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MINI REVIEW

Physiological function of seminal vesicle secretions on male fecundity

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Abstract

Background: A mixture of spermatozoa and accessory gland secretions (from seminal vesicles, prostates, and coagulating glands) is ejaculated into the female reproductive tract at copulation. However, the physiological function of accessory glands on male fecundity remains unclear.

Methods: Publications regarding the physiological functions of male accessory glands were summarized.

Main findings (Results): The functions of accessory glands have been studied using male rodents surgically removed coagulating glands (CG), prostates (PR), or seminal vesicles (SV). CG-removed males are fertile or subfertile, while the fecundity of PR-removed males is controversial. SV-removed males show copulatory plug defects, leading to fewer sperm in the uterus and severe subfertility. TGM4, SVS2, and PATE4 were identified as essential factors for copulatory plug formation. When the sufficient number of epididymal spermatozoa was artificially injected into a uterus (AI method), they could efficiently fertilize oocytes, implicating that accessory gland secretions are not essential. Seminal vesicle secretions (SVSs) improved fertilization rates only when low numbers of spermatozoa were used for AI. The changes of uterine environment by SVSs could not improve the pregnancy rate.

Conclusion: Accessory gland factors are critical for copulatory plug formation and support sperm fertilizing ability.

KEYWORDS

artificial insemination, copulatory plug, male accessory gland, sperm fertilizing ability, uterine environment

1 | INTRODUCTION

Testicular spermatozoa are incapable of fertilizing eggs. Spermatozoa acquire their fertilizing ability (e.g., motility, capacitation, acrosome reaction, and sperm-egg fusion capabilities) during transition through the epididymis. At copulation, a mixture of cauda epididymal spermatozoa

and accessory gland secretions is ejaculated into the female reproductive tract. The accessory gland secretions mainly come from the seminal vesicles (SV), prostates, bulbourethral gland (also known as "Cowper's gland"), and urethral glands.¹ Specifically, men ejaculate 3–3.5 mL of semen into the female reproductive tract, which is mainly composed of secretions from SV (1.5–2.0 mL), prostates (0.5 mL), and

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bulbourethral gland and urethral glands (0.1 mL).² As summarized in Table 1, the role of accessory glands in male fecundity has been studied using mice and rats by surgically removing accessory glands individually. The prostate is composed of four regions (ventral, lateral, dorsal, and anterior regions), and the fecundity of males having undergone an anterior prostatectomy (also known as “coagulating glands”; CG) was either reduced^{3,4} or comparable to control males.⁵⁻⁷ The remaining regions in the prostate tightly adhere to the SV and urinary bladder,⁸ complicating surgical removal of each region. In fact, there are discrepancies between previous studies on the fecundity of male mice and rats with ventral and dorsal prostatectomies.^{3,5,9} Thus, the physiological function of these separate regions of the prostates on male fecundity remains unclear. There is no report on male fecundity after surgically removing the bulbourethral gland or urethral glands. When the SV of male mice and rats was surgically removed, the males become severely subfertile.³⁻⁷ Thus, the SV is thought to play a beneficial role in fertilization *in vivo*. Here, we mainly introduce the physiological function of SV on male fecundity at the molecular level based on recent finding.

2 | PHYSIOLOGICAL FUNCTIONS OF ACCESSORY GLAND SECRETIONS

2.1 | Copulatory plug

As one of the physiological functions of accessory gland secretions, copulatory plug formation is well known in several primates (e.g. chimpanzee) and rodents.^{10,11} Proteins from CG and SV are required for copulatory plug formation *in vitro*.¹² In fact, CG-removed male mice and rats show decreases in the copulatory plug weight, but these males are fertile or subfertile (Table 1).^{3,4,5,6,7} SV-removed males hardly make the copulatory plug (Figure 1 and Table 1), and these males become severely subfertile.^{3,4,5,6,7} We revealed that plug formation defects caused semen leakage from the vagina, resulting in a decrease in sperm numbers in the uterus and male fecundity (Figure 1).⁶ When the females without copulatory plugs after mating were immediately re-caged with other males, the females had subsequent productive matings.⁶ Thus, we concluded that the copulatory plug has the dual function of not

