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Variability in human semen content and its potential effects in the female reproductive tract

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Abstract

Human semen is a complex medium containing high concentrations of cytokines, chemokines, and growth factors that play key roles in orchestrating immune responses during reproduction. These factors are essential to establishing conditions that facilitate fertilization and embryogenesis through modulation of local immune responses in the female reproductive tract. Typically, semen initiates a biphasic process of inflammation that is gradually resolved, leading to immune cell recruitment pivotal to clearing excess sperm and establishing tolerance of the fetal allograft. However, the identity and concentration of factors found in semen may be altered in the male reproductive tract as a consequence of sexually transmitted infections and infertility conditions. As a result, imbalances in semen content can skew the secretory response of the cervicovaginal epithelium after deposition during heterosexual intercourse, which may distort local immune activity and lead to embryo rejection or enhanced pathogen transmission. Recognizing the array of factors contained in semen and the degree to which they vary is an essential part of understanding the impact of variations in semen content on reproductive biology and the transmission of sexually transmitted disease pathogens.

Keywords: Semen, cytokine, growth factors, female reproductive tract, variation

Introduction

There is a growing body of information in the general area of reproductive biology that has indicated a more active role for semen in the female reproductive tract (FRT) than initially suspected. A review of semen and female genital tract secretions in the context of microbicide development cited unpublished experiments that suggested the presence of factors in seminal fluid that were likely modulating innate immune responses in the FRT [1]. More recent studies involving FRT-derived epithelial cells exposed to semen suggested that transforming growth factor beta (TGF-β), present in very high concentrations within semen, may be responsible for directing a local immune response within the FRT that favors embryo implantation [2]. It was concluded that TGF-β was a major factor responsible for initiating the early, local inflammatory response through the induction of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin 6 (IL-6) expression from cervical epithelial cells [2,3]. Additional studies demonstrated that

seminal TGF-β was also responsible for inducing a local anti-inflammatory response that favored tolerance of the paternal antigens and embryo implantation during the resolution phase of inflammation [4]. These studies strongly suggest that the introduction of semen has a profound effect on the immunological environment within the FRT, which may influence both reproduction and heterosexual disease transmission.

Gaining an understanding of the effects of semen within the FRT is confounded by multiple factors, not the least of which is the complexity presented by the involvement of two separate systems-the male reproductive tract (MRT) and the FRT-each with their own anatomical and immunological aspects to consider. Semen is a complex mixture of cytokines, chemokines, and biologically active molecules. The concentration of these factors is influenced by donor-specific variables at multiple levels (health, diet, age, infection, and substance abuse) and can be further altered as a consequence of infertility. Studies have demonstrated significant differences in seminal cytokine

and chemokine content between infertile and fertile men, which can vary depending on the type of infertility condition and disease progression. The activities of these factors once deposited in the FRT add another level of variability. The FRT, in turn, is subject to its own unique set of variables, including hormones, age, and conditions associated with concurrent infections or other physiological conditions [3]. Studies of semen-mediated effects will need to identify which responses are separately controlled by female ormale factors,and which outcomes result from combined interactions.

The goal of this review is to documentthe variability of semen and semen-derived factors and explore their roles in initiating the local immune responses within the FRT that are key to successful reproduction and prevention of infection.

Review
Semen has a complex and variable composition
Mature sperm cells in the testes that are ready for ejaculation pass through the epididymis where prostate fluid, which is rich in proteins and other factors such as citric acid and zinc [5], is added (**Figure 1**). Prior to release, semen is further augmented by fluid from the seminal vesicles, which are responsible for establishing the alkaline pH of semen [5]. The average volume of seminal fluid ejaculated is 3.5 ml, but can range anywhere from 100 µl to 11 ml [6]. Just as the total volume varies, the concentrations of biologically active factors, including hormones, mucin, cadaverine, putrescine, spermine, enzymes, cytokines/chemokines, fructose, and vitamin D, and other soluble factors present in seminal fluid [7], can also vary significantly not only between donors but also within one individual over time. Semen content can also be affected by otherfactors, such as changes in fertility, age, frequency of ejaculation, infection by sexually transmitted disease (STD) pathogens, substance abuse, prescription medications, and other factors that reflect an individual's lifestyle [8,9]. To address the elements of intra- and inter-donor variability, experiments requiring semen have either used large cohorts or often incorporated combined seminal fluid samples from five or more donors, creating working samples with greater volume and content more representative of the "average" male semen content.

