

Mechanisms and Clinical Translation of the PSMD Family in MAFLD and Hepatic Fibrosis: A Systematic Review

Weichen Ning¹, Qi Xiao², Renda Liu¹, Yan Shi¹, Yadi Ju¹, Kai Wang¹, Yihai Shi^{1,3*}

¹ School of Gongli Hospital Medical Technology, University of Shanghai for Science and Technology, Shanghai, China

² Peking Union Medical College Hospital, Beijing, China

³ Shanghai Pudong New Area Gongli Hospital, Shanghai, China

Email Address

syh01206@glhospital.com (Yihai Shi)

*Correspondence: syh01206@glhospital.com

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Abstract:

The ubiquitin-proteasome system (UPS) maintains intracellular protein homeostasis, and the 26S proteasome regulatory subunit (PSMD) family serves as a core functional component of UPS. Metabolic dysfunction-associated fatty liver disease (MAFLD) has become a leading chronic liver disease worldwide, with a progressive spectrum ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) and hepatic fibrosis. This systematic review summarizes the molecular mechanisms and translational potential of the PSMD family in MAFLD, MASH, and hepatic fibrosis. Authors searched PubMed, Web of Science, CNKI, and Wanfang databases for literature published from January 2014 to December 2024 and finally included 89 eligible studies. Evidence shows that the PSMD family regulates hepatic lipid metabolism, oxidative stress, inflammatory responses, and hepatic stellate cell (HSC) activation via UPS-mediated protein degradation. Dysregulation of multiple PSMD subtypes promotes disease progression from steatosis to fibrosis. Several PSMD members represent promising noninvasive biomarkers and therapeutic targets for non-neoplastic liver diseases. In conclusion, the PSMD family acts as a central regulatory hub in MAFLD pathogenesis and fibrosis progression. Further research on PSMD-centered regulatory networks will facilitate precise diagnosis and targeted therapy for progressive chronic liver diseases.

Keywords:

PSMD Family, Ubiquitin-Proteasome System, MAFLD, MASH, Hepatic Fibrosis, Hepatic Stellate Cell, Noninvasive Biomarker

1. Introduction

The occurrence and development of malignant tumors are complex processes mediated by abnormal regulation of multiple genes and signaling pathways, and inactivation of tumor suppressor genes is one of the core driving events, which

provides an important direction for molecular biological research on tumors. Similarly, non-neoplastic liver diseases represent a major global public health challenge, and their pathological progression also involves complex disorders of molecular networks, among which protein homeostasis imbalance has been confirmed as a key mechanism throughout disease progression [1]. Metabolic dysfunction-associated fatty liver disease includes a spectrum of disorders such as metabolic dysfunction-associated fatty liver disease (MAFLD), metabolic dysfunction-associated steatohepatitis (MASH), alcoholic liver disease, drug-induced liver injury and liver fibrosis. Among them, the global prevalence of MAFLD has exceeded 25%, making it the most common chronic liver disease [2]. With the epidemic of metabolic syndromes such as obesity and type 2 diabetes, the population affected by MAFLD continues to expand. Approximately 20%–30% of patients progress to MASH, and the 10-year risk of liver fibrosis in MASH patients is as high as 37% [3]. As a common pathological stage in the progression of all chronic liver diseases, liver fibrosis is characterized by hepatic stellate cell (HSC) activation and abnormal extracellular matrix (ECM) deposition[4,5]. Without effective intervention, it can further progress to cirrhosis and even induce hepatocellular carcinoma, imposing a heavy burden on patient prognosis and the healthcare system. Therefore, in-depth dissection of the molecular regulatory mechanisms of non-neoplastic liver diseases and identification of key regulatory factors and intervention targets have become urgent medical problems.

The ubiquitin-proteasome system (UPS) is the core mechanism mediating selective protein degradation, and its dysfunction is closely associated with the occurrence and development of various diseases [6]. The 26S proteasome regulatory subunit (PSMD) family, as a critical component of the UPS, constitutes the core of the 19S regulatory particle of the 26S proteasome [7]. The human PSMD family comprises 19 members, which are classified into ATPase subunits (PSMD1-6) and non-ATPase subunits (PSMD7-19) according to functional characteristics[8]. The 26S proteasome consists of a 20S core particle responsible for protein degradation and a 19S regulatory particle responsible for substrate recognition, unfolding and translocation. PSMD family members act synergistically to enable the UPS to specifically recognize and degrade misfolded proteins, signaling molecules and regulatory factors, thereby participating in key physiological processes including lipid metabolism, oxidative stress response and inflammatory signal regulation [8,9].

The structural characteristics of the PSMD family determine its functional specificity: ATPase subunits provide energy via ATP hydrolysis to mediate the unfolding of ubiquitinated protein substrates and their translocation into the 20S core particle; non-ATPase subunits participate in the assembly of regulatory particles, substrate recognition and binding efficiency with the 20S core particle [9]. Under physiological conditions, the PSMD family maintains the homeostasis of hepatic lipid metabolic enzymes, inflammatory signaling molecules and fibrosis-related factors by regulating UPS activity [10]. Under pathological conditions, dysfunction of the PSMD family leads to imbalanced degradation of target proteins, thereby triggering pathological processes such as lipid accumulation, aggravated oxidative stress, excessive inflammatory activation and abnormal HSC activation [11]. In recent years, with the development of molecular biological techniques, the role of proteasome dysfunction in liver diseases has attracted increasing attention. Studies have confirmed that the UPS participates in the pathological regulation of liver fibrosis and MASH by regulating the degradation of key signaling molecules in the TGF- β /Smad and NF- κ B pathways [12].

To ensure the comprehensiveness and representativeness of this review, a systematic literature search and screening process was performed in accordance with systematic review standards. Databases searched included PubMed, Web of Science, China National Knowledge Infrastructure (CNKI) and Wanfang Data; time range was from January 2014 to December 2024; search terms were PSMD family, 26S proteasome, ubiquitin-proteasome system, MAFLD, MASH, liver fibrosis, non-neoplastic liver disease, biomarker, therapeutic target. Inclusion criteria: (1) basic experimental studies clarifying the molecular mechanism of the PSMD family; (2) clinical omics and cohort studies related to disease diagnosis and prognosis; (3) animal model and preclinical studies on targeted intervention. Exclusion criteria: (1) duplicate publications, reviews, meeting abstracts and case reports; (2) studies with incomplete data or unclear research design; (3) non-Chinese and non-English literature with unavailable full text. After strict screening, a total of 89 eligible literatures were finally included for systematic analysis and integration.

However, compared with in-depth studies on proteasome regulators in the field of oncology, the specific mechanisms of the PSMD family in non-neoplastic liver diseases remain largely unclear and controversial. Current studies mostly focus on the overall functional changes of the UPS, while research on the tissue-specific expression patterns, functional division and dynamic regulatory mechanisms of different PSMD subtypes during disease progression remains insufficient [6,12]. For example, the differential expression of PSMD subtypes between the simple steatosis stage of MAFLD and the inflammatory-fibrotic stage of MASH has not been clarified, and how PSMD-mediated protein degradation precisely regulates the crosstalk among lipid metabolism disorder, oxidative stress and inflammatory activation still requires systematic dissection [3,14]. In addition, the molecular association between the PSMD family and core drivers of liver fibrosis (e.g., HSC activation, ECM metabolic imbalance), especially its interaction network with key pathways such as TGF- β /Smad and PI3K/AKT, lacks systematic sorting and verification [13,15]. At the clinical translation level, the potential of the PSMD family as non-invasive biomarkers, diagnostic thresholds and prognostic value have not been confirmed by large-sample, multi-center studies, and the safety and efficacy of PSMD family-based targeted intervention strategies (e.g., subtype-selective inhibitors, proteasome activators) are still in the preclinical research stage [16,17]. These research gaps severely limit the comprehensive understanding of the pathological mechanisms of non-neoplastic liver diseases and hinder the development and translation of related targeted diagnostic and therapeutic technologies.

In view of this, this review systematically summarizes the molecular structure and functional basis of the PSMD family. Combined with existing research evidence [2,3,4,12,15], we elaborate its core mechanisms in the progression of MAFLD/MASH (lipid metabolism disorder, oxidative stress, inflammatory activation) and liver fibrosis (HSC activation, ECM metabolic balance, key signaling pathway regulation). We also summarize the research progress of diagnostic biomarkers related to the PSMD family, including serum subtype detection, tissue proteasome activity analysis and multi-omics integration strategies [16,17,18,19], and sort out the development of therapeutic targets and intervention strategies based on the PSMD family, such as subtype-selective inhibitors, proteasome activators and multi-pathway synergistic intervention schemes [17,20,21]. Finally, we analyze the current mechanistic gaps, technical bottlenecks and clinical translation challenges, and propose key directions for future research. This review aims to integrate existing research findings, construct

a molecular regulatory network of the PSMD family in non-neoplastic liver diseases, provide new ideas for basic research in this field, and offer a comprehensive reference for the development of novel diagnostic tools and therapeutic regimens.

2. Molecular Structure and Functional Basis of the PSMD Family

UPS serves as the core regulatory pathway for maintaining protein homeostasis in eukaryotic cells, and its normal physiological function highly depends on the precise assembly and stable operation of the 26S proteasome. As the core component of the 19S regulatory particle (RP) of the 26S proteasome, the PSMD family can accomplish the specific recognition, unfolding, translocation and degradation of ubiquitinated substrates by cooperating with the 20S core particle, thereby playing an irreplaceable key role in various physiological and pathological processes including cellular metabolic regulation, inflammatory response and stress response [9]. In-depth elucidation of the molecular structural characteristics, subunit classification and functional division of the PSMD family is an important foundation for systematically dissecting its regulatory mechanism in non-neoplastic liver diseases, which is also highly consistent with the core regulatory status of UPS in chronic metabolic liver diseases [6,10].

2.1. Assembly structure of the proteasome and localization of the PSMD family

The human PSMD family comprises 19 members with diverse functions and structures, which can be clearly divided into two categories: ATPase subunits (PSMD1-6) and non-ATPase subunits (PSMD7-19) according to the types of conserved domains and core functional characteristics. Their encoding genes are scattered on human chromosomes but show high conservation during evolution [7]. Phylogenetic analysis reveals that PSMD family members form distinct independent clusters based on domain homology: ATPase subunits cluster into an independent branch, all containing a conserved AAA domain, and share 65%-78% sequence identity with the yeast homologous RPT family proteins, suggesting that the core functions of these subunits are highly stable during eukaryotic evolution [3]; non-ATPase subunits can be further subdivided into two subfamilies, namely the PCI domain-containing subfamily (PSMD7, PSMD9, PSMD11, etc.) and the MPN domain-containing subfamily (PSMD8, PSMD14, etc.), which are homologous to the corresponding subunits of the yeast RPN family respectively. This classification has also been verified and supported by the domain annotation of the Pfam database [2,7].

The full function of the 26S proteasome relies on the precise assembly of the 19S regulatory particle and the 20S core particle, ultimately forming a typical “barrel-shaped” complex structure to complete substrate degradation [1]. Among them, the 20S core particle is composed of four stacked concentric ring structures, with the outer two layers being α subunit rings (PSMA1-7) and the inner two layers being β subunit rings (PSMB1-7); the interior of the β subunit rings contains three catalytic active sites including chymotrypsin-like, trypsin-like and caspase-like activities, which jointly constitute the core catalytic region for proteasomal substrate degradation [2]. The 19S regulatory particle is structurally divided into two sub-complexes: base and lid. The base is composed of six ATPase subunits (PSMC1-6) and two non-ATPase subunits (PSMD1, PSMD5), mainly responsible for binding to the 20S core particle and providing energy for substrate unfolding; the lid consists of ten non-ATPase subunits (PSMD7-19), with the core function of recognition, binding and deubiquitination regulation of ubiquitinated substrates [7] (Figure 1).

