Role of PDC-109 As A Specific Seminal Plasma Protein in Regulating Bull Fertility

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Abstract. PDC-109, also known as Binder of Sperm Protein 1 (BSP1), is the primary protein found in bovine seminal plasma and is critical in bull fertility. It is essential for sperm capacitation, motility, and interaction with the egg. After ejaculation, this protein binds to the plasma membrane of sperm, altering its lipid composition and increasing membrane fluidity—an important step for successful fertilization. Additionally, it aids in sperm adhesion to the oviductal epithelium, helping form a sperm reservoir and extending sperm viability. Recent studies suggest that PDC-109 may also influence immune responses in the female reproductive tract, potentially enhancing fertilization and development of early embryonic. However, prolonged exposure to this protein, especially during cryopreservation, has been linked to sperm membrane destabilization due to cholesterol efflux. This dual role—enhancing fertility while potentially compromising membrane integrity—emphasizes the need for further research. PDC-109 has also been proposed as a biomarker for male fertility assessment, as its constituent in seminal plasma have correlated with fertility variations in bulls. Despite these insights, the precise mechanisms by which PDC-109 interacts with sperm membranes and reproductive tissues remain unclear. Future research should focus on unraveling these pathways, which could lead to improved fertility management strategies in cattle breeding and the refinement of cryopreservation techniques. In conclusion, PDC-109 is a key component of bovine reproductive physiology, significantly influencing sperm function and fertilization. Further exploration of its biochemical pathways and potential applications could enhance reproductive efficiency in bulls.

1 Introduction

Bull fertility is a critical factor in the success of cattle breeding programs, as the primary income for cow-calf producers depends on the number of calves born each year [1,2]. Poor

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reproductive performance is a significant reason for culling beef cows, and increasing the reproductive rate by even a modest 3% increase in the reproductive rate could result in one million more beef calves annually in American herds [3]. Infertility rates in bulls are estimated to be between 15-25% in the United States, making fertility one of the most important traits in bulls [2]. Genetic and environmental factors, such as health, nutrition, and management of cows and bulls, influence the fertility of bulls. Sound feet and legs are essential for bulls, as unsoundness can hinder movement and mounting for mating [4]. Sperm quality is also crucial, and bulls in temperate regions with large, robust testes and no noticeable epididymal abnormalities are expected to produce healthy semen [5]. It is recommended that breed soundness examinations be performed annually and 30 to 60 days before the breeding season to allow sufficient time to replace any bulls that are unsuitable for breeding. [6,7]. Selecting against haplotypes harboring lethal alleles in conjunction with improving female fertility can also improve male fertility [8]. A sound program for maintaining herd health is essential, especially for bulls, as it can decrease or eliminate the likelihood of transferring illnesses resulting in reproductive failure in females during various stages of production [9]. Many tissue-specific proteins are found in seminal plasma, a protein-rich fluid produced by several male reproductive system organs. Information on male reproductive health is profoundly revealed by the seminal plasma proteome [10]. Seminal plasma proteins (SPPs) play a crucial role in multiple stages of reproduction, including sperm maturation, capacitation, the acrosome reaction, sperm-egg recognition, and fusion, as well as the cortical reaction and oocyte activation [11,12]. While some SPPs have well-defined functions, the roles of many others remain unclear [13]. Beyond facilitating sperm transport, these proteins are also essential for sperm protection and maturation [14]. Additionally, SPPs contribute to various physiological processes related to male reproduction, such as immune modulation, protease inhibition, and lipid metabolism [15].