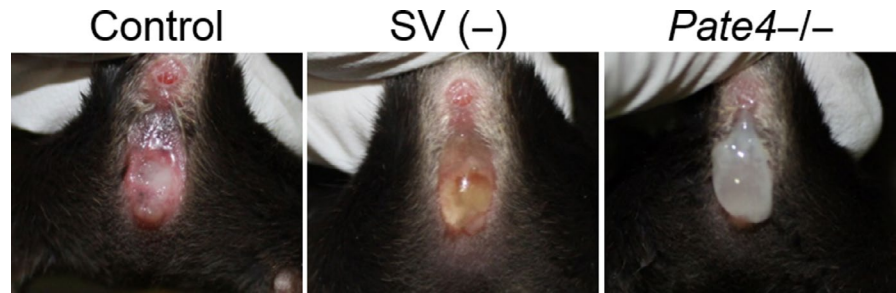
Reference	Treated	Pregnancy rate (%)	Litter size	Plug weight (mg)
Mouse				
Pang <i>et al.</i> ⁵	Control	73	9.4 ± 0.3	ND
	VP and DP (-)	38	9.8 ± 0.9	ND
	CG (-)	73	9.2 ± 2.8	ND
	SV (-)	7	4	ND
Peitz and Olds-Clarke ²⁸	Control	95.2 ± 1.9	8.3 ± 0.3	ND
	SV (-)	77.8 ± 5.1	8.0 ± 0.4	ND
Kawano <i>et al.</i> ⁷	Control	ND	13.6 ± 0.5	ND
	CG (-)	ND	9.6 ± 2.0	ND
	SV (-)	ND	0	0
Noda <i>et al.</i> ⁶	Control	1.4 ± 0.3 [#]	8.8 ± 2.0	43.5 ± 13.8
	CG (-)	1.5 ± 0.0 [#]	9.1 ± 2.4	21.6 ± 11.2
	SV (-)	0.6 ± 0.5 [#]	6.1 ± 3.7	3.5 ± 3.6
Rat				
Gunn and Gould ⁹	Control	61.4 ± 1.9	9.9 ± 0.4	ND
	DP (-)	58.4 ± 7.8	9.1 ± 0.4	ND
Queen <i>et al.</i> ³	Control	100	5.5 ± 0.5 ^{##}	ND
	VP (-)	100	5.3 ± 0.4 ^{##}	ND
	DP (-)	0	0	ND
	CG (-)	25	5.2 ± 1.6 ^{##}	ND
	SV (-)	0	0	ND
Carballada and Esponda ⁴	Control	N.D	14.8 ± 0.6	58.5 ± 3.7
	CG (-)	33.3	13.0 ± 4.6	14.2 ± 18.4
	SV (-)	N.D	0	0

TABLE 1 Fecundity of male mice and rats with accessory glands surgically removed

Note: Sham-operated males were used as the control.

Abbreviations: #, No. of litters/female/month; ##, Some data from Table 1 of Queen *et al.* [3] were used; (-), males with specified organ surgically removed; CG, coagulating gland; DP, dorsal prostate; N.D., not determined; SV, seminal vesicle; VP, ventral prostate.

FIGURE 1 Observation of vaginas immediately after mating. Sham-operated (control), seminal vesicle removed, and *Pate4* KO males were mated with wild-type females



only inhibiting sequential matings but to maintain spermatozoa in the uterus to ensure male fecundity, as a winner-take-all strategy to advance male reproduction.

In copulatory plug formation, it is thought that transglutaminase 4 (TGM4) from prostates and coagulating glands catalyze the formation of ϵ -(γ -glutamyl)lysine cross-bridges among seminal vesicle secretion 1 (SVS1) to SVS3 (Table 2).^{6,11,13-20} In fact, previous papers showed that single KO males of *Tgm4* or *Svs2* are subfertile due to plug formation defects.^{7,21} Lin *et al.* showed that the peptide sequence “QXK(S/T)” within SVS3 acts as the cross-linking sites by reacting of guinea pig liver transglutaminase with recombinant polypeptides from SVS3.¹⁶ SVS2 also contains this peptide sequence.⁶ Although SVS1 does not