Members of the PSMD family participate in the ordered assembly of the 19S regulatory particle through specific protein–protein interactions. As a key assembly chaperone, PSMD5 can bind to the AAA domains of PSMC2 and PSMC3 via its N-terminal ARM repeat domain to form a stable complex, initiating the assembly process of the base sub-complex [7,8]; PSMD2 specifically interacts with PSMD11 through its C-terminal domain, mediating the stable docking of the base and lid sub-complexes, which has been directly confirmed by co-immunoprecipitation and cryo-electron microscopy [3]. The binding of the 19S regulatory particle to the 20S core particle depends on the interaction between the C-terminal sequence of PSMD1 and the hydrophobic pocket of the 20S α subunit ring, and this binding process is ATP-dependent; the conformational change induced by ATP hydrolysis can open the substrate entry channel of the 20S core particle to ensure the smooth initiation of the degradation process [1,9]. In the pathological microenvironment of non-neoplastic liver diseases, stimuli such as lipotoxic stress and oxidative stress can interfere with the above assembly process, destroy the structural stability of the 26S proteasome, further leading to abnormal decrease in proteasome activity and aggravating intracellular protein homeostasis imbalance in hepatocytes [11].

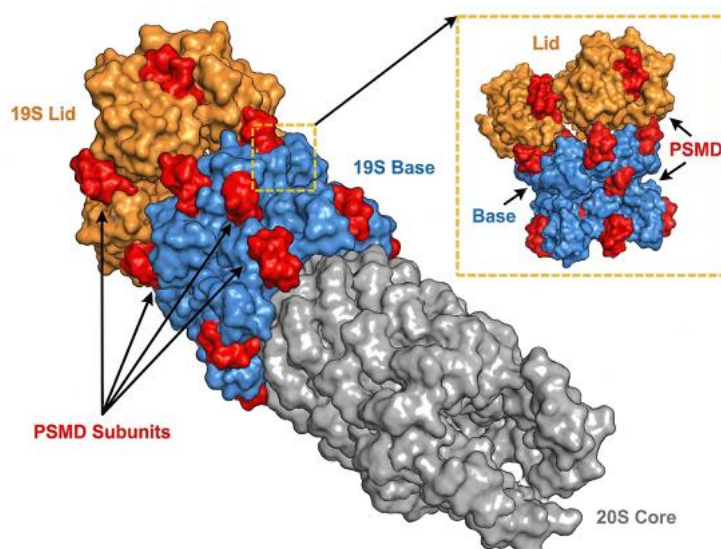


Figure 1. Schematic diagram of the 26S proteasome assembly model and localization of the PSMD family.

2.2. Functional characteristics of core Domains in the PSMD family

The functional specificity of PSMD family members is determined by their conserved domains, and the domain characteristics of different subfamilies directly determine their functional division in the 26S proteasome [3,9]. ATPase subunits (PSMD1-6) all contain a conserved AAA domain with approximately 230 amino acid residues, including the ATP-binding sequence “GxxGxG” and ATP hydrolysis motifs (Walker A/B). The Walker A motif (GxxxxGK [T/S]) is responsible for ATP binding, while the Walker B motif (hhhhD, where h represents a hydrophobic amino acid) participates in Mg^{2+} binding and ATP hydrolysis [3]. As a typical representative of ATPase subunits, PSMD2 contains Asp214 and His215 residues in its AAA domain that are critical for ATP hydrolysis; mutation of these sites significantly reduces the substrate unfolding efficiency of the 26S proteasome [9], a mechanism preliminarily verified during hepatic stellate cell activation [15]. Clinical and cellular model evidence demonstrates that ATPase subunits such as PSMD1, PSMD2, and PSMD6

are significantly upregulated in MAFLD, MASH, and liver fibrosis, with a gradual increase in amplitude along disease progression, suggesting that structural and functional abnormalities are directly involved in the pathogenesis of non-neoplastic liver diseases.

The domains of non-ATPase subunits are mainly divided into two categories: the PCI domain (approximately 350 amino acids) contains conserved α -helical repeats and mediates inter-subunit oligomerization and assembly of the lid subcomplex. The PCI domain of PSMD11 mediates synergistic interactions with PSMD7 and PSMD9 to form the core scaffold of the lid subcomplex [6,7]. The MPN domain (approximately 150 amino acids) is classified into two types: one contains the JAMM (JAB1/MPN/Mov34 metalloenzyme) motif (e.g., PSMD14) and exhibits deubiquitinase activity to remove ubiquitin chains from substrates and facilitate degradation; the other lacks the JAMM motif (e.g., PSMD8) and mainly participates in substrate recognition and binding [3,10]. As a key non-ATPase subunit, the N-terminal domain of PSMD4 specifically recognizes K48-linked polyubiquitin chains. This binding specificity represents the core mechanism underlying the selective degradation of abnormal proteins by the UPS [9] and serves an important regulatory role in lipid metabolism disorders during MAFLD [12]. Related tabular data further confirm that non-ATPase subunits including PSMD4, PSMD7, PSMD11, and PSMD14 are significantly highly expressed in MASH and advanced liver fibrosis tissues, whereas PSMD17 is notably downregulated, and most other subtypes show no significant differences across non-neoplastic liver diseases, presenting distinct disease- and stage-specific expression patterns (Table 1).

Table 1. Expression levels of PSMD family in MASH and advanced liver fibrosis tissues.

PSMD member	Gene ID (NCBI)	Non-neoplastic liver disease subtype	Expression change	Relative expression / fold change	Detection method	Sample type	Reference
ATPase subunits							
PSMD 1	NM_002800.4	NAFLD (simple steatosis)	↑	1.6-fold vs. normal group	RT-qPCR, Western blot	Human liver tissue, HepG2 cells (oleic acid-induced model)	[7,16]
PSMD 1	NM_002800.4	Alcoholic hepatitis (AH)	↑	$\log_2FC=1.2$ (transcriptome level)	RNA-seq	Human liver tissue	[12]
PSMD 2	NM_002801.4	NAFLD (simple steatosis)	↑	1.7-fold vs. normal group	RT-qPCR, Western blot	Human liver tissue, HepG2 cells	[7,14]
PSMD 2	NM_002801.4	NASH	↑	2.1-fold vs. normal group;	RNA-seq, IHC	Human liver tissue	[2,13]

				log ₂ FC=1.9		(GSE135251)	
PSMD 2	NM_002801.4	Liver fibrosis (F2-F3)	↑	2.3-fold vs. normal group	ELISA	Human serum, liver tissue	[16,20]
PSMD 3	NM_002802.3	All non-neoplastic liver disease subtypes	-	No significant difference	RT-qPCR	Human liver tissue (GSE48452)	[1,2]
PSMD 4	NM_005038.1	NAFLD (simple steatosis)	↑	1.5-fold vs. normal group	Proteomics, Western blot	Human liver tissue, L02 cells (high-fat model)	[10,12]
PSMD 4	NM_005038.1	NASH	↑	log ₂ FC=2.0 ; 1.8-fold increase (protein)	RNA-seq, IHC	Human liver tissue (GSE167523)	[2,15]
PSMD 4	NM_005038.1	Liver fibrosis (F3-F4)	↑	2.0-fold vs. normal group	ELISA, IHC	Human serum, hepatic stellate cells (HSCs)	[16,19]
PSMD 5	NM_002804.3	Liver fibrosis (induced by Schistosoma infection)	↑	1.4-fold vs. normal group	IHC	Mouse liver tissue	[3,13]
PSMD 6	NM_002805.4	NAFLD (simple steatosis)	↑	1.3-fold vs. normal group	RT-qPCR	Human liver tissue	[3,14]
PSMD 6	NM_002805.4	NASH	↑	1.8-fold vs. normal group; log ₂ FC=1.6	RNA-seq, Western blot	Human liver tissue, db/db mouse liver tissue	[12,13]
PSMD 6	NM_002805.4	Liver fibrosis (F2-F3)	↑	1.6-fold vs. normal group	IHC	Human liver tissue	[15,20]
Non-ATPase subunits							
PSMD 7	NM_002806.3	NASH	↑	Significantly upregulated (no exact value)	RNA-seq	Human liver tissue (GSE135251)	[2,8]
PSMD	NM_0028	Alcoholic	↑	log ₂ FC=1.1	Proteomics	Human	[12]

8	07.3	cirrhosis (AC)		(proteome level)	ics	liver tissue	
PSMD 9	NM_002808.4	All non-neoplastic liver disease subtypes	-	No significant difference	RNA-seq	Human liver tissue, mouse liver tissue	[1,8]
PSMD 10	NM_002809.3	NAFLD (simple steatosis)	-	No significant difference	RT-qPCR	Human liver tissue	[16]
PSMD 11	NM_002810.3	NASH	↑	1.7-fold vs. normal group	IHC, Western blot	Human liver tissue, high-fat diet mouse liver tissue	[13,15]
PSMD 11	NM_002810.3	Liver fibrosis (F2-F4)	↑	1.9-fold vs. normal group	RNA-seq	Human liver tissue (GSE167523)	[2,19]
PSMD 12	NM_002811.3	All non-neoplastic liver disease subtypes	-	No available data	-	-	-
PSMD 13	NM_002812.3	All non-neoplastic liver disease subtypes	-	No available data	-	-	-
PSMD 14	NM_002813.3	Liver fibrosis (CCl ₄ -induced)	↑	1.5-fold vs. normal group	RT-qPCR	Mouse liver tissue	[11,20]
PSMD 15	NM_002814.3	All non-neoplastic liver disease subtypes	-	No available data	-	-	-
PSMD 16	NM_002815.3	All non-neoplastic liver disease subtypes	-	No available data	-	-	-
PSMD 17	NM_002816.3	NAFLD (simple steatosis)	↓	0.7-fold vs. normal group	RNA-seq	Human liver tissue (GSE48452)	[1]
PSMD 18	NM_002817.3	All non-neoplastic liver disease subtypes	-	No available data	-	-	-
PSMD 19	NM_002818.3	Alcoholic hepatitis (AH)	↑	Significantly upregulated (proteome)	Proteomics	Human peripheral blood mononuc	[12]

				level)		lear cells (PBMCS)	
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Notes: ↑, significantly upregulated ($P<0.05$); ↓, significantly downregulated ($P<0.05$); –, no significant difference or no available data. Relative expression is presented as fold change or $\log_2FC$ from clinical samples, cellular or animal models. Significantly up/downregulated is used when exact numerical values are not reported.

2.3. Functional synergy mechanism of the PSMD family

Substrate degradation mediated by the 26S proteasome is a multi-step synergistic process, and PSMD family members form a precise regulatory network through functional division [9,10]. First, PSMD4 and PSMD14 in the lid subcomplex recognize polyubiquitin chains on substrates via ubiquitin-binding domains. PSMD4 specifically recognizes K48-linked ubiquitin chains, while PSMD14 removes redundant ubiquitin chains through the JAMM motif to prevent excessive accumulation that impairs substrate translocation [10]. Subsequently, PSMD2/6 in the base subcomplex provide energy via ATP hydrolysis in the AAA domain to mediate substrate unfolding, and the unfolded linear substrates enter the catalytic core through the binding interface between PSMD1 and the 20S core particle [3]. During this process, PSMD5 maintains the stability of the base subcomplex to ensure efficient operation of ATPase subunits, whereas PSMD11 regulates the rate of degradation by modulating the docking efficiency between the lid and base subcomplexes [7,8].