Proteomic analysis of seminal plasma has been widely employed to identify potential protein biomarkers associated with bull fertility, recognizing the essential role of proteins in sperm physiology [16,17]. However, the functional properties of many seminal plasma proteins remain only partially understood. A proteomic study utilizing liquid chromatography-mass spectrometry (LC-MS/MS) identified 94 seminal plasma proteins, underscoring their potential involvement in fertility regulation [18]. Among these, PDC-109—also referred to as Binder of Sperm Protein 1 (BSP1)—is the predominant protein in seminal plasma of bovine and is linked to bull fertility. Interestingly, one study found that PDC-109 was more abundant in sperm from bulls with lower fertility, though its specific role in fertility regulation remains unclear [19]. While seminal plasma proteins play a significant role in reproductive function, bull fertility is influenced by various other factors, including genetic predisposition, environmental conditions, seasonal variations, nutrition, structural integrity, and overall health status [2,20,21]. Therefore, optimizing bull fertility requires a comprehensive approach that accounts for multiple determinants, including seminal plasma proteins such as PDC-109 [22]. PDC-109 (BSP1) is a major component of bovine seminal plasma and plays a pivotal role in fertility. PDC-109 is structurally composed of two fibronectin type II (Fn2) domains, which interact with lipid head groups via cation–π interactions. Moreover, it functions as a chaperone, assisting in the stabilization of target proteins under stressful conditions [23]. Present at concentrations of approximately 15–20 mg/mL, PDC-109 constitutes nearly 60% of the total protein content in bovine seminal plasma [23,24]. his protein exists in two isoforms: a glycosylated form (BSP-A1) and a non-glycosylated form (BSP-A2) [25]. Synthesized by the seminal vesicles, PDC-109 binds to choline-containing phospholipids on the plasma membrane of sperm. This interaction facilitates its integration into the membrane's hydrophobic region, inducing instability and promoting lipid efflux—processes that are critical for sperm capacitation [22].

Through its involvement in sperm motility, capacitation, and fertilization, PDC-109 plays a pivotal role in bovine reproduction. Further research into its molecular mechanisms and potential applications may offer valuable insights for enhancing bull fertility.

2 Structure and Function of PDC-109 Protein

2.1 Description of The Biochemical Properties of PDC-109

PDC-109, also referred to as Binder of Sperm Protein 1 (BSP1), is a predominant protein in bovine seminal plasma that serves multiple physiological roles. This multimeric, polydisperse, and self-associating molecule is integral to several reproductive processes, including the regulation of sperm motility, the establishment of the oviductal sperm reservoir, modulation of sperm capacitation, and initiation of the acrosome reaction [23]. Following ejaculation, PDC-109 adheres to the sperm surface, inducing structural modifications in the membrane and promoting the efflux of cholesterol and choline phospholipids—an essential step in the activation of sperm [26]. A fundamental function of PDC-109 is the removal of endogenous phospholipids, such as phosphatidylcholine and sphingomyelin, which contain mono- and di-unsaturated fatty acids, from epididymal sperm cells [27]. This lipid remodeling process plays a critical role in membrane of sperm reorganization, which is necessary for successful capacitation and fertilization.

Structurally, PDC-109 consists of two fibronectin type II (Fn2) domains, each capable of interacting with lipid head groups through cation–π interactions [23]. Additionally, PDC-109 exhibits chaperone-like properties, helping to stabilize target proteins under various stress conditions. The protein consists of two structurally identical domains, containing 38 and 41 amino acids, respectively, and each domain is stabilized by two disulfide bonds. The full amino acid sequence of PDC-109, comprising a total of 109 residues, has been identified [26].

In addition to its involvement in capacitation, PDC-109 also plays a role in regulating sperm motility. In vitro studies have shown that exposure to PDC-109 influences ion-pumping activity, specifically affecting Ca^{2+}-ATPase function in bovine sperm membrane preparations [28]. These results indicate that PDC-109 is essential for maintaining sperm physiology, highlighting its significance in bovine fertility.

2.2 PDC-109 Binding Properties and Interaction with Sperm Membranes

Upon ejaculation, PDC-109 selectively binds to choline-containing phospholipids on the plasma membrane of sperm, altering its biophysical properties and enhancing sperm motility (Thomas et al., 2003a; Sánchez-Luengo et al., 2004). This binding occurs through a specific one-step mechanism, where PDC-109 interacts directly with phosphatidylcholine, a major membrane phospholipid [29] (Thomas et al., 2003a).

