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Review

The role of PSMD9 in human disease: future clinical and therapeutic implications

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Abstract: PSMD9 was first characterized as a component of the PA700 proteasomal regulator, and was found to stimulate association of PA700 with the catalytic 20S proteasomal core to form the active 26S proteasome. It was also independently identified under the name "bridge-1" as a transcriptional co-activator that modulates function of the transcription factors PDX-1, E12, and E47, and interacts with the co-activator histone acetyltransferase p300. Here, we discuss the molecular and genetic data linking PSMD9 to a diverse range of conditions including diabetes, cancer, mental health problems, polycystic ovary syndrome and neurodegenerative diseases, and thereby highlight its potential as a therapeutic target in these multiple settings.

Keywords: PSMD9; proteasome; bridge-1; PDX-1; NF-κB

1. Introduction

PSMD9 (26S Proteasome Non-ATPase Regulatory Subunit 9; also known as bridge-1, p27 or Rpn4) is a 25kDa protein encoded by the *PSMD9* gene on chromosome 12q24.31-q24.32. Also known in humans as p27 (not to be confused with $p27^{KIP1}$), the protein is highly conserved in model organisms such as rodents (in which it is often referred to as bridge-1), yeast (nas2) and nematodes (PSMD9). PSMD9 is ubiquitously expressed in mammalian cell types and appears to be at particularly high levels in lymphatic, endocrine, kidney, and skin epidermis tissues [1].

PSMD9 was first characterised though its interaction with the proteasomal chaperones PSMC6 and PSMC3, with which it forms a complex that modulates the assembly of the 26S proteasome from the constituent 20S catalytic and 19S (PA700) regulatory subunits (Figure 1) [2]. In addition to this proteasomal role, it is also apparent that PSMD9 has a separate role as a transcriptional co-regulator

although this role was first described under the alternative name of bridge-1. PSMD9 regulates gene expression of specific target genes by binding of its PDZ domain to the transcription factors PDX-1, E12 and E47 [3,4]. A comprehensive 3D structure of PSMD9 is yet to be elucidated but analyses of the secondary structure have revealed the presence of a unique PDZ domain, a motif associated with specific protein-protein interactions, and it is assumed that this motif underpins both functional roles. The regulatory impact of PSMD9 on both proteasomal activity and transcription remains unclear. The ubiquitin/proteasome pathway is the main non-lysosomal route for intracellular protein degradation and is responsible for the turnover of > 80% of cellular proteins [5]. Despite its role in proteasome assembly, it is unknown whether changes in PSMD9 expression impact on overall proteasomal activity, although it has been reported that PSMD9 mediates the specific proteasomal degradation of IκBα leading to regulation of NF-κB signalling [6]. Similarly, the range of transcriptional targets for the transcriptional co-activator role of PSMD9 is unknown, with experimentally confirmed targets limited to the insulin gene at this time [4]. PSMD9 has, however, been linked with a wide range of human diseases and may, in some contexts, present a novel therapeutic target.