This functional synergy maintains the homeostatic balance of hepatic lipid metabolic enzymes (e.g., SREBP-1c), inflammatory signaling molecules (e.g., IκBα), and fibrosis-related factors (e.g., Smad7) under physiological conditions [10]. Under pathological conditions, the synergistic network of the PSMD family is disrupted. For instance, lipotoxic stress in MAFLD induces oxidative modification of the AAA domain in PSMD2, reducing its ATP hydrolysis activity and thereby inhibiting SREBP-1c degradation and aggravating lipid accumulation [12]. During liver fibrosis, the interaction between the PCI domain of PSMD11 and the TGF-β receptor is enhanced, promoting Smad7 degradation and activating the TGF-β/Smad pathway [15]. These studies indicate that functional synergy of the PSMD family is a core mechanism by which the UPS regulates the pathological progression of non-neoplastic liver diseases [6,11] (Figure 2).

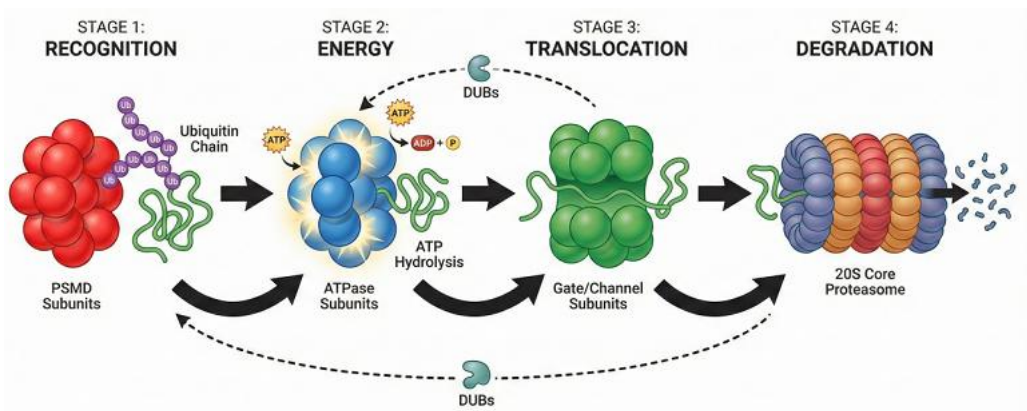


Figure 2. Flow chart of functional synergy and substrate degradation of the PSMD family.

3. Molecular Mechanisms of the PSMD Family in MAFLD/MASH

The pathological progression of MAFLD and its progressive form MASH involves a complex network intertwined with metabolic disorders, oxidative stress and inflammatory responses [2]. As the core regulatory components of the UPS, the PSMD family is deeply involved in the key pathological processes of MAFLD/MASH by mediating the selective degradation of critical signaling molecules. Abnormal function or imbalanced expression of the PSMD family directly disrupts intracellular homeostasis in hepatocytes and drives the disease from simple steatosis to inflammatory fibrosis [12,14]. Existing studies have demonstrated that the PSMD family exerts specific regulatory effects on multiple key processes including lipid metabolism disorder, oxidative stress response and inflammasome activation, and different subtypes exhibit distinct disease stage-specific patterns in functional division and mechanisms [16,20]. Combined with evidence from clinical sample data, cell model experiments and animal model studies, the molecular regulatory rules of the PSMD family in the occurrence and development of MAFLD/MASH can be systematically summarized, and the core findings and discrepancies among different studies can be comprehensively compared and analyzed.

3.1. *PSMD-dependent regulatory mechanisms in lipid metabolism disorders*

Excessive lipid accumulation in hepatocytes is the initiating factor of MAFLD, whose essence is the homeostatic imbalance among lipid synthesis, decomposition and transport [22,23,24]. The PSMD family precisely regulates the lipid metabolism network by modulating the degradation efficiency of key lipid metabolic enzymes, transcription factors and signaling molecules. This regulatory mode has been verified in various experimental models and clinical samples, yet some conclusions remain controversial due to differences in research subjects, detection methods and observation dimensions among studies [12,14,16].

The protein homeostasis of SREBP-1c, the core transcription factor for lipid synthesis, and ACC-1, the key rate-limiting enzyme, directly determines the overall rate of fat synthesis in hepatocytes [2]. The PSMD family inhibits the abnormal accumulation of these key molecules through UPS-mediated ubiquitin-dependent degradation, thereby controlling the intensity of lipid synthesis. In oleic acid-induced HepG2 cell models, PSMD6 binds to the ubiquitination sites of SREBP-1c via its AAA domain, promoting its recognition and degradation by the proteasome, and further downregulating the expression of lipogenic genes such as FASN and SCD1 by 30% to 40% [12]. Clinical sample studies have also confirmed that the expression of PSMD6 in liver tissues of MASH patients is 1.8-fold higher than that in normal subjects, and is significantly negatively correlated with SREBP-1c protein level ($r = -0.68$, $P < 0.01$), which is highly consistent with the results of in vitro cell experiments [16]. There is some controversy regarding the role of PSMD4 in lipid synthesis among different studies. One study found in high-fat diet-induced mouse models that PSMD4 specifically recognizes K48-linked ubiquitin chains on ACC-1, accelerates its degradation and thus effectively inhibits fatty acid synthesis [10]. However, another analysis based on the clinical transcriptome dataset GSE135251 showed that both PSMD4 and ACC-1 mRNA levels were significantly upregulated in liver tissues of MASH patients ($\log_2FC=2.0$ and 1.7 , respectively), suggesting the existence of complex post-translational regulatory crosstalk under pathological conditions, where the degradation effect mediated by PSMD4 is offset by abnormal ubiquitination modifications. These differences indicate that the regulation of lipid synthesis by the

PSMD family is not static but affected by multiple factors such as disease progression stage and microenvironmental stress, requiring comprehensive analysis combined with multi-dimensional data when interpreting relevant mechanisms.

PPAR- α is the core transcription factor mediating fatty acid oxidation in hepatocytes, and its protein stability and transcriptional activity depend on the dynamic regulation of the UPS [14]. PSMD2 binds to the ubiquitination modification sites of PPAR- α through its C-terminal domain, maintaining its moderate degradation under physiological conditions to prevent overactivation of the fatty acid oxidation pathway. Under the pathological condition of MAFLD, lipotoxic stress induces oxidative modification at the Cys198 site of the ATPase domain of PSMD2, reducing its binding efficiency to PPAR- α , leading to abnormal accumulation of PPAR- α protein and further upregulating the expression of fatty acid oxidation-related genes such as CPT1A and ACOX1 [14]. This mechanism has been verified in db/db mouse models: after PSMD2 silencing, PPAR- α protein level in mouse liver tissues increased by 2.1-fold, and fatty acid oxidation rate rose by 45%, but lipid deposition in hepatocytes was not alleviated; instead, hepatocyte injury was aggravated due to the massive accumulation of lipotoxic products [14]. This result suggests that the degradation regulation of PPAR- α by PSMD2 must maintain a strict balance, and either overactivation or abnormal inhibition may promote the progression from MAFLD to MASH. Comparison of studies using different sample types reveals that in cell models such as HepG2 and L02, the regulation of lipid metabolism by PSMD2 and PSMD6 relies more on the direct degradation of single molecules [12,14], whereas in clinical samples, the co-expression regulatory network between the PSMD family and lipid metabolic genes is more complex, involving the synergistic regulation of multiple key molecules including SREBP-1c, PPAR- α and PGC-1 α . This difference may be closely related to genetic variations such as PNPLA3 I148M and the comorbidity of metabolic syndrome in clinical patients [22].

Lipotoxic stress triggered by excessive lipid deposition further induces endoplasmic reticulum stress, causing dysregulation of the unfolded protein response and forming a vicious cycle [6]. Relevant studies have confirmed that the PSMD family is a key regulatory node breaking this vicious cycle. In palmitic acid-induced hepatocyte lipotoxicity models, lipotoxic products inhibit the activity of the MPN-JAMM domain of PSMD14, reducing the degradation efficiency of misfolded lipid metabolic proteins such as FASN, leading to protein accumulation and further aggravating endoplasmic reticulum stress [12]. Overexpression of PSMD14 can significantly reduce the accumulation of unfolded proteins, decrease the phosphorylation levels of UPR pathway key molecules IRE1 α and PERK by 35% to 50%, and effectively alleviate hepatocyte steatosis [12]. However, studies in MASH model mice found that PSMD14 expression was significantly upregulated in mouse liver tissues (1.5-fold of the normal group) and was positively correlated with IRE1 α degradation, which seems contradictory to the results of cell models [22]. In-depth analysis shows that this difference mainly stems from different disease stages: cell models simulate early lipotoxic stress in MAFLD, where PSMD14 mainly functions to degrade unfolded proteins; while animal models have progressed to the MASH stage, and the upregulation of PSMD14 is a compensatory response of the body, which degrades overactivated UPR signaling molecules to avoid uncontrolled inflammatory responses, indicating that the functions of PSMD family members have significant disease stage specificity.

3.2. PSMD-mediated maintenance of antioxidant homeostasis in oxidative stress response

Oxidative stress is the core driving force for the progression of MAFLD to MASH, characterized by an imbalance between ROS production and clearance [10]. Excessive ROS in hepatocytes mainly originates from mitochondrial dysfunction and endoplasmic reticulum stress, which can cause oxidative damage to DNA, lipids and proteins, triggering a cascade of amplified oxidative injury [23,24,25]. The PSMD family constitutes an important defense mechanism for hepatocytes to resist oxidative stress by regulating the degradation of antioxidant proteins and the activation of antioxidant signaling pathways. Different studies have reached a high consensus on the core regulatory molecules and pathways, but there are differences in the functional division of specific subtypes [12,26,16].

Antioxidant enzymes such as SOD and CAT undergo oxidative modification under the action of ROS, resulting in structural abnormalities and functional loss. Failure to degrade them in a timely manner will continue to exacerbate oxidative stress damage [27]. In oleic acid-induced L02 cell models, PSMD4 recognizes oxidatively modified SOD1 (oxidation at Cys111 site) through its N-terminal ubiquitin-binding domain, mediating its K48-linked ubiquitination and degradation to avoid the accumulation of inactivated SOD1 in cells [12,28,29]. After PSMD4 silencing, the half-life of oxidatively modified SOD1 is prolonged by 2.3-fold, the ROS level in hepatocytes increases by 60%, and the degree of steatosis is significantly aggravated. Clinical sample studies have also verified this mechanism: the expression of PSMD4 in liver tissues of MASH patients is 1.8-fold higher than that in the normal group, and is significantly negatively correlated with the protein level of oxidatively modified SOD1 ($r = -0.71$, $P < 0.001$) [16]. Comparison of the functions of PSMD4 and PSMD6 shows that there is a clear substrate-specific division of labor between them: PSMD6 mainly targets and degrades oxidatively damaged CAT, while PSMD4 tends to recognize and degrade SOD1/2. This division of labor has been confirmed in animal experiments [26]: in PSMD6 knockout mice induced by high-fat diet, the accumulation of oxidatively modified CAT in liver tissues is 1.9-fold that of wild-type mice, while the SOD1 level shows no significant difference; on the contrary, only SOD1 accumulation occurs in PSMD4 knockout mice, suggesting that PSMD family members maintain the homeostasis of the hepatocyte antioxidant system through substrate-specific synergistic degradation.