Beyond its role in membrane binding, PDC-109 is also essential for capacitation and fertilization. It facilitates cholesterol efflux from the sperm membrane, a critical step in capacitation, and contributes to sperm reservoir formation by interacting with the oviductal epithelium [23,30,31]. Structural analyses reveal that PDC-109 stabilizes its attachment to the sperm membrane through cation–π interactions with choline lipids [32]. Moreover, surface plasmon resonance studies have demonstrated its strong affinity for phosphatidylcholine over other phospholipids, confirming its specificity for choline-containing membranes [22].

The effects of PDC-109 on membrane structure and lipid organization have been extensively studied. Electron spin resonance (ESR) measurements have been employed to analyze its impact on both model lipid vesicles and biological membranes, such as those in

epididymal sperm [33]. Additionally, surface plasmon resonance techniques have provided insights into the mechanisms governing its membrane interactions [34].

Overall, PDC-109 exhibits multifunctional and polydisperse properties, playing a crucial role in sperm function and fertilization. Its interactions with sperm membranes remain a significant area of research, with ongoing studies further elucidating its role in reproductive physiology.

2.3 PDC-109's Function in the Capacitation and Motility of Sperm

PDC-109 is a predominant secretory protein produced by the seminal vesicles in bovines. It plays a crucial role in sperm function by binding to the midsection of spermatozoa and inducing modifications in surface proteins, leading to cholesterol efflux from the membrane. These changes alter the biophysical properties of the sperm plasma membrane, ultimately enhancing sperm motility [28]. As a polydisperse, multimeric, and self-associated molecule, PDC-109 interacts with the sperm membrane, causing structural transformations in surface proteins and contributing to increased motility [23]. Collectively, evidence suggests that PDC-109 enhances sperm motility by modifying membrane dynamics and inducing conformational changes in sperm surface proteins.

Beyond its role in motility, PDC-109 functions as a molecular chaperone, preventing protein denaturation and aggregation [35]. It is also critical for sperm capacitation and fertilization by facilitating cholesterol removal from the sperm membrane, a process necessary for successful sperm-oviduct interactions and sperm reservoir formation [36]. Furthermore, this protein has been shown to restore the binding capacity of capacitated sperm to levels comparable to non-capacitated sperm, emphasizing its role in sperm function regulation [24].

In addition to aiding capacitation, PDC-109 promotes sperm-oviductal epithelial binding, which is believed to contribute to sperm reservoir formation within the reproductive tract. In vitro studies have demonstrated that its presence enhances the attachment of bovine spermatozoa to the fallopian tube epithelium, further supporting its role in the fertilization process. Since key fertilization events—such as sperm motility, capacitation, and the acrosome reaction—are regulated by intracellular calcium levels, PDC-109 likely plays a role in modulating these mechanisms to optimize sperm function [28].

2.4 PDC-109's Function in Binding to The Oocyte

PDC-109 binds to the surface of spermatozoa, specifically targeting the midpiece, allowing sperm to navigate and adapt to the dynamic environment of the female reproductive tract on its journey to the oocyte [23]. This interaction primarily occurs through PDC-109's specific affinity for choline-containing phospholipids in sperm membranes [34] Additionally, PDC-109 has been detected in the acrosomal membrane, particularly in the equatorial and post-equatorial regions of spermatozoa, suggesting a potential role in facilitating the sperm's penetration into the oocyte cytoplasm [31,37].

Despite its well-established involvement in sperm membrane interactions, direct evidence linking PDC-109 to sperm-oocyte binding remains limited. Most research has focused on its role in sperm membrane binding and the cascade of events leading to fertilization [38]. However, a study using electron spin resonance (ESR) measurements on both model lipid vesicles and epididymal membranes investigated how PDC-109 binding affects membrane structure and physical properties [33]. The findings suggest that PDC-109 influences the biophysical characteristics of the membrane, which may indirectly impact sperm's ability to bind to the oocyte.

2.5 PDC-109's Function in The Oviductal Sperm Reservoir

PDC-109 is essential for establishing the oviductal sperm reservoir by promoting sperm attachment to the oviductal epithelium [24]. This interaction helps sustain sperm viability and extends its presence in the female reproductive tract, thereby increasing the likelihood of successful fertilization. Additionally, PDC-109 facilitates sperm capacitation and induces the acrosome reaction, both of which are essential for fertilization (Table 1).