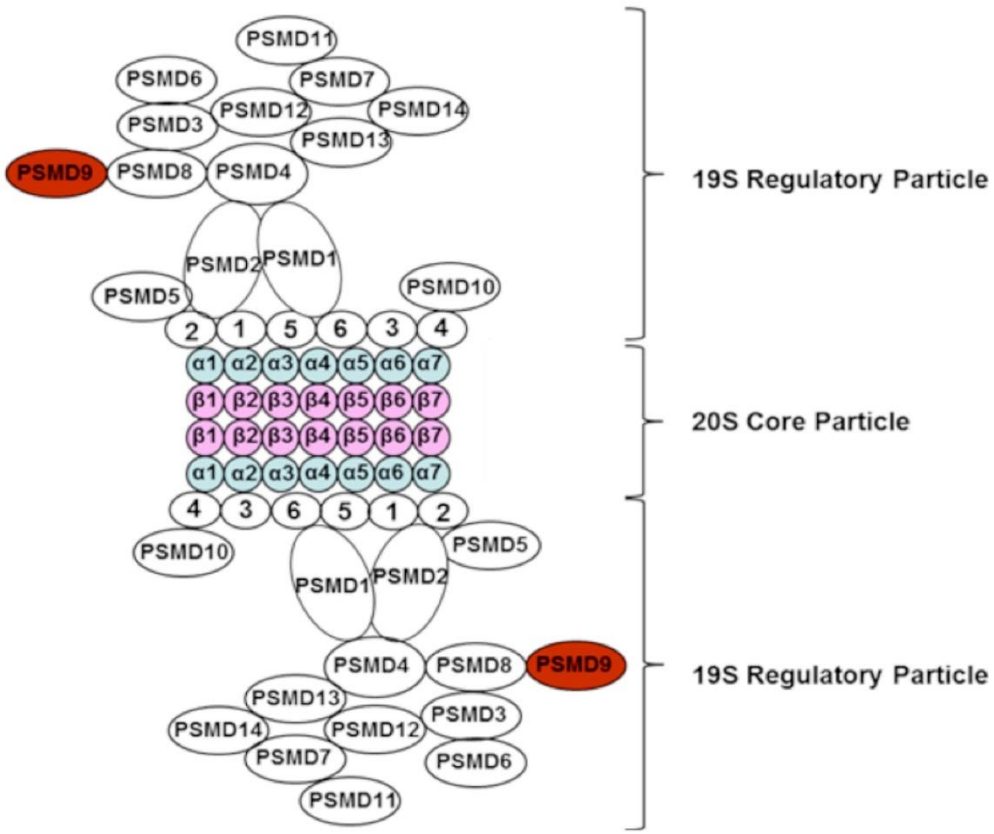

Figure 1. The 26S proteasome. PSMD9 is a constituent of the 19S regulatory, non-ATPase, particle that binds to the 20S core particle to assemble the complete 26S complex.

2. PSMD9 in cancer

Banz et al. were the first to comment on the potential relevance of PSMD9 in cancer [7]. They demonstrated that treatment of breast cancer cell lines with the TGFβ family ligand Activin A stimulated PSMD9 expression together with increased levels of the signal transduction proteins Smad2,

Smad3, and Smad4. PSMD9 knock-down was also associated with decreases in the levels of these Smads, implicating PSMD9 in the transmission of Activin A signalling through the regulation of Smad proteins. Activin A has roles in various potentially cancer-related pathways including those controlling inflammation, immunity, wound repair [8] and glucose metabolism [9], and has been implicated in pro- and anti-carcinogenic roles in several tissue types [10–12]. The team concluded that PSMD9 is a potential regulator of cell cycle progression. Further to this, we have recently published that low expression of PSMD9 within breast cancer tissues significantly associates with reduced incidence of local recurrence in patients receiving adjuvant radiotherapy but not in those treated without [13]. There is currently no standardized methodology by which to assess the radio-sensitivity of a tumour before treatment, although potential molecular markers have been reported, including p53 [14], Bcl-2 [15] and survivin [16]. Notably, we used a clinically routine immunohistochemistry methodology for our assessment, therefore identifying PSMD9 as a clinically-translatable biomarker of radiotherapy response. We also showed that *in vitro* depletion of PSMD9 in breast cancer cell lines acts to sensitize cells to radiotherapy, indicating that PSMD9 may have a direct role in cellular response to radiotherapy and may represent a novel target for radio-sensitizing drugs. As yet, it is unclear whether this influence of PSMD9 relates to its role in the proteasome or as a transcriptional co-regulator, however data showing the proteasome inhibitor Bortezomib to induce similar radio-sensitization [17] imply it may be the former.

3. PSMD9 in type II diabetes

3.1. Genetics

Genome-wide linkage studies have identified a type 2 diabetes (T2D) locus called "non-insulin-dependent diabetes mellitus" *(NIDDM)* 2 [18,19]. The *PSMD9* gene lies within the *NIDDM2* locus and SNPs within the *PSMD9* gene have been linked to the onset of T2D [20,21]. In a fine-mapping study Gragnoli and Cronsell performed direct sequencing in 237 Italian T2D patients and uncovered four rare *PSMD9* mutations/variants that were associated with the disease [21]. Significant linkage of the *PSMD9* SNPs rs74421874, rs3825172 and rs1043307/rs2514259 was later identified in late onset T2D [20] as well as early-onset T2D/maturity-onset diabetes of the young (MODY) type 3 [22] in Italian families. These *PSMD9* SNPs have also been significantly linked to particular pathological features of this disease including T2D-neuropathy [23], microvascular [24] and macrovascular pathology [25] and hypertension [26]. The impact of these SNPs on PSMD9 function or expression has not yet been determined.

