted therapies, facilitating better management and potentially improving outcomes for patients with MASLD/MASH.

AUTHOR CONTRIBUTIONS

Writing—original draft preparation, S.P. and N.V.; writing—review and editing, S.P., N.V., E.S., and F.R.J. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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