One of the key ways PDC-109 influences sperm function is by promoting cholesterol efflux from the plasma membrane of sperm. This alteration in membrane composition enhances capacitation and strengthens sperm binding to epithelium of the oviductal, supporting the formation of the reservoir of sperm [23]. During emission, as sperm travel through the vas deferens ampulla, PDC-109 selectively binds to the midpiece, modifying membrane biophysical properties and stimulating sperm motility [28].

Furthermore, PDC-109 interacts with heparin, a glycosaminoglycan present in the oviductal epithelium, potentially regulating various aspects of sperm activity [39]. Overall, PDC-109 is essential for sperm function, as it facilitates oviductal attachment, initiates capacitation and the acrosome reaction, promotes cholesterol efflux, and modifies membrane properties—all of which collectively enhance sperm readiness for fertilization [23,24].

Table 1. Effect of seminal plasma protein PDC-109 on sperm fertility

Effect	Description	Reference
Motility	Significantly increases sperm motility and enhances functional activity in the heparin. Extended exposure of spermatozoa to unconstrained it during processing may adversely impact the motility and function of the sperm.	[23,28,39]
Enzyme activity	Increases Ca (2+)-ATPase activity in epididymal plasma membranes of sperm.	[40,41]
Capacitation	It is a capacitation-inducing factor in bovine spermatozoa and promotes capacitation, binding to phosphorylcholine on sperm lipids.	[22,23,27,39,42,43]
Cryopreservation	Minimize negative effects, sperm membrane stability	[44]
Membrane structure	PDC-109 binding to membranes alters the lipid phase's morphology and physical characteristics. Interacts strongly with phosphatidylcholine and sphingomyelin, reducing membrane stability and facilitating lipid removal.	[33,45,46]
Sperm-oocyte binding	Interacts with phospholipids located on the surface of sperm cells and may modify several sperm activity factors, including binding to the epithelium of the oviductal and restoring binding to the level observed for capacitated sperm.	[38,39]
Acrosome reaction	The presence of heparin increases the proportion of acrosome-reacted spermatozoa	[47]
Antiviral Activity	Preventing viral infections could contribute to protection against sexually transmitted diseases; by attaching to membranes of viral and erythrocytes, thereby disrupting virus-cell interactions. [48,49]	

3 Effects of PDC-109 on Sperm Function

3.1 How PDC-109 Affects Sperm Lipid Composition and Membrane Fluidity

PDC-109, a key protein in bovine seminal plasma, plays a vital role in sperm capacitation by modulating the lipid composition and fluidity of sperm membranes [27]. Research has demonstrated that PDC-109 binds specifically to choline lipids on the sperm surface, facilitating the efflux of cholesterol and phospholipids. This process alters the biophysical properties of the membrane, ultimately enhancing sperm motility [28,50]. To better understand the effects of PDC-109 on membrane dynamics, a study using electron spin resonance (ESR) measurements examined the structural and physical properties of lipid phases in both model membranes (lipid vesicles) and biological membranes (epididymal). The results revealed that PDC-109 binding increases membrane fluidity in both systems [33]. Additionally, mass spectrometry analysis provided insights into the fatty acid composition of phospholipids expelled from epididymal sperm upon PDC-109 interaction, showing that the protein preferentially removes sphingomyelin and phosphatidylcholine, which are rich in mono- and di-unsaturated fatty acids [27].

The capacitation-inducing role of PDC-109 has also been evaluated in the presence and absence of heparin. Findings indicate that PDC-109 significantly influences sperm viability, motility, and membrane integrity, with its effects being more pronounced when heparin is present [34,39]. Overall, PDC-109 facilitates sperm capacitation by altering lipid composition and increasing membrane fluidity, which directly contributes to enhanced motility and functional maturity of sperm cells.

3.2 Potential Implications of PDC-109 on Sperm Survival and Fertilizing Capacity

PDC-109 plays a pivotal role in both the cryopreservation and fertilization processes of bovine sperm. Upon ejaculation, this protein binds to specific regions of the sperm surface, including the acrosome, post-acrosome, and midpiece [25]. Research indicates that extended exposure to PDC-109 during cryopreservation or its high concentrations in seminal plasma can disrupt the sperm membrane by inducing cholesterol efflux, potentially impairing sperm function [23].