3.2. Pathogenesis

Thomas et al demonstrated that PSMD9 interacted with the basic helix-loop-helix (BHLH) transcription factors E12 and E47 via its PDZ domain and increased activation of enhancers of glucose-response within the insulin promoter. Functional investigations showed that increased expression of PSMD9 promoted pancreatic β-cell survival *in vivo* [4,27,28] whereas decreased expression of endogenous PSMD9 in rat insulinoma (INS-1) cells diminished insulin promoter activity suggesting that reduced expression of this protein may be linked with diabetes development [4]. In contrast, Volinic et al. found that increased expression of pancreatic PSMD9 led to insulin deficiency and diabetes in a murine model, and proposed a biphasic pattern of insulin promoter activation to explain

their findings [29]. They showed that increasing levels of exogenous PSMD9 resulted in a shift from transcriptional activation to repression of the insulin promoter, and suggested that this may be the result of an incremental dosage effect in which increased levels first promote but then uncouple the optimal stoichiometric assembly of transcriptional regulatory complexes [29]. This suggested that individuals with reduced or augmented PSMD9 expression levels could be at an increased risk of diabetes and that modulation of this molecule may provide an effective therapeutic strategy.

It is now established that the inflammatory response is a major contributing pathway in both the development and progression of T2D. Chronic inflammation is triggered by the metabolic stress associated with hyperglycaemia in pancreatic islets that may lead to defective insulin secretion or response [30]. A study by Liu et al. into the role of the proteasome in diabetes demonstrated that the production of oxidative species due to hyperglycaemic conditions in diabetic models led to an increase in proteasome function in a PA700 dependant manner and that this caused subsequent activation of NF-κB [31], providing a further pointer for a mechanism of PSMD9's influence as both a component of the PA700 complex and a known regulator of NF-κB.

4. PSMD9 in mental health disorders

4.1. Genetics

Major depressive disorder (MDD) and generalised anxiety disorder (GAD) are the most prevalent mental health disorders in the UK, with approximately 1 in 5 people affected by these disorders in their lifetime. Familial connections have been indicated in these conditions, with heritability values of 30–40% [32]. Similarly, the rarer condition of Schizophrenia (SCZ), which affects approximately 1 in 100 individuals during their lifetimes [33], has a remarkably high heritability value of up to 80% [34], suggesting strong genetic contributions to the pathogenesis of these mental health illnesses. In addition, frequent connections have been made between T2D and mental health issues, with each an established comorbidity of the other [35,36]. Due to this, Gragnoli et al. further investigated the *PSMD9* SNPs from their previous T2D studies and found that rs74421874, rs3825172 and rs1043307/rs2514259 were also significantly associated with both GAD [37] and MDD [38] development in T2D backgrounds. In support of this, a number of other studies have also linked *PSMD9* SNPs to mental health disorders [39–41]. A number of *PSMD9* SNPs has also been demonstrated to associate with individuals with clinically diagnosed cases of SCZ [41] and MDD [40]. Furthermore, *PSMD9* rs1043307 has been correlated with a more positive response to tricyclic antidepressants [39]. This study predicted a link between PSMD9 and BHLH transcription factor binding pathway, again suggesting a possible transcriptional co-activator role for the protein, this time in the context of mental health. These data suggest that SNPs in *PSMD9* may be used to identify individuals with increased risk of developing MDD or GAD in T2D patients or SCZ in the general population.