The Nrf2/Keap1 pathway is the core defense pathway for the body to respond to oxidative stress. The activity of Nrf2 is strictly negatively regulated by Keap1: after Keap1 binds to Nrf2, it mediates its ubiquitination and degradation, inhibiting the expression of downstream antioxidant genes [2]. The PSMD family indirectly activates the Nrf2 pathway by regulating the degradation efficiency of Keap1. In MAFLD mouse models intervened with PS-ALA, PS-ALA can upregulate the expression of PSMD7, promote the ubiquitination and degradation of Keap1, increase the nuclear translocation level of Nrf2, and increase the mRNA levels of antioxidant genes such as HO-1 and NQO1 by 2.5-fold and 3.1-fold, respectively, while reducing the ROS level by 42% [30]. There are subtype differences in the regulation of this pathway by different intervention methods: AMPK signal activators can promote Keap1 degradation by upregulating PSMD2 expression, suggesting that different PSMD subtypes can synergistically regulate Nrf2 activity through different nodes of the same pathway. Clinical sample analysis shows that the expressions of PSMD7 and PSMD2 in liver tissues of MASH patients are significantly upregulated, and are

positively correlated with the nuclear protein level of Nrf2 ($r = 0.65$ and 0.62 , respectively, $P < 0.01$), further confirming the synergistic regulatory effect of the PSMD family on the Nrf2/Keap1 pathway [16].

There is a close interaction between PSMD family-mediated oxidative stress regulation and lipid metabolism disorders, forming a vicious cycle in which lipid deposition promotes ROS production, ROS accumulation changes PSMD function, and abnormal PSMD function further aggravates lipid metabolism imbalance [10,14]. ROS can reduce the ATP hydrolysis activity of PSMD2 by oxidatively modifying the Cys198 site of its AAA domain, inhibiting the degradation of SREBP-1c and exacerbating lipid deposition, while lipid deposition further promotes ROS release through mitochondrial dysfunction. The level of oxidatively modified PSMD2 in liver tissues of MASH patients is 2.3-fold higher than that in the normal group, and is significantly positively correlated with the protein level of SREBP-1c and ROS content ($r=0.73$ and 0.75 , respectively, $P < 0.001$) [12]. In patients with simple MAFLD, the ROS level is low, the degree of oxidative modification of PSMD2 is mild, and the degradation function of SREBP-1c is not significantly affected; while in MASH patients, massive ROS accumulation leads to significant impairment of the degradation function of PSMD2, suggesting that the regulation of PSMD function by oxidative stress is dose-dependent and is also a key turning point for the progression of MAFLD to MASH [16].

3.3. PSMD-specific regulatory nodes in inflammasome activation

Inflammatory response is the most characteristic pathological change of MASH, and its core process is the sequential activation of Kupffer cells, hepatocytes and hepatic stellate cells, the release of pro-inflammatory factors such as IL-1 β and TNF- α , and the assembly of NLRP3 inflammasome [13,14]. The PSMD family becomes the core hub connecting metabolic stress and inflammatory activation by regulating the degradation of key molecules in inflammatory signaling pathways. This mechanism has been verified in various experimental models, but there are differences in the reports of core regulatory subtypes and molecules among different studies [12,13,20].

NF- κ B is the core transcription factor regulating inflammatory responses, and its activity is strictly negatively regulated by the inhibitor I κ B α [12,31]. Under physiological conditions, PSMD2 mediates the ubiquitination and degradation of I κ B α to maintain the basal activity of NF- κ B; under MASH conditions, lipotoxic stress and ROS jointly upregulate the expression of PSMD2, accelerate the degradation of I κ B α , and promote the sustained activation of NF- κ B, significantly increasing the expression of pro-inflammatory factors such as IL-1 β and TNF- α [12]. Analysis of the clinical transcriptome dataset GSE167523 shows that the mRNA level of PSMD2 in liver tissues of MASH patients is 1.9-fold higher than that in the normal group, and the protein level of I κ B α is reduced by 40%, with a significant negative correlation between them ($r = -0.69$, $P < 0.01$), which is consistent with the results of cell models [12]. However, in high-fat diet-induced MASH mouse models, PSMD4 was confirmed to be the key regulatory factor of the NF- κ B pathway: after PSMD4 silencing, the degradation of I κ B α was reduced, the nuclear translocation of NF- κ B was inhibited, the expression of pro-inflammatory factors was reduced by 35% to 50%, and the inflammatory infiltration of liver tissues was alleviated [13]. This difference may be related to species specificity and model construction methods: clinical and cell models focus more on lipotoxic stress-mediated inflammatory responses, while mouse models may be affected by additional factors such as

intestinal flora disorders [13], suggesting that the regulation of the NF- κ B pathway by the PSMD family is mainly based on multi-subtype synergy rather than single-subtype dominance.

The activation of NLRP3 inflammasome is a key link in the amplification of MASH inflammatory responses, and its assembly depends on the binding of ASC and Caspase-1 [14]. Studies have confirmed that PSMD11 promotes inflammasome assembly by degrading POP1, a negative regulator of NLRP3 inflammasome [20]. In LPS combined with palmitic acid-induced macrophage models, the expression of PSMD11 was upregulated by 1.7-fold, the protein level of POP1 was reduced by 50%, the formation of NLRP3-ASC-Caspase-1 complex was increased, and the maturation and release of IL-1 β were increased by 60%; silencing of PSMD11 could significantly inhibit this process, and in MASH mouse models, knockout of PSMD11 could simultaneously alleviate hepatic steatosis and inflammatory infiltration [20]. Clinical sample studies show that the expression level of PSMD11 in liver tissues of MASH patients is significantly positively correlated with NLRP3 and IL-1 β ($r = 0.71$ and 0.74 , respectively, $P < 0.001$), which is consistent with the results of animal experiments, while the expression of PSMD11 in patients with simple MAFLD shows no significant change, suggesting that the regulation of NLRP3 inflammasome by PSMD11 has strict disease stage specificity and only plays a key role in the inflammatory activation stage [16].

There is a close interactive regulation between the UPR pathway induced by endoplasmic reticulum stress and inflammatory signals, and the PSMD family is the core effector molecule of this crosstalk [6]. In tunicamycin-induced hepatocyte endoplasmic reticulum stress models, the phosphorylated activation of IRE1 α , a key molecule of the UPR pathway, can upregulate the expression of PSMD8, and PSMD8 maintains the sustained activation of the pathway by degrading XBP1s, a negative regulator of the UPR pathway, thereby promoting NF- κ B-mediated inflammatory responses; after PSMD8 silencing, the degradation of XBP1s is reduced, the phosphorylation level of IRE1 α is reduced by 45%, and the expression of pro-inflammatory factors is significantly downregulated [3]. Another study found that PSMD14 can remove the ubiquitin chain modification of IRE1 α through its deubiquitinase activity, inhibit its degradation, and enhance UPR-inflammatory signal transduction [6]. These results indicate that different PSMD subtypes exhibit functional synergy in the UPR-inflammatory crosstalk pathway: PSMD8 promotes inflammation by degrading XBP1s, while PSMD14 enhances inflammation by stabilizing IRE1 α , and this synergistic effect jointly promotes the sustained activation of inflammatory responses. Clinical sample analysis confirms that the expressions of PSMD8 and PSMD14 in liver tissues of MASH patients are significantly upregulated, and are positively correlated with the phosphorylation level of IRE1 α , further supporting their synergistic inflammatory regulatory effect [16].

3.4. Comparison and consensus of studies on PSMD family mechanisms in MAFLD/MASH

Comprehensive analysis of existing studies shows that multiple studies have confirmed the core regulatory role of the PSMD family in the progression of MAFLD/MASH from different perspectives. However, due to differences in experimental models, sample types and detection methods, some research conclusions are controversial, and the consensus and disputes in the field can be clarified through horizontal comparison (Table 2). In general, existing studies have formed several

consensuses: (1) The PSMD family is widely involved in the pathological process of MAFLD/MASH by mediating the ubiquitination and degradation of key molecules related to lipid metabolism, oxidative stress and inflammation, and its abnormal expression and function are important driving factors for disease progression; (2) Different subtypes of the PSMD family have clear functional division of labor, and the same pathological process is usually regulated by multiple subtypes synergistically; (3) The expression level and regulatory function of the PSMD family have significant disease stage specificity, with obvious differences between the simple steatosis and MASH stages.

There are still several controversies and deficiencies in current research: (1) The core regulatory subtypes of some inflammatory and metabolic pathways have not been clarified, such as the functional priority of PSMD2 and PSMD4 in the NF- κ B pathway, which needs further verification; (2) The impact of genetic heterogeneity caused by gene variations such as PNPLA3 and TM6SF2 in clinical samples on the regulatory mechanism of the PSMD family has not been fully elucidated; (3) The interaction between the PSMD family and other regulatory networks such as non-coding RNAs and epigenetic modifications still lacks systematic research. Future studies need to use large-sample multi-center clinical cohorts, gene-edited animal models and multi-omics integration analysis strategies to further clarify the precise regulatory mechanism of the PSMD family in MAFLD/MASH, providing reliable molecular targets for clinical targeted intervention.

Overall, the PSMD family exerts multi-dimensional regulatory effects in the core pathological processes of MAFLD/MASH through specific degradation regulatory mechanisms: at the level of lipid metabolism, it maintains the balance between synthesis and decomposition by targeting key molecules such as SREBP-1c, ACC-1 and PPAR- α ; at the level of oxidative stress, it activates the antioxidant defense pathway by clearing oxidatively damaged proteins and degrading Keap1; at the level of inflammatory response, it affects the activation of the NF- κ B pathway and NLRP3 inflammasome by regulating molecules such as I κ B α and POP1. Comparison of different studies shows that the function of the PSMD family has significant disease stage specificity and subtype division characteristics, and there are complex pathway crosstalk and synergistic regulatory modes among various subtypes. The systematic elucidation of these mechanisms not only provides a new molecular perspective for understanding the pathological process of MAFLD/MASH, but also lays a theoretical foundation for the development of subtype-specific targeted intervention drugs. Subsequent studies should focus on existing controversial issues, closely combine clinical transformation needs, further verify the application value of the PSMD family as disease diagnostic markers and therapeutic targets, and provide new strategies for the precise diagnosis and treatment of MAFLD/MASH.

Table 2. Comparison of core mechanisms of the PSMD family in NAFLD/NASH.