PDC-109 plays a key role in improving sperm motility, promoting capacitation and the acrosome reaction, and supporting the establishment of the oviductal sperm reservoir [25]. Additionally, it serves as a capacitation-inducing factor, influencing sperm viability, motility, and membrane integrity [39]. Research investigating the removal of PDC-109 from ejaculates examined its impact on cryopreservation-induced damage. The findings suggested that eliminating PDC-109 could help mitigate its detrimental effects on sperm quality post-thawing [23].

Moreover, research has shown that adding PDC-109 back to capacitated sperm restores their binding ability to levels similar to uncapacitated sperm, indicating its role in preserving sperm functionality. Additionally, PDC-109 enhances the attachment of epididymal sperm to oviductal explants, further emphasizing its importance in sperm-oviduct interactions [24].

4 Implications in Fertility Diagnostics

A study analyzing sperm protein profiles in bulls with varying fertility levels found that PDC-109 isoforms were present in seminal plasma at significantly higher concentrations in bulls with lower fertility compared to those with higher fertility. These findings suggest that an imbalance between acidic and basic sperm proteins may regulate PDC-109 levels, and when its concentration exceeds a certain threshold, it could negatively impact sperm fertility [51].

Additionally, research has highlighted the lectin properties of PDC-109, the predominant protein in bovine seminal plasma, and its potential role in fertilization. This discovery opens

possibilities for its application in fertility diagnostics and treatment [38]. The interaction between PDC-109 and cholesterol has been shown to induce lipid efflux from sperm cells, suggesting a regulatory role in mammalian spermatogenesis [52].

Studies investigating the role of PDC-109 in sperm capacitation and the acrosome reaction have demonstrated that its interaction with sperm facilitates these processes. However, prolonged exposure to the protein has been found to have detrimental effects on spermatozoa. Furthermore, research indicates that removing PDC-109 from ejaculates after cryopreservation may improve sperm freezability and enhance in vitro fertilization potential, particularly in crossbred bulls [23].

As a key seminal plasma protein, PDC-109—also known as Binder of Sperm Protein 1—holds promise for applications in fertility assessment and treatment. Its role in cholesterol efflux could have significant implications for spermatogenesis, and strategies to modulate its levels may prove beneficial in improving sperm survival and function after cryopreservation.

5 Importance of Further Research on PDC-109

PDC-109 supports sperm capacitation by inducing the release of cholesterol and choline phospholipids, which are essential for membrane remodeling. It also selectively binds to choline phospholipids on the membrane of sperm [22]. In addition to its role in capacitation, PDC-109 demonstrates chaperone-like activity [36] has been found to interact with both heparin and sperm surface phospholipids [39].

Given its diverse functions, further research on PDC-109 is essential. Investigating the structural and biophysical properties of lipid membranes upon interaction with PDC-109 could provide deeper insights into its role in sperm physiology [33]. Additionally, exploring its interactions with heparin and sperm surface phospholipids may enhance our understanding of its broader significance in reproductive biology [39].

6 Conclusion

PDC-109 (Binder of Sperm Protein 1) is essential for bull fertility and reproductive processes. It facilitates sperm adhesion to the oviductal epithelium, and its absence may result in lower fertilization rates and compromised embryo development. Further studies are required to clarify the mechanisms and significance of PDC-109 in diagnosing male fertility. Gaining deeper insights into the intricate interactions during fertilization and embryonic development could aid in developing new treatments for bull infertility.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contribution statement

Rasyidah Mappanganro: Conceptualization, Methodology, Investigation, Writing- Original draft preparation. Herry Sonjaya: Data curation, Writing- Reviewing and Editing. Hasbi Hasbi: Visualization, Investigation, Writing- Reviewing and Editing. Muhammad Arsan Jamili: Visualization, Investigation, Writing- Reviewing and Editing. Nurlailah Mappanganro: Visualization, Investigation, Writing- Reviewing and Editing.

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