contain the sequence “QXK(S/T),” Tseng *et al.* showed that two glutamine residues in SVS1 (Q²³² and Q²⁵⁴) were the major site for TGM4 cross-linking by mass spectrometry.¹⁴ Recently, we reported that prostate and testis expression 4 (PATE4; also known as SVS7) is the essential factor for copulatory plug formation with *Pate4* KO mice (Figure 1 and Table 2).⁶ Though we could not find “QXK(S/T)” in PATE4, our results suggest that PATE4 may be cross-linked by a TGM4-dependent/independent manner or have an unknown function to facilitate copulatory plug formation. Other reports suggest that several glutamine and lysine residues (eg, Q⁸⁶ and K⁵⁹) in SVS4 are the target sites for TGM4 cross-linking (Table 2).²²⁻²⁴ Thus, the mechanism of copulatory plug formation may be more complicated than expected.

TABLE 2 Physiological functions of proteins in accessory gland secretions

Function		Proteins	Summary of results
Copulatory plug formation		SVS1	Two glutamines (Q ²³² and Q ²⁵⁴) in SVS1 are the site for TGM4 cross-linking ¹⁴
		SVS2	SVS2 has the TGM4 cross-linking site and conserves the peptide sequence “QXK(S/T)” for TGM4. ^{6,11,13} <i>Svs2</i> KO males show plug formation defects ⁷
		SVS3	The peptide sequence “QXK(S/T)” in SVS3 was identified as the site for TGM4 cross-linking ¹⁶
		SVS4	Several glutamine and lysine residues (eg, Q ⁸⁶ and K ⁵⁹) in SVS4 were identified as the substrate for TGM4 ²²⁻²⁴
		PATE4	<i>Pate4</i> KO males show plug formation defects ⁶
		TGM4	TGM4, an enzyme from prostates and coagulating glands, catalyzes the formation of ϵ -(γ -glutamyl)lysine cross-bridges among SVSs. ^{6,11,13-20} <i>Tgm4</i> KO males show plug formation defects ²¹
Sperm fertilizing ability	Motility	SPMI	These proteins from seminal vesicles function as sperm motility inhibitors <i>in vitro</i> (SPMI ^{42,43} and SVA ⁴⁴)
		SVA	
		PATE4	
	Capacitation	SVS2	These proteins were identified as decapacitation factors <i>in vitro</i> (SVS2, ⁴⁸ SPINKL, ^{49,50} and SERPINE2 ⁵¹)
		SPINKL	
	SERPINE2		
Survival	SVS2	SVS2 protects the spermatozoa from an immunological response in the uterus using <i>Svs2</i> KO males ⁷	
Uterine environment		TGF β	These proteins in seminal plasma are involved in the inflammatory response of the uterus to seminal fluid ^{55,56,58-60}
		Prostaglandin E	
		TLR4 ligands	

Abbreviations: PATE, prostate and testis expression; SERPINE2, serine protease inhibitor, clade E, member 2; SPINKL, serine protease inhibitor Kazal-type-like; SPMI, seminal plasma motility inhibitor; SVA, seminal vesicle autoantigen; SVS, seminal vesicle secretion; TGF, transforming growth factor; TGM, transglutaminase; TLR, Toll-like receptor.

2.2 | Sperm fertilizing ability

It is known that the accessory gland secretions aid the sperm fertilizing ability (e.g., sperm motility, capacitation, sperm survival). Seminal plasma components improve the sperm motility in human^{25,26} and boar.²⁷ In addition, ejaculated spermatozoa from SV-removed male mice show decreased motility.²⁸ The ejaculated spermatozoa acquire fertilizing ability after they stay in the female reproductive tract for several hours (known as "sperm capacitation").²⁹⁻³¹ Spermatozoa from some subfertile bulls display the premature capacitation,³² and it has been shown components of seminal plasma can inhibit sperm capacitation.³³ These results suggest that the accessory gland secretions regulate the timing of sperm capacitation to improve male fertility. Accessory gland secretions help the survival and cervical transit of epididymal spermatozoa³⁴ and to prevent an immunological response to spermatozoa in the female reproductive tract.³⁵

Interestingly, the ejaculated spermatozoa of SV-removed boars³⁶ and bulls³⁷ could efficiently fertilize eggs with artificial insemination (AI). Also, cauda epididymal spermatozoa from mice,^{6,38,39} bulls,⁴⁰ and boars⁴¹ can fertilize oocytes when these spermatozoa were used for AI. From these results, accessory gland secretions appear to be unnecessary for sperm fertilizing ability. Recently, we observed improvement of sperm fertilization rates by SVSs only when the low sperm numbers were used for AI.⁶ Thus, we concluded that the positive effects of accessory gland secretions on the sperm fertilizing ability only appear when the amount of sperm numbers in the uterus is low referring at least in mice.