Studies of male infertility have provided numerous opportunities to assess the concentrations of biologically active factors contained in semen. These studies have clearly shown that (i) semen contains a diverse and wide range of immunomodulatory factors that likely participate in reproduction as well as pathogen defense, and (ii) the concentrations of these factors can vary greatly with changes in reproductive health or infection.
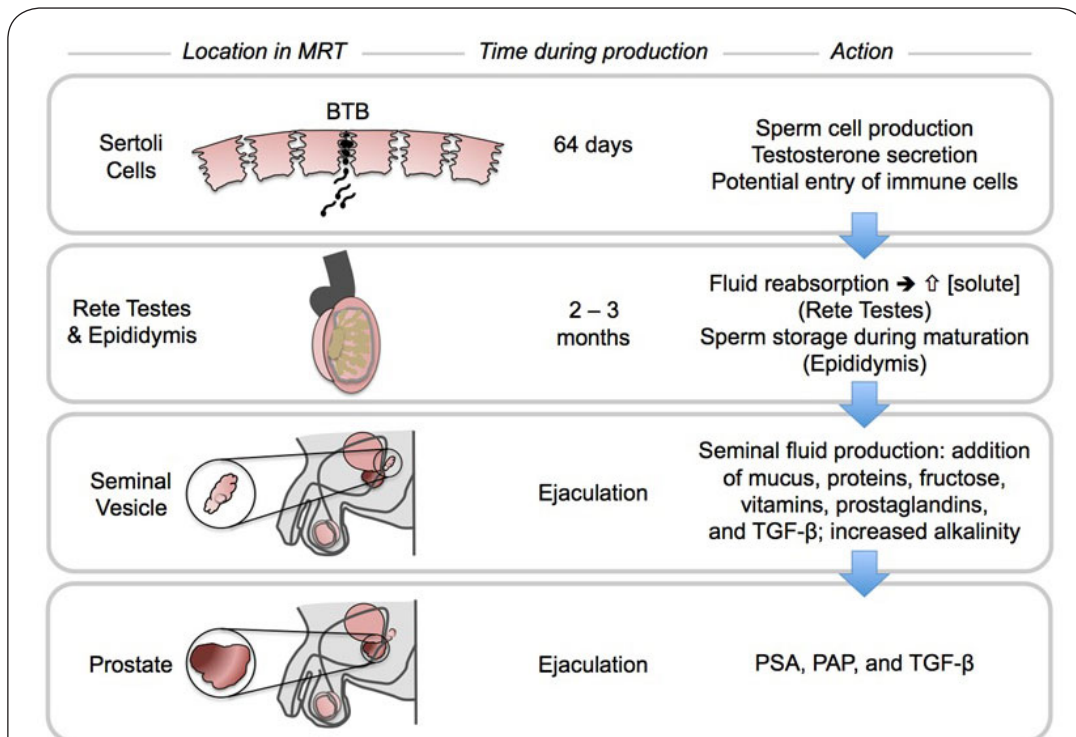
Figure 1. Flow diagram of semen production within the human male reproductive tract (MRT).
This schematic representation of the MRT illustrates the tissues involved in semen production within the MRT, the timing of semen production, and the points at which seminal fluid volume and content are altered. BTB, blood-testes barrier; PSA, prostate-specific antigen; PAP, prostatic acid phosphatase; TGF-β, transforming growth factor beta.

Table 1 is a compilation of biological factors shown to vary in concentration with MRT pathology. Details about their concentrations, clinical conditions under which they were collected, and the degree to which their concentrations varied with MRT pathology are available in **Supplementary Tables S1** through **S5** in Supplementary Information. Some of these factors are highlighted in this review.

Factors in semen modulate immunity essential to establishing fertilization

Factors in seminal fluid must be present at optimal concentrations in order to achieve successful reproduction. Fertility is more than just a function of sperm count; the components of seminal fluid not only control the concentration of sperm in semen, but also influence the quality of the spermatozoa and alter the environment within the FRT to orchestrate tolerance of the paternal antigens in support of fertilization and embryo implantation. Many studies of healthy human males, infertile human males, and animals have provided insights into the intricate processes that take place in the FRT during reproduction.