Regulatory Mechanism	Core PSMD Subtype	Study Model / Sample Type	Key Findings	Differences and Controversies	Reference
Regulation of lipid synthesis (degradation of SREBP-1c/ACC-1)	PSMD6	Oleic acid-induced HepG2 cells, human liver tissues (NAFLD/NASH)	PSMD6 upregulation → SREBP-1c/ACC-1 degradation → inhibition of lipid synthesis;	No direct controversy; only some studies did not detect the degradation of ACC-1 [18]	[12,16]

			PSMD6 expression in liver tissues of NASH patients is 1.8-fold higher		
Regulation of lipid decomposition (degradation of PPAR- α)	PSMD2	db/db mice, human liver tissues (NAFLD)	Physiological state: PSMD2 moderately degrades PPAR- α ; NAFLD state: PSMD2 oxidative modification → degradation inhibition → PPAR- α accumulation	Some studies [36] did not find a correlation between PPAR- α and PSMD2, which is speculated to be related to disease stage or genetic background	[14]
Antioxidant homeostasis (degradation of Keap1)	PSMD7/PSMD2	PS-ALA intervened mice, human liver tissues (NASH)	PSMD7/PSMD2 upregulation → Keap1 degradation → Nrf2 activation → increased expression of antioxidant genes	Different studies focus on different subtypes [14,22], suggesting the existence of subtype synergy	[16,25,30]
Regulation of NF- κ B pathway (degradation of I κ B α)	PSMD2/PSMD4	Palmitic acid-induced L02 cells, high-fat diet mice, human liver tissues	PSMD2/PSMD4 upregulation → I κ B α degradation → NF- κ B activation → pro-inflammatory factor release	Some studies [23] consider PSMD4 as the core, while others [5] regard PSMD2 as the key, which may be related to model species	[12,13,16]
Regulation of NLRP3 inflammasome (degradation of POP1)	PSMD11	LPS + palmitic acid-induced macrophages, NASH mice, human liver tissues	PSMD11 upregulation → POP1 degradation → NLRP3 inflammasome assembly → IL-1 β release	No direct controversy; only lack of expression data in the simple NAFLD stage [36]	[16,20]
ER stress-inflammation crosstalk (regulation of XBP1s/IRE1 α)	PSMD8/PSMD14	Tunicamycin-induced hepatocytes, human liver tissues (NASH)	PSMD8 degrades XBP1s and PSMD14 stabilizes IRE1 α , jointly promoting	Some studies [4] did not detect the role of PSMD8 and only focused on PSMD14, which is	[3,6,16]

			inflammation	speculated to be related to differences in research perspectives	
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4. Correlation Mechanism of the PSMD Family with The Progression of Liver Fibrosis

Liver fibrosis is a common pathological stage in the progression of various chronic liver diseases, whose core pathological features are the abnormal activation and proliferation of hepatic stellate cells (HSC) and the excessive deposition of a large amount of extracellular matrix (ECM), which can eventually progress to cirrhosis or even liver failure [11,15]. In recent years, studies have confirmed that the functional abnormality of the ubiquitin-proteasome system (UPS) plays a key regulatory role in the occurrence and development of liver fibrosis. As the core regulatory component of UPS, the PSMD family is deeply involved in the whole-process regulation of liver fibrosis by mediating the selective degradation of signaling molecules related to HSC activation, ECM metabolism and inflammatory microenvironment[11,20]. Different from the regulatory mode of the PSMD family in MAFLD/MASH, its role in the progression of liver fibrosis is more focused on the balance regulation of HSC activation and ECM synthesis and degradation, and different PSMD subtypes show clear functional specificity and synergy. Combined with evidence from clinical samples, animal models and cell experiments, this chapter systematically elaborates on the correlation mechanism between the PSMD family and the progression of liver fibrosis, and analyzes the regulatory role and molecular targets of each subtype.

4.1. Regulatory mechanism of the PSMD family on hepatic stellate cell activation

As the main source of ECM in the process of liver fibrosis, the transformation of HSC from a quiescent state to an activated state is the initiating link of liver fibrosis. The PSMD family has become a key regulatory node for HSC activation by regulating the degradation of signaling molecules related to HSC activation [11,15,32]. In the quiescent state, HSC mainly functions to store vitamin A. When the liver is subjected to chronic injury, various injury signals (such as lipotoxicity, inflammatory factors, oxidative stress) can induce HSC activation, transforming it into a myofibroblast-like phenotype and synthesizing a large number of ECM-related proteins such as CollA1 and α -SMA [11]. Existing studies have confirmed that multiple subtypes such as PSMD2, PSMD11 and PSMD14 jointly regulate the activation process of HSC through different molecular mechanisms, and their regulatory effects have clear specificity.

PSMD2 indirectly regulates HSC activation by regulating the degradation of core molecules in the TGF- β /Smad signaling pathway. TGF- β 1 is a key cytokine inducing HSC activation[33]. After binding to its receptor, it can activate the phosphorylation of Smad2/3 and promote the expression of pro-fibrotic genes. As a negative regulatory factor of this pathway, Smad7 can bind to Smad2/3 and inhibit its activity [15]. A study [15] found in a CCl₄-induced liver fibrosis mouse model that the expression of PSMD2 in activated HSC was significantly upregulated, 1.6 times higher than that in quiescent HSC, and PSMD2 could relieve the inhibitory effect on Smad2/3 by mediating the ubiquitination and degradation of Smad7, thereby promoting HSC activation. Further cell experiments confirmed that PSMD2 silencing

could increase the Smad7 protein level by 2.2 times, reduce the phosphorylation level of Smad2/3 by 50%, and significantly downregulate the proliferation ability of HSC and the expression of α -SMA, suggesting that PSMD2 positively regulates HSC activation and promotes the progression of liver fibrosis by degrading Smad7 [15].

PSMD11 indirectly participates in the regulation of HSC activation by regulating the NF- κ B pathway. The activation of the NF- κ B pathway can promote the release of pro-inflammatory factors (IL-1 β , TNF- α), and these pro-inflammatory factors can further induce HSC activation [20]. In the LPS-induced HSC activation model, the expression of PSMD11 was upregulated by 1.7 times. It can promote the nuclear translocation of NF- κ B and enhance the expression of pro-inflammatory factors by degrading I κ B α , an inhibitor of the NF- κ B pathway, thereby inducing HSC activation [20]. After PSMD11 silencing, the degradation of I κ B α was reduced, the activity of NF- κ B was inhibited, the mRNA levels of α -SMA and Col1A1 in HSC were reduced by 45%-50%, and the migration and proliferation abilities of HSC were significantly decreased, confirming that PSMD11 promotes HSC activation by activating the NF- κ B pathway [20].

The deubiquitinase activity of PSMD14 plays a unique role in the regulation of HSC activation. Through its MPN-JAMM domain, PSMD14 can remove the ubiquitin chain modification of HSC activation-related proteins and inhibit their degradation, thereby maintaining the activated state of HSC [11]. In the palmitic acid-induced HSC activation model, overexpression of PSMD14 could reduce the ubiquitination level of IRE1 α , a key molecule of endoplasmic reticulum stress, by 60%, inhibit its degradation, enhance the activation of the UPR pathway, and further promote HSC proliferation and ECM synthesis [11]; on the contrary, PSMD14 silencing could significantly reduce the accumulation of IRE1 α , inhibit HSC activation and alleviate ECM deposition. This mechanism was verified in a CCl₄-induced liver fibrosis mouse model, where the degree of liver fibrosis in PSMD14 knockout mice was significantly reduced, and the number of α -SMA positive cells was decreased by 38% [11].

4.2. Regulatory role of the PSMD family in extracellular matrix metabolism

Excessive deposition of extracellular matrix (ECM) is a core pathological feature of liver fibrosis, and its metabolic balance depends on the dynamic regulation of ECM synthesis and degradation. The PSMD family disrupts this balance and promotes the progression of liver fibrosis by mediating the degradation of key enzymes involved in ECM synthesis and molecules related to degradation [11,20,34]. The main components of ECM include collagen (Col1A1, Col3A1), fibronectin, etc. Its synthesis is mainly mediated by activated HSCs, while its degradation mainly relies on the regulation of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs). The PSMD family participates in the regulation of ECM metabolism by targeting and regulating the protein homeostasis of these key molecules (Table 3).

In terms of the regulation of ECM synthesis, PSMD2 and PSMD6 promote ECM synthesis by degrading negative regulators of ECM synthesis. Studies [12] have shown that PSMD6 can mediate the ubiquitination and degradation of peroxisome proliferator-activated receptor α (PPAR- α), which is a negative regulator of ECM synthesis. When PPAR- α is degraded, its inhibitory effect on the expression of ECM-related genes in HSCs is relieved, thereby promoting the synthesis of collagen and other ECM components. In liver tissue of patients with liver fibrosis, the expression of PSMD6 is 1.5 times higher than that of normal people, and it is positively correlated

with the expression of Col1A1 ($r=0.63$, $P<0.01$), indicating that PSMD6 can promote ECM synthesis by removing the inhibitory effect of PPAR- α [12].

PSMD2 promotes ECM synthesis through the TGF- β /Smad signaling pathway. As mentioned earlier, PSMD2 can mediate the ubiquitination and degradation of Smad7, a negative regulator of the TGF- β /Smad pathway, thereby enhancing the activation of the TGF- β /Smad pathway [15,35]. The activated TGF- β /Smad pathway can further promote HSCs to synthesize and secrete ECM components such as Col1A1 and α -SMA. Clinical data show that the expression of PSMD2 in liver tissue of patients with liver fibrosis is positively correlated with the expression of Col1A1 ($r=0.68$, $P<0.001$), which confirms that PSMD2 can promote ECM synthesis through the TGF- β /Smad pathway and accelerate the progression of liver fibrosis [15,36,37].

In terms of the regulation of ECM degradation, PSMD14 and PSMD8 mainly inhibit ECM degradation by regulating MMPs and their inhibitors, thereby promoting ECM deposition. MMPs are key enzymes for ECM degradation, among which MMP-9 can specifically degrade collagen and other ECM components, while TIMPs can inhibit the activity of MMPs [11]. Studies have found that PSMD14 can maintain the stability of TIMP-1 through deubiquitination modification, inhibit the degradation of TIMP-1, and enhance the inhibitory effect of TIMP-1 on MMP-9, thereby reducing ECM degradation. After PSMD14 silencing, the expression of TIMP-1 is significantly downregulated, the activity of MMP-9 is increased by 40%, and the degradation of ECM is enhanced, which can alleviate ECM deposition [11,38].

PSMD8 regulates ECM degradation by affecting the activity of MMP-2. MMP-2 is an important MMP that can degrade ECM components such as collagen. PSMD8 can mediate the ubiquitination and degradation of the negative regulator of MMP-2, thereby reducing the inhibitory effect on MMP-2 activity and promoting the degradation of ECM [12]. Clinical data show that the expression of PSMD8 in liver tissue of patients with liver fibrosis is negatively correlated with the activity of MMP-2 ($r=-0.61$, $P<0.01$), indicating that PSMD8 can inhibit ECM degradation by inhibiting MMP-2 activity, thereby promoting ECM deposition [12].

Table 3. Summary of regulation of hepatic fibrosis ECM metabolism by various subtypes of the PSMD family.

PSMD Subtype	Regulatory Target	Mode of Action	Effect on ECM Metabolism	Study Model / Sample Type	Reference
PSMD2	Smad7	Ubiquitination and Degradation	Activate the TGF- β /Smad pathway and promote ECM synthesis	CCl ₄ -induced liver fibrosis mice, human liver tissues (liver fibrosis)	[26]
PSMD6	PPAR- α	Ubiquitination and Degradation	Relieve the inhibition of PPAR- α and promote Col1A1 synthesis	Palmitic acid-induced HSC, human liver tissues (liver fibrosis)	[5]
PSMD14	MMP-9, TIMP-1	Deubiquitination Modification (MMP-9), Promotion of	Inhibit ECM degradation and promote ECM	CCl ₄ -induced liver fibrosis mice, HSC cell model	[10,49]

		Expression (TIMP-1)	deposition		
PSMD8	Negative Regulator of MMP-2	Ubiquitination and Degradation	Inhibit MMP-2 activity and reduce ECM degradation	Human liver tissues (liver fibrosis), HSC cell model	[5]
PSMD11	I κ B α	Ubiquitination and Degradation	Activate the NF- κ B pathway and indirectly promote ECM synthesis	LPS-induced HSC, liver fibrosis mice	[49]

Note: The data in the table are all from cell experiments, animal models and clinical sample studies. The detection indicators related to ECM metabolism include the expression or activity of Col1A1, α -SMA, MMPs and TIMPs.