There are several functional studies of accessory gland secretions on sperm fertilizing ability at the molecular level (Table 2). Specifically, seminal plasma motility inhibitor,^{42,43} seminal vesicle autoantigen,⁴⁴ and PATE4⁴⁵ were reported as modulators of sperm motility in seminal vesicle secretions. Also, Ca²⁺ signaling cascades induced by the extracellular vesicles secreted from prostate epithelial cells (known as prostasomes) improved sperm motility.^{46,47} SVS2,⁴⁸ a serine protease inhibitor Kazal-type-like (SPINKL),^{49,50} and a serine protease inhibitor, clade E, member 2 (SERPINE2)⁵¹ from SV were identified as decapacitation factors. SVS2 and SPINKL attached on the plasma membrane of spermatozoa immediately after ejaculation, which then disappear in spermatozoa by the time they reach the oviduct.^{48,50} This result suggests that decapacitation factors on the sperm surface are removed while the spermatozoa pass through the uterus. Further, SVS2 acts to protect the spermatozoa against the uterus-derived cytotoxic factors.⁷ As more than 700 proteins from accessory glands were identified with proteomics,⁵² the functional analysis of these proteins will be required to further dissect the physiological function of accessory gland secretions on sperm fertilizing ability at the molecular level.

2.3 | Uterine environment

It is known that the seminal plasma is not only involved in sperm fertilizing ability, but also in female reproductive physiology in

insects and mammals (e.g., immune tolerance for pregnancy).^{53,54} Seminal plasma contains the signaling molecules that interact with estrogen-primed epithelial cells lining the female reproductive tract to accelerate the expression levels of cytokine and chemokine genes.^{55,56} These upregulated genes facilitate leukocyte recruitment and activation of the innate and adaptive immune system that resembles an inflammatory cascade, leading to the preparation of the female reproductive tract for pregnancy.^{53,55,57} The inflammatory-like response to seminal fluid depends on seminal plasma factors, such as transforming growth factor (TGF β), E-series prostaglandins, and Toll-like receptor 4 (TLR4) ligand (such as bacterial lipopolysaccharide [LPS]; Table 2).^{55,56,58-60} The lack of accessory gland secretions causes the slower cleavage rates in embryogenesis and placental hypertrophy *in vivo*, from studies using mouse and hamster males with accessory glands surgically removed,^{61,62} leading to changes of postnatal growth and fetal programming.^{62,63} Despite these effects, the females artificially injected with cauda epididymal spermatozoa become pregnant.^{38,64} Recently, we revealed no differences in the pregnancy rate and the litter size between uterine environments with and without stimulation by SVSs when the cauda epididymal spermatozoa were injected into a uterus by AI.⁶ Thus, factors in accessory gland secretions may contribute to regulate the uterine environment, but the physiological functions on embryogenesis and pregnancy remain limited. The detailed effects of accessory gland secretions on postnatal growth and fetal programming need further examination.

3 | CONCLUSION

In this review, we mainly highlighted positive functions of SV on copulatory plug formation and sperm fertilizing ability. More than 700 proteins were detected in the accessory glands with proteomics,⁵² but the physiological functions of these proteins remain unknown. The emergence of the clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 system opened a new era in mammalian genome editing.⁶⁵⁻⁶⁷ Our previous works demonstrated that CRISPR/Cas9-mediated KO mice generation and phenotypic analysis are a cost-effective and labor-effective approach to quickly identify essential gene functions *in vivo*.⁶⁸⁻⁷⁰ Thus, utilizing CRISPR/Cas9 genome editing to examine the function of these 700 genes identified as accessory glands will accelerate elucidation of accessory glands on male fecundity at the molecular level.

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CONFLICT OF INTEREST

The authors have declared that no conflict of interest exists.

HUMAN AND ANIMAL SUBJECTS

This review article does not contain any studies with human and animal subjects performed by any of the authors.

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