Events begin with the deposition of semen in the FRT. Initially, semen is recognized by the local female innate immune system as a foreign entity due to the presence of paternalantigens and MHC class I and II on spermatozoa [10]. As a result, an inflammatory reaction is incited, characterized by a massive infiltration of neutrophils that are likely recruited by the high concentrations of IL-8 (**Table 1** and **Supplementary Table S4**) and GM-CSF (**Table 1** and **Supplementary Table S5**) found in seminal fluid [11]. The initial phase of inflammation is important to clear excess and abnormal sperm as well as various waste products found within semen [11,12]. It is vital, however, that the inflammatory phase be quickly resolved, as uncontrolled inflammation could lead to the clearance of the healthy sperm cells by neutrophils and result in a reduced capacity for fertilization. In order to suppress the female immune system and allow the paternal antigens to go unrecognized, a state of tolerance must be induced, likely mediated by the pleiotropic cytokine TGF-β. Both pro-TGF-β and active TGF-βare secreted into semen by the seminal vesicles and prostate, and arepresent at very high concentrations within the seminal fluid (**Table 1** and **Supplementary Table S3**) [11,13].

In combination with seminal IL-15, TGF-β tilts the immune balance from the initial Th1 response to a Th2 type response through the induction of regulatory T (T_{reg}) cell differentiation of T cells from the periphery [4,13]. As T_{reg} cells increase in number, a concurrent opposing shift in the local immune cell population results in the suppression of Th17 switching, the overabundance of which has been correlated with preeclampsia [14]. Additional studies suggest that semen may further bias a type 2 response by inducing the production of type 2 cytokines from local and intraepithelial T cells and dendritic cells (DCs), possibly through semen-associated prostaglandins [15,16]. These studies highlight the active role of semen in inducing the immune changes that prevent the semi-allograft fetus from being recognized as a foreign antigen and protect it from clearance [11].

TGF-β, however, is in no way the only important immunomodulatory factor found in semen. Another important suppressive component found in high concentrations is prostaglandin E_2 (PGE_2), which also originates in the seminal vesicles (**Table 1** and **Supplementary Table S1**). Prostaglandins are key in dampening the immune response through inhibition of macrophage cytokine production and T cell proliferation [11-13,17,18]. Like IL-15, PGE_2 also works in combination with TGF-β to promote tolerance of paternal and fetal antigens, contributing to the differentiation and expansion of T_{reg} cells in the FRT [4,13]. Abnormalities in any one of the functions directed by the factors in seminal fluid, such as embryo implantation and development, could lead to a state of dysregulation, as evidenced by the many types of male infertility that have been identified and described in literature (**Table 1**).

Table 1. Human semen contains numerous biologically active factors that change with MRT pathology.

Miscellaneous Biologically Active Factors (**see also Supplementary Tables S1**)	Sperm Count, Adrenaline, Chloride, Citrate, Dopamine, E2, FSH, Fructose, Glucose, LH, Magnesium, Noradrenaline, PAP, PGE2, Potassium, PRL, Putrescine, Sodium, Sodium Citrate, Spermidine, Spermine, Testosterone, Vitamin A, Vitamin C, Vitamin E, Zinc
Pro-inflammatory Cytokines (see also **Supplementary Tables S2**)	IFN-α, IFN-γ, IL-1α, IL-1β, IL-6, IL-12, IL-17, IL-18, IL-23, MIF, TNF-α
Anti-inflammatory Cytokines (see also **Supplementary Tables S3**)	IL-5, IL-10, TGF-β (1, 2, and 3)
Chemokines (see also **Supplementary Tables S4**)	IL-8, IP-10, I-TAC, MCAF/MCP-1, MIG, MIP-1α, MIP-1β, RANTES, SDF-1α
Growth and Signaling Factors (see also **Supplementary Tables S5**)	BDNF, EGF, G-CSF, GM-CSF, IL-2, sIL-2R, sIL-6R, IL-7, IL-11, IL-13, NGF, VEGF

The table lists biologically active factors in semen found to vary in concentration with disease and infection. For more details, including concentration ranges, diseases and pathologies associated with changes in each factor, and source references, refer to **Supplementary Tables S1** through **Supplementary Tables S5**.

Changes in semen-associated immune factors correlated with infertility in the MRT