4.2. Pathogenesis

A definitive understanding of the molecular pathogenesis of these mental health disorders remains frustratingly evasive. Current theory focuses on dysregulation of various important proteins within the brain including stress hormones, cytokines and monoamines which may lead to decreased neuronal activity or inappropriate activation of inflammatory pathways [42–45]. In particular, a decrease in the expression of several specific proteins has been associated with SCZ with the most prominent example

being the protein dysbindin [46–49]. Han et al. recently demonstrated that PSMD9 and dysbindin could be co-immunoprecipitated from mouse neuronal tissue [50], a direct interaction that supports a role for PSMD9 analogous to that previously discussed with respect to the degradation of Iκβα, in which PSMD9 may act to enhance delivery of dysbindin to the proteasome for degradation. Similarly, as part of their study into antidepressant treatment response, Wong et al. proposed that the *PSMD9* SNP rs1043307 may be associated with a change in antigen processing or degradation that may lead to an alteration in the immune response of those individuals who responded more positively to anti-depressant treatments in comparison to those who do not [39]. Gragnoli et al. added to this with the suggestion that PSMD9, as a component of the 26S proteasome, may be involved in the immune-tolerance checking process [38] and dysregulation of this pathway through changes in proteasome-associated PSMD9 may lead to an autoimmune response that could trigger these mental health conditions.

5. PSMD9 in other diseases

5.1. Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age. Polycystic ovaries are generally enlarged and contain multiple follicles that do not undergo cyclic luteal differentiation, increasing infertility rates. Previous to their described work in breast cancer, Banz et el. examined PSMD9 function in ovary cells [51]. They performed *in vitro* experiments treating granulosa cells with activin A, and showed the same trends as those in cancer cells, with an increase in PSMD9 levels following activin A treatment and a decrease in Smad levels following PSMD9 knock down. The team suggested that PSMD9 may perform a regulatory role in granulosa cell proliferation and differentiation. Interestingly, PCOS demonstrates frequent correlations with T2D [52] and in many women raised levels of testosterone are indicative of the condition, which is reportedly triggered by hyperinsulinemia following a reduction in insulin sensitivity [53]. Therefore, through its relationship with the insulin signalling and activin A pathways, it is plausible that PSMD9 may become a potentially interesting new target in the treatment of PCOS and associated infertility, once data in humans with these disorders have been established.

5.2. Neurodegeneration

PSMD9 has been associated with a group of chronic neurodegenerative diseases broadly termed synucleinopathies, which include Parkinson's disease and multiple system atrophy [54]. These diseases are characterised by the presence of amyloid fibrils containing α-synuclein (α-Syn) in neuronal cells [55–57]. Over-expression of α-Syn in the dopaminergic neurons of the model organism *C. elegans* resulted in an up-regulation of PSMD9 expression [58]. The authors conclude that proteasome-associated PSMD9 is likely to be a component of the α-Syn degradation pathway that may have an important role in all synucleinopathies. Indeed, proteasomal disruptions have been strongly implicated in the formation of α-Syn aggregates [59,60] and although the mechanisms remain unclear, depletion of the 26S proteasome in transgenic mice has led to the development of Parkinson's disease-like symptoms [61]. Further to this, aggregation of α-Syn is attributed to misfolding of the protein and Sangith et al. speculated that PSMD9 may have the capacity to perform quality control of protein misfolding. They suggest that proteasome associated PSMD9 located on the endoplasmic reticulum

would have the ability to bind directly to the C-terminal motifs of exiting proteins via its PDZ domain, offering a way to circumvent the ubiquitination pathway [62]. Interestingly, although α-Syn has traditionally been studied within the brain, this protein is also present in pancreatic beta cells where it is proposed to have a regulatory role in insulin secretion [63,64] and might well be involved in the development of T2D. Epidemiological data suggests that T2D may be a risk factor in the development of PD [65] and may be associated with a more severe form of the disease [66] and, although conclusive data are limited, it has been suggested that 50–80% of PD patients may have abnormal glucose tolerance [67,68]. Through its association with metabolism and proteostasis PSMD9 may therefore provide a novel avenue of research for ageing related neurodegenerative diseases.

6. Conclusions

PSMD9 is a component of the 26S proteasome; a mediator of protein turnover, and has been shown to act as a transcriptional co-activator. PSMD9 has been associated with the pathogenic pathways of several important human disorders. Commonalities in the pathways regulating these disorders include changes in insulin secretion, alterations in protein turnover and immune dysregulation. Here, we suggest that targeting PSMD9 might be a novel therapy for the treatment of a range of diseases.

Conflicts of interest

All authors declare no conflicts of interest in this paper.

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