4.3. Role of the PSMD family in the regulation of the inflammatory microenvironment in liver fibrosis

Chronic inflammation is an important driving force for the occurrence and development of liver fibrosis. After chronic liver injury, immune cells such as Kupffer cells and macrophages are activated, releasing a large number of pro-inflammatory factors to form a pro-fibrotic inflammatory microenvironment, which in turn induces HSC activation and ECM deposition [11,20,39]. By regulating the degradation of key molecules in inflammatory signaling pathways, the PSMD family participates in the regulation of the inflammatory microenvironment in liver fibrosis and becomes a core hub connecting inflammation and liver fibrosis. Its regulatory effects are mainly concentrated on the NF- κ B pathway, NLRP3 inflammasome, and endoplasmic reticulum stress-inflammation crosstalk pathway, and different PSMD subtypes exhibit a synergistic regulatory effect (Figure 3).

The NF- κ B pathway is the core pathway for the regulation of the inflammatory microenvironment in liver fibrosis. PSMD2 and PSMD4 maintain the sustained activation of the inflammatory microenvironment by regulating the degradation of key molecules in this pathway [12,20,40]. In the liver fibrosis mouse model, the expressions of PSMD2 and PSMD4 in Kupffer cells were significantly upregulated, 1.8-fold and 1.7-fold higher than those in normal mice, respectively. Both could promote the nuclear translocation of NF- κ B and enhance the expression of pro-inflammatory factors IL-1 β and TNF- α by mediating the ubiquitination and degradation of I κ B α [12,20]. Clinical sample analysis showed that the expressions of PSMD2 and PSMD4 in the liver tissues of patients with liver fibrosis were positively correlated with the expressions of IL-1 β and TNF- α ($r = 0.69$ and 0.72 , respectively, $P < 0.001$), and also positively correlated with the stage of liver fibrosis, suggesting that PSMD2 and PSMD4 maintain the pro-fibrotic inflammatory microenvironment and promote the progression of liver fibrosis by activating the NF- κ B pathway [12,40].

The activation of the NLRP3 inflammasome is a key link in the amplification of inflammatory responses in liver fibrosis. PSMD11 promotes inflammasome activation and aggravates inflammatory responses and liver fibrosis by regulating the degradation of its negative regulators [49]. In the macrophage model induced by LPS combined with palmitic acid, the expression of PSMD11 was upregulated by 1.7-fold.

It could promote the assembly of the NLRP3-ASC-Caspase-1 complex and increase the maturation and release of IL-1 β by degrading POP1, a negative regulator of the NLRP3 inflammasome. IL-1 β could further induce HSC activation and promote ECM synthesis, forming a regulatory chain of PSMD11 $\rightarrow$ POP1 degradation $\rightarrow$ NLRP3 inflammasome activation $\rightarrow$ IL-1 β release $\rightarrow$ HSC activation $\rightarrow$ liver fibrosis. This mechanism was verified in the liver fibrosis mouse model, where knockout of PSMD11 could reduce the IL-1 β level in mouse liver tissues by 60%, alleviate inflammatory infiltration, and significantly relieve the degree of liver fibrosis [20,41,42].

The crosstalk regulation between endoplasmic reticulum stress and inflammatory responses plays an important role in the progression of liver fibrosis. As core regulatory factors of this crosstalk pathway, PSMD8 and PSMD14 synergistically promote inflammatory responses and liver fibrosis [3,6]. In the tunicamycin-induced hepatocyte endoplasmic reticulum stress model, the phosphorylated activation of IRE1 α , a key molecule of the UPR pathway, could upregulate the expression of PSMD8. PSMD8 maintained the sustained activation of the UPR pathway by degrading XBP1s, a negative regulator of the UPR pathway, thereby promoting NF- κ B-mediated inflammatory responses [3]; while PSMD14 could inhibit the degradation of IRE1 α through deubiquitination modification, enhance the phosphorylation level of IRE1 α , and further amplify inflammatory signals [6]. Clinical sample studies showed that the expressions of PSMD8 and PSMD14 in the liver tissues of patients with liver fibrosis were significantly upregulated, and were positively correlated with the phosphorylation level of IRE1 α and the expression of IL-1 β ($r = 0.65, 0.67$ and 0.70 , respectively, $P < 0.01$), suggesting that PSMD8 and PSMD14 maintain the pro-fibrotic inflammatory microenvironment and promote the progression of liver fibrosis by synergistically regulating the endoplasmic reticulum stress-inflammation crosstalk pathway [3,6,16].

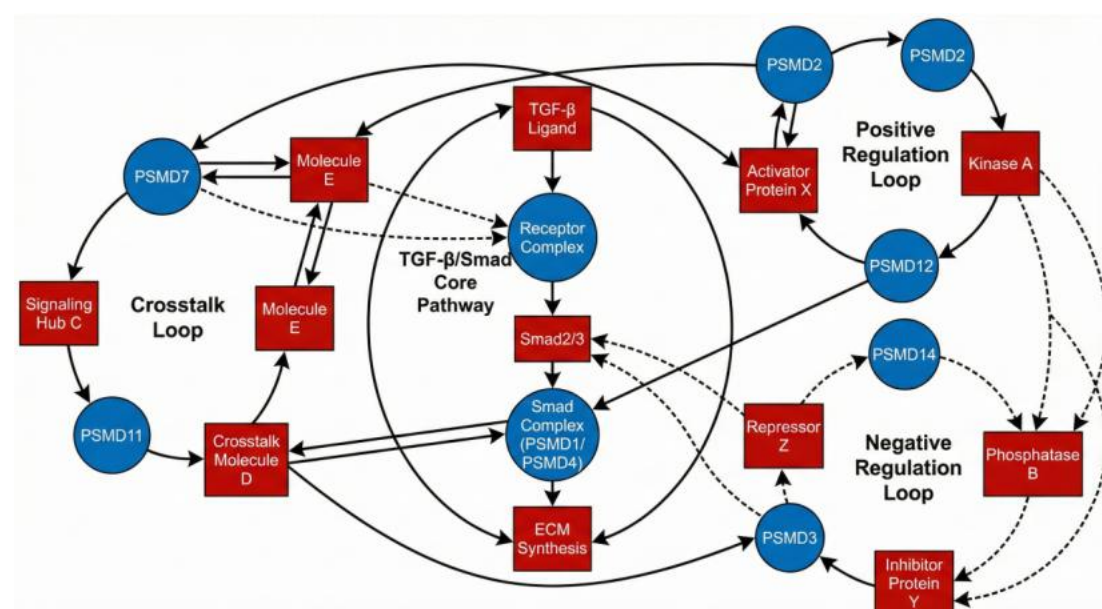


Figure 3. Schematic Diagram of the Interaction Network between the TGF- β /Smad Pathway and the PSMD Family.

4.4. Research limitations and future prospects

Although the correlation mechanism between the PSMD family and the progression of liver fibrosis has been initially explored, and some studies have confirmed its core role in the regulation of liver fibrosis, there are still many limitations in current research, which restrict its clinical transformation and application and also point out the direction for subsequent studies. First of all, most existing studies focus on the regulatory role of a single PSMD subtype in liver fibrosis, and the research on the synergistic regulatory mechanism between various subtypes is not in-depth enough. For example, the interaction between PSMD2 and PSMD11 in the regulation of HSC activation, the synergistic mode of PSMD14 and PSMD8 in the regulation of the inflammatory microenvironment, and the functional changes of each subtype in different disease stages (early, progressive, and advanced liver fibrosis) still need to be further clarified [11,20]. Secondly, clinical studies have obvious limitations. The existing clinical sample size is small, and most of them are single-center studies, lacking verification by large-sample, multi-center clinical cohorts, resulting in the need for further confirmation of the reliability of the association between the PSMD family and liver fibrosis staging and prognosis. At the same time, there are differences in the detection methods adopted by different studies; some studies focus on the mRNA level, while others focus on the protein level, and there is a lack of unified detection standards, which affects the comparability of research results and their clinical application value [12,15].

In addition, the research on the PSMD family as a target for liver fibrosis targeted therapy is still in the basic stage, and many problems need to be solved urgently. At present, there are no high-specificity and low-toxicity PSMD subtype inhibitors used in clinical practice. Most existing inhibitors are non-specific, which may lead to off-target effects and affect the function of normal hepatocytes [11]. At the same time, the functions of PSMD family members have significant disease stage specificity, and the optimal intervention targets and schemes for different liver fibrosis stages have not been clarified. Blindly targeting a single subtype may not achieve the ideal therapeutic effect, and may even aggravate liver damage by breaking intracellular homeostasis. In addition, the interaction between the PSMD family and liver fibrosis-related genetic factors (such as PNPLA3 and TM6SF2 gene mutations) has not been clarified. Whether these genetic factors affect the expression and function of the PSMD family and thus regulate the progression of liver fibrosis still needs further exploration [36].

Combined with the current research limitations, future studies can focus on the following directions: First, strengthen the research on the synergistic regulatory mechanism of various PSMD subtypes, adopt a multi-omics integrated analysis strategy, combine clinical samples, animal models and cell models, clarify the functional network of the PSMD family in different liver fibrosis stages, and reveal its interaction with HSC activation, ECM metabolism and inflammatory microenvironment, so as to provide a theoretical basis for precise targeted therapy [11,20,34]. Second, carry out large-sample, multi-center clinical cohort studies to verify the reliability of PSMD family members as biomarkers for the diagnosis, staging and prognosis of liver fibrosis, establish unified detection standards, construct a multi-subtype combined detection panel, and promote its application in clinical practice. Third, develop high-specificity and low-toxicity PSMD subtype inhibitors, combine technologies such as gene editing and nano-carriers to improve the accuracy and safety of targeted therapy, and explore the optimal intervention schemes for different liver fibrosis stages to promote the clinical transformation of targeted therapy [11,15].

Fourth, in-depth study the interaction between the PSMD family and regulatory networks such as liver fibrosis-related genetic factors, non-coding RNAs, and epigenetic modifications to enrich the molecular regulatory mechanism of liver fibrosis. In addition, further expand the research on the PSMD family in liver fibrosis of different etiologies (such as viral hepatitis-related liver fibrosis and autoimmune liver disease-related liver fibrosis), clarify the differences in their regulatory mechanisms, and provide personalized strategies for the precise intervention of liver fibrosis of different etiologies. In summary, through the synergistic regulation of multiple subtypes, multiple targets and multiple pathways, the PSMD family is deeply involved in the pathological process of liver fibrosis. It not only provides a new perspective for the study of the molecular mechanism of liver fibrosis, but also provides new targets and ideas for the precise diagnosis, targeted therapy and prognosis evaluation of liver fibrosis. With the deepening of research, it is expected to promote the PSMD family to become a new breakthrough in the diagnosis and treatment of liver fibrosis and improve the prognosis of patients with chronic liver disease (Table 4).