Due to the complex composition of seminal fluid, male infertility may be correlated with an increase or decrease in a multitude of factors noted for their immunomodulatory activities (**Table 1**). The presence of interleukin 1β (IL-1β), a pro-inflammatory cytokine, has been inversely correlated with sperm motility (**Table 1** and **Supplementary Table S2**). Similarly, increases in interleukin 6 (IL-6), possibly secreted by lymphocytes in semen or hormonally regulated Sertoli cells in the MRT, havebeen correlated with decreases in sperm count and motility, as well as decreases in semen volume (**Table 1** and **Supplementary Table S2**) [**19-21**]. Interleukin 8 (IL-8), a chemotactic cytokine found at higher levels in the semen of individuals diagnosed with infertility due to leukocytospermia, has been suggested to be responsible for recruiting excessive numbers of white blood cells (WBCs), resulting in abnormally high T-lymphocyte counts in semen as well as a decrease in spermatozoa viability (**Table 1** and **Supplementary Table S4**) [**19**]. Increased IL-8 has also been correlated with increases in pro-inflammatory cytokines interleukin 1α (IL-1α) (**Table 1** and **Supplementary Table S2**) and granulocyte colony-stimulating factor (G-CSF) (**Table 1** and **Supplementary Table S5**), which may be released into semen by macrophages or endothelial cells lining the MRT. IL-1α and G-CSF are responsible for activating T cell proliferation and stimulating neutrophil production, which are both key to eliciting an inflammatory immune response [**22**]. Increased interleukin 18 (IL-18), which was shown to be present at higher concentrations in semen of men suffering from combined infertility/urogenital infections, was correlated with decreased sperm concentration and mobility (**Table 1** and **Supplementary Table S2**) [**23**]. Several studies have noted an increase in tumor necrosis factoralpha (TNF-α) in semen in conjunction with low or undetectable sperm counts (**Table 1** and **Supplementary Table S2**). TNF-α has also been correlated with reductions in testosterone and sperm motility, alterations in sperm morphology, and increases in reactive oxygen species (ROS) [**20,21,24**]. Similarly, increases in interferongamma (IFN-γ) across multiple infertility conditions werealso associated with decreased sperm count, motility, and morphology (**Table 1** and **Supplementary Table S2**) [**20**].

The protein monocyte chemotactic and activating factor (MCAF) provides a particularly illustrative example of a biological factor contained in semen that may impact reproductive fitness through variations in concentration. Levels of MCAF in seminal fluid of men with leukocytospermia are increased over those of other infertile-type conditions or fertile males (**Table 1** and **Supplementary Table S4**), indicating that specific infertility diagnoses can be associated with specific cytokine concentrations [**25**]. Increased levels of MCAF may originate from monocytes, endothelial cells, or fibroblasts present in the MRT and be involved in protecting the reproductive tract from infection bybacterial pathogens [**25**]. The role of MCAF

in reproductive biology, however, is not limited to the male. It has been speculated that once semen has been deposited into the FRT, MCAF may be responsible for the local recruitment and activation of monocytes, which are important in clearing excess sperm [**25**]. In leukocytospermia, MCAF stimulation has also been associated with the release of IL-6 from monocytes, which in conjunction with increased IL-8, results in further activation and differentiation of monocytes into macrophages and recruitment of neutrophils [**25**]. An increase in the local presence and activation of phagocytes could result in increased clearance of sperm cells, hindering fertility.Cumulatively, these factors and effects directly influence mechanisms that may alter local immune responses that affect not only reproductive events, but may also contribute to the risk of STD pathogen infection within the FRT [**3**].

Effects of seminal factors in the FRT

In addition to its direct influence on immune cells, semen can also have indirect effects on the immune response mediated through the epithelial cells lining the reproductive tract of the female. While the FRT is a large and complex environment, the epithelial lining can essentially be broken down into three main regions: the vagina, which has the largest surface area in the FRT and is characterized by a squamous epithelium that can be up to 25 cell layers thick; the ectocervix, which encompasses the portion of the epithelium that transitions from a multi-layer squamous phenotype into a simple columnar phenotype characterized by low tight junction expression; and the endocervix, which is describedas a single columnar epithelial layer with high levels of tight junction expression [**26**]. Interestingly, our group and others have observed that each of these regions is not only unique in phenotype or tight junction expression, but in responsiveness to stimuli, such as seminal fluid, revealing that the epithelium is more than just a mechanical barrier -it is also a dynamic tissue [**27**]. In fact, seminal fluid seems to elicit this response on tight junctions on epithelial cells in a variety of environments [**28**]. When epithelial cells derived from the three main regions of the reproductive tract were incubated with seminal fluid in submerged culture, a wide array of factors were released, the most predominant of which were the inflammatory cytokines [**16,27**]. However, the concentrations and specific cytokine release profiles were unique to each region [**27**]. In one study, cells derived from the ectocervix were the most responsive compared to cells of the vaginal tract. These results suggest that the vaginal epithelium, which is regularly exposed to bacteria, pathogens, irritants, and foreign entities (including semen), has a greater tolerance for damage or inflammatory stimuli [**27**]. The cervix, on the other hand, is considered to be essentially sterile due to its remote placement relative to the vaginal opening, and is protected from external insults by a layer of mucus. Because this region is exposed to a lower level of stimuli relative the vaginal epithelium, the tolerance of the