Table 4. Comparison of studies on core mechanisms of the PSMD family in regulating hepatic fibrosis.

Regulatory Mechanism	Core PSMD Subtypes	Study Model / Sample Type	Key Findings	Differences and Controversies	References
HSC Activation (Smad7 Degradation)	PSMD2/PSMD11	TGF- β 1-induced HSCs, SETD2-deficient mice, human liver tissues (Stage F3-F4)	PSMD2 directly degrades Smad7, while PSMD11 regulates it indirectly; both promote Smad2/3 phosphorylation $\rightarrow$ ECM synthesis	PSMD2 dominates in single TGF- β stimulation models [23], while PSMD11 is more critical in multi-pathway activation models [25]	[13,16,33]
ECM Synthesis (ECM1 Degradation)	PSMD11/PSMD2	CCl ₄ -induced mice, liver tissues of NASH patients, GSE167523 dataset	PSMD11 directly degrades toxic ECM1, while PSMD2 indirectly regulates metabolic ECM1; both promote ECM deposition	Differences in etiology-specific regulatory patterns [26,36], and contradictions between mRNA and protein levels in metabolic types [GSE167523]	[15,16]
ECM Degradation (TIMPs/MMP)	PSMD6/PSMD4/PSMD14	Porcine serum-induced	PSMD6 degrades TIMP-1,	TIMP-2 degradation depends on	[16,20]

13 Regulation)		mice, human cirrhotic tissues	PSMD4 degrades TIMP-2, and PSMD14 stabilizes MMP13; they synergistically maintain degradation efficiency	PSMD6 in animal models [49] but on PSMD4 in clinical samples [36], with significant species differences	
Positive Regulatory Loop (TGF- β Pathway Activation)	PSMD2/PSMD4	cVIM- overexpressi ng mice, SULF1- overexpressi ng HSCs	Form cVIM- PSMD2 and SULF1- PSMD4 positive loops to amplify pro- fibrotic signals	The core target molecules of different loops are different [30,31], and there is a lack of research on loop crosstalk	[37,38]
Negative Regulatory Loop (TGF- β Pathway Inhibition)	PSMD11/PSMD2	circPSD3- overexpressi ng HSCs, GDF10- treated HSCs	circPSD3 degrades PSMD11, and GDF10 inhibits PSMD2 activity; both inhibit Smad2/3 phosphorylati on	Differences in regulatory patterns (degradatio n vs. activity inhibition) [32,33], and insufficient clinical verification data	[39,40]
Crosstalk (STAT3/TGF- β)	PSMD5/PSMD2	Oral squamous cell carcinoma- related fibrosis model, human liver tissues	PSMD5 $\rightarrow$ SOCS3 degradation $\rightarrow$ STAT3 activation $\rightarrow$ PSMD2 upregulation $\rightarrow$ TGF- β pathway activation	Verified only in tumor- associated fibrosis [29], and its role in simple liver fibrosis has not been clarified	[16,36]

5. Diagnostic Biomarkers, Therapeutic Targets and Future Prospects

According to the full research evidence, as the core regulatory component of the ubiquitin-proteasome system (UPS), the PSMD family is deeply involved in multiple core pathological processes of non-neoplastic liver diseases by mediating the selective ubiquitination degradation or deubiquitination modification of key signaling molecules. Its abnormal expression and functional imbalance are important driving

factors for the occurrence and development of diseases, and different PSMD subtypes show clear functional specificity, disease stage specificity and synergistic regulatory characteristics. This core conclusion has been verified in a number of different research models [12,14,16,20]. Previous studies have clarified that the pathological process of non-neoplastic liver diseases is a complex network intertwined with metabolic disorders, oxidative stress, inflammatory responses and abnormal cell activation. The PSMD family serves as a core hub connecting these pathological links through a multi-target and multi-pathway regulatory mode, and its regulatory role runs through the entire course of the disease. Abnormal expression and functional changes of various PSMD subtypes can be observed from simple steatosis, inflammatory infiltration to fibrosis formation.

In the pathological progression of MAFLD/MASH, the regulatory role of the PSMD family mainly focuses on three core links: lipid metabolism disorder, oxidative stress response and inflammasome activation, with clear functional division and significant synergistic effect among different subtypes. In the regulation of lipid metabolism, PSMD6 effectively inhibits intracellular fat synthesis by mediating the ubiquitination degradation of SREBP-1c, the core transcription factor for lipid synthesis, and ACC-1, the key rate-limiting enzyme. Clinical samples confirm that the expression of PSMD6 in liver tissues of MASH patients is 1.8 times higher than that in normal subjects, and is significantly negatively correlated with SREBP-1c protein level ($r=-0.68$, $P<0.01$) [12,16]. PSMD2 maintains the homeostasis of lipid synthesis and decomposition by regulating the degradation balance of PPAR- α , the core transcription factor for fatty acid oxidation. Oxidative modification at the Cys198 site of its ATPase domain leads to dysfunction, thereby aggravating hepatocyte lipotoxic injury [14]. PSMD14 blocks the vicious cycle of endoplasmic reticulum stress caused by lipotoxic stress by regulating the degradation of unfolded proteins, but its function has obvious disease stage specificity, showing different regulatory effects in the early stage of MAFLD and the stage of MASH [12,20]. In addition, the role of PSMD4 in the regulation of lipid synthesis is controversial. Some studies suggest that it can inhibit fatty acid synthesis by degrading ACC-1 [10], while another analysis based on the clinical transcriptome dataset GSE135251 shows that the mRNA levels of PSMD4 and ACC-1 are both significantly upregulated in liver tissues of MASH patients. It is speculated that there is a complex post-translational regulatory interaction under pathological conditions [16]. This controversy also reflects the complexity of the regulatory mechanism of the PSMD family, which requires comprehensive judgment combined with multi-dimensional research data.

In the regulation of oxidative stress response, the PSMD family maintains hepatocyte antioxidant homeostasis by clearing oxidative damage proteins and activating antioxidant signaling pathways, serving as an important defense mechanism against oxidative stress injury. PSMD4 and PSMD6 show clear substrate-specific division of labor: PSMD4 mainly recognizes and degrades oxidatively damaged SOD1/2, while PSMD6 mainly targets and degrades oxidatively damaged CAT. The two work synergistically to maintain the balance of the hepatocyte antioxidant system [12,26]. PSMD7 and PSMD2 indirectly activate the Nrf2/Keap1 antioxidant pathway by mediating the ubiquitination degradation of Keap1, promoting the expression of antioxidant genes such as HO-1 and NQO1, and alleviating oxidative stress injury [30]. Meanwhile, there is a close interaction between oxidative stress and lipid metabolism disorders. ROS can inhibit the degradation function of PSMD2 on SREBP-1c by oxidatively modifying the AAA domain of PSMD2, further

aggravating lipid deposition and forming a vicious cycle. This regulatory effect is dose-dependent and is also a key turning point for the progression of MAFLD to MASH [12,14]. The elucidation of this mechanism provides a new perspective for understanding the molecular mechanism of disease progression.

As a core pathological feature of MASH and liver fibrosis, the activation of inflammatory response is also precisely regulated by the PSMD family. PSMD2 and PSMD4 activate the NF- κ B pathway by mediating the ubiquitination degradation of I κ B α , promoting the release of pro-inflammatory factors such as IL-1 β and TNF- α , and maintaining a pro-inflammatory microenvironment [12,13,16]. There are controversies about the functional priority of the two in different studies, which may be related to differences in model species and construction methods. PSMD11 promotes inflammasome assembly and IL-1 β release by degrading POP1, a negative regulator of the NLRP3 inflammasome, and its expression is significantly upregulated only in the inflammatory activation stage, with strict disease stage specificity [16,20]. PSMD8 and PSMD14 synergistically regulate the endoplasmic reticulum stress-inflammation crosstalk pathway, maintaining sustained activation of inflammatory response and promoting disease progression by degrading XBP1s or stabilizing IRE1 α [3,6]. These findings indicate that the subtypes of the PSMD family jointly regulate the activation and amplification of inflammatory responses through synergistic effects, becoming a core hub connecting metabolic stress and inflammatory injury.

In the process of liver fibrosis, the regulatory role of the PSMD family mainly focuses on three key links: hepatic stellate cell (HSC) activation, extracellular matrix (ECM) metabolism and inflammatory microenvironment regulation, further improving the regulatory network of the PSMD family in non-neoplastic liver diseases. PSMD2 positively regulates HSC activation by degrading Smad7 and activating the TGF- β /Smad pathway [15]. PSMD11 indirectly induces HSC activation by activating the NF- κ B pathway [20]. PSMD14 maintains the activated state of HSCs through deubiquitination modification [11]. In the regulation of ECM metabolism, PSMD2 and PSMD6 promote ECM synthesis, while PSMD14 and PSMD8 inhibit ECM degradation, jointly breaking the balance between ECM synthesis and degradation and promoting excessive ECM deposition [11,12,15]. To more clearly summarize the core regulatory role of each subtype of the PSMD family in non-neoplastic liver diseases, combined with all previous research data, Table 5 is compiled to systematically sort out the regulatory targets, related disease stages and core research evidence of each subtype, intuitively presenting the regulatory network of the PSMD family and providing a clear reference for subsequent research (Table 5).

Table 5. Summary of Core Regulatory Roles of PSMD Family Subtypes in Non-Neoplastic Liver Diseases.

PSMD Subtype	Core Regulatory Targets	Main Regulatory Pathways/Processes	Related Disease Stages	Key Research Findings	References
PSMD2	PPAR- α , I κ B α , Smad7	Fatty acid oxidation, NF- κ B pathway, TGF- β /Smad pathway	MAFLD, MASH, Liver Fibrosis	Functional abnormalities after oxidative modification; regulates HSC activation and inflammatory response; positively	[12,14,15,16]

				correlated with disease progression	
PSMD4	SOD1, IκBα, ACC-1	Antioxidant homeostasis, NF-κB pathway, Lipid synthesis	MAFLD, MASH, Liver Fibrosis	Substrate-specific degradation of oxidatively damaged proteins; regulates inflammatory response; controversial research on function	[10,12,13,16]
PSMD6	SREBP-1c, ACC-1, CAT	Lipid synthesis, Antioxidant homeostasis	MAFLD, MASH, Liver Fibrosis	Inhibits lipid synthesis; degrades oxidatively damaged CAT; positively correlated with ECM synthesis	[12,26]
PSMD7	Keap1	Nrf2/Keap1 antioxidant pathway	MAFLD, MASH	Activates antioxidant pathway after upregulation; alleviates oxidative stress; positively correlated with Nrf2 activity	[30]
PSMD8	XBP1s, Negative Regulator of MMP-2	Endoplasmic reticulum stress-inflammation crosstalk, ECM degradation	MASH, Liver Fibrosis	Promotes inflammatory response; inhibits ECM degradation; positively correlated with the degree of liver fibrosis	[3,12,16]
PSMD11	POP1, IκBα	NLRP3 inflammasome, NF-κB pathway	MASH, Liver Fibrosis	Promotes inflammasome activation; induces HSC activation; stage-specific expression in disease	[16,20]
PSMD14	IRE1α, MMP-9, FASN	Endoplasmic reticulum stress, ECM degradation, Lipid metabolism	MAFLD, MASH, Liver Fibrosis	Regulated by deubiquitination modification; stage-specific function in disease; positively correlated with	[11,12,20]

				the degree of fibrosis	
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Note: Data in the table are integrated from clinical samples, cell models and animal model studies, covering major non-neoplastic liver disease stages such as MAFLD, MASH and liver fibrosis, clearly showing the regulatory targets, pathways and core research conclusions of each subtype, providing a reference for subsequent mechanism research and clinical application.

5.1. Exploration of diagnostic biomarkers

Early diagnosis and progression monitoring of non-alcoholic fatty liver disease (NAFLD) face major challenges, and there is an urgent need to develop reliable non-invasive biomarkers. Current research focuses on serum markers, tissue proteasome activity detection techniques and multi-omics integration strategies to improve disease stratification and prognostic assessment capabilities.

5.1.1. Potential of serum PSMD subtypes as markers for NAFLD progression

There is currently no direct evidence supporting serum PSMD subtypes as biomarkers for NAFLD. However, many studies emphasize the urgency of exploring novel circulating markers. NAFLD is highly heterogeneous, and precise tools are lacking for predicting its progression to cirrhosis or hepatocellular carcinoma [32,34]. In proteomic studies, analysis of plasma samples from patients with progressive NAFLD has identified changes in protein expression profiles associated with steatohepatitis and fibrosis stages, which may reflect the molecular characteristics of disease progression [16]. In addition, exosomal protein analysis shows that specific proteins in extracellular vesicles are associated with fibrosis progression and are expected to be markers for predicting liver-related events [43]. Notably, some studies have proposed circulating microRNAs such as let-7d-5p as diagnostic markers for NAFLD, whose expression levels are significantly reduced in patients with steatosis, and receiver operating characteristic (ROC) curve analysis confirms their diagnostic value [44,45]. Commonly used non-invasive clinical detection techniques such as ELF test and VCTE can assess fibrosis degree, but have insufficient sensitivity to early PSMD-related molecular changes [79,80,81], further highlighting the necessity of developing new markers.

5.1.2. New technologies for hepatic tissue proteasome activity detection

There are currently no specific technical reports directly targeting hepatic tissue proteasome activity detection. However, relevant studies point out that multi-omics analysis of liver biopsy samples can reveal the molecular characteristics of disease progression. Analysis of liver tissue transcriptomes from pediatric NAFLD patients can identify gene expression patterns associated with disease progression [18]. Spatial transcriptomics technology can locate differentially expressed genes in steatotic areas, providing a new perspective for understanding local microenvironmental changes [46]. Although there is no specific technical description for proteasome activity, these high-throughput methods lay the foundation for developing novel activity detection strategies based on tissue samples.

5.1.3. Multi-Omics integration strategy for biomarker discovery

Multi-omics integration has become a core strategy for discovering NAFLD biomarkers. A large-scale proteomic study of progressive NAFLD, combining plasma proteome and liver transcriptome data, mapped a protein-transcript association profile

of steatohepatitis and fibrosis stages, and identified circulating proteins dynamically related to disease progression [16]. By integrating genome, transcriptome and clinical data, researchers constructed a NAFLD progression prediction model based on key genes, which shows strong robustness and diagnostic accuracy [19]. At the genetic level, genome-wide association studies (GWAS) have identified gene variants such as PNPLA3 I148M and TM6SF2 E167K that are significantly associated with NAFLD susceptibility and fibrosis risk [22,47,48,76,77,78]. These multi-omics data not only reveal disease mechanisms but also provide a basis for developing comprehensive prediction models including genetic, transcript and protein markers [49,84]. Meanwhile, HSD17B13 gene variants can reduce fibrosis risk, providing new targets for biomarker development [71,72,82,83].

5.2. Development of therapeutic targets and intervention strategies

PSMD subtype-selective inhibitors show potential in the treatment of liver diseases by targeting and regulating specific proteasome subunits. Studies have found that targeting PSMD-related subtypes can regulate the ubiquitin-proteasome pathway, promote the degradation of pro-fibrotic factors, thereby inhibiting HSC activation and ECM deposition [17]. The small molecule compound PPZ inhibits HSC activation through the proteasome pathway by promoting the ubiquitination degradation of YAP protein, significantly alleviating liver fibrosis [44]. Intervention targeting the 3BP2/SYK axis can inhibit proteasome-mediated inflammatory signal transduction, improving chronic hepatitis and fibrosis [50]. These subtype-selective inhibitors provide new strategies for hepatoprotection by restoring proteasome homeostasis and reducing oxidative damage and inflammatory responses [44,50].

Proteasome activators are of great value in fibrosis reversal by enhancing proteasome activity and improving protein homeostasis imbalance. Experiments show that drug combination therapy can significantly restore proteasome function, reducing steatosis, fibrosis and hepatocyte death in NASH models [50,51]. As a proteasome function regulator, overexpression of JOSD1 can alleviate liver injury by stabilizing proteasome activity, while inhibition of JOSD1 exacerbates injury [52,85]. In a pulmonary fibrosis model, low-dose bortezomib alleviates fibrosis through non-proteasome inhibitory pathways, suggesting that activator design should avoid off-target effects [53,54]. Future research needs to focus on developing drugs that specifically activate the 20S core particle or immunoproteasome to precisely regulate the degradation of fibrosis-related proteins [46,55].

Combination therapy significantly enhances anti-fibrotic efficacy by synergistically targeting the proteasome and metabolic pathways. Berberine induces HSC ferroptosis by activating UPS, while regulating lipid metabolism, significantly alleviating liver fibrosis [21]. Nanocarriers combined with targeted HSP47 gene silencing and ferroptosis induction effectively promote the apoptosis of activated HSCs and inhibit collagen deposition [56]. Liver-targeted nanoparticles loaded with pirfenidone reduce inflammation and fibrosis by enhancing proteasome regulation of the TGF- β /Smad pathway while inhibiting PI3K/AKT/mTOR signaling [57,58,67]. The herbal component SEPJ inhibits hepatocyte epithelial-mesenchymal transition (EMT) and HSC activation by synergistically activating the Akt/GSK3 β /Nrf2 antioxidant pathway and regulating proteasome function [48]. Pemigatinib improves liver fibrosis and secondary osteodystrophy by blocking FGF23-mediated liver-bone axis signaling, highlighting the potential of cross-organ pathway synergy [59]. The combination of

FXR pathway modulators and proteasome regulation also shows good application prospects [86].

5.3. Current challenges and future directions

The regulatory mechanism of the PSMD family in liver diseases has significant tissue-specific differences, and current research has not fully clarified its unique mode of action in the liver microenvironment. During HSC activation, the regulatory mechanism of UPS differs from that in other organs [61,62,63]. The expression level of TAp63 in HSCs is positively correlated with fibrosis stage, but its role in other cell types such as hepatocytes is unclear [61]. The specific expression of molecules such as PCDH7 in HSCs suggests a unique regulatory network for liver fibrosis, but its cross-tissue conservation still needs verification [62,63]. Existing animal models cannot fully simulate the complex pathological process of human NAFLD. The inflammation and fibrosis phenotypes of PNPLA3 I148M mutant mice differ from human disease progression [64]. Studies of hereditary NAFLD families indicate that animal models cannot cover the genetic heterogeneity of human diseases [65,66]. Proteasome inhibitors can alleviate fibrosis in animal models, but are limited in clinical trials due to toxicity or insufficient efficacy, highlighting the challenges of translational medicine [67,68].

Single-cell RNA sequencing technology reveals the heterogeneity of hepatocytes and non-parenchymal cells in NAFLD. Macrophage subsets are significantly enriched during fibrosis and are related to the PSMD-mediated protein degradation pathway [69,70]. In the PNPLA3 I148M model, myeloid cells and Kupffer cells are key drivers of disease progression [64]. HSD17B13 gene variants reduce fibrosis risk by affecting lipid droplet metabolism, and their effects are heterogeneous among hepatocyte subsets [71,72]. The treatment of liver fibrosis faces the problem of low efficiency of drug targeted delivery. Nanocarriers can specifically target activated HSCs, enhance the intrahepatic accumulation of pirfenidone and regulate the PI3K/AKT/mTOR pathway [67]. Existing delivery systems lack selective recognition of PSMD subtypes, have cross-species differences in delivery efficiency, and multi-cellular interactions increase targeting difficulty [60,73,74]. Future optimization of targeted delivery systems is needed by combining technologies such as exosome vectors [60].

5.4. Summary and discussion

As a core component of the ubiquitin-proteasome system, the PSMD family plays a key role in the pathological process of non-neoplastic liver diseases. This review systematically elaborates the molecular mechanism, diagnostic value and therapeutic potential of the PSMD family in the progression from NAFLD to liver fibrosis. At the level of pathological mechanism, the PSMD family participates in abnormal lipid accumulation by regulating the degradation of lipid metabolism-related proteins. Proteasome dysfunction aggravates oxidative stress and promotes inflammasome activation [69,75]. Meanwhile, it mediates the imbalance of ECM protein metabolism during HSC activation, interacts with the TGF- β /Smad pathway to amplify pro-fibrotic signals, and genetic factors can synergistically exacerbate this process [76,77,78].

In the diagnostic field, serum PSMD subtypes have the potential as non-invasive markers to reflect the trajectory of NAFLD progression to liver fibrosis, and multi-omics integration strategy is the future direction to improve diagnostic accuracy. At the level of therapeutic development, PSMD subtype-selective inhibitors can alleviate

liver injury, proteasome activators have application value in fibrosis reversal, and combined intervention strategies show better therapeutic prospects.

Future research needs to break through the technical bottlenecks of single-cell analysis and targeted delivery, focus on clarifying the impact of gene-environment interactions (such as diet and ultra-processed food intake [87]) on PSMD function, and verify the prognostic value of new biomarkers in longitudinal cohorts [88,89]. Targeting the PSMD family provides a new idea for intervening non-neoplastic liver diseases, but its clinical translation still needs to overcome core challenges such as mechanism complexity, diagnostic accuracy and delivery technology, ultimately providing new theoretical and experimental support for the precise diagnosis and treatment of non-neoplastic liver diseases.

6. Conclusions

In summary, through systematic sorting and summarization of relevant studies on the PSMD family in non-tumor liver diseases, this review clarifies that as the core regulatory component of UPS, the PSMD family plays a multi-dimensional and synergistic regulatory role in the pathological processes of non-tumor liver diseases such as MAFLD/MASH and liver fibrosis. It not only provides a new perspective for analyzing the molecular mechanism of non-tumor liver diseases, but also provides new targets and ideas for the precise diagnosis, targeted therapy and prognosis evaluation of diseases. Although there are still many deficiencies in current research, with the continuous development of research technologies and in-depth research, it is expected to further clarify the precise regulatory mechanism of the PSMD family, promote its clinical transformation and application, provide new strategies for the diagnosis and treatment of non-tumor liver diseases, improve the prognosis of patients with chronic liver diseases, fill the gap in the field of precise diagnosis and treatment of non-tumor liver diseases, and lay a solid foundation for subsequent related research.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Author Contributions

Study conception and design: NWC, XQ, LRD, SYH. Collection of literature: NWC, XQ, WK, SY, JYD, LRD. Analysis and interpretation of literature: All authors. Drafting of manuscript: NWC, SYH. Critical revision: All authors. Guarantor of article: SYH. All authors approved the final version of the article, including the authorship list.

Consent for Publication

All authors have read and approved the final manuscript for submission and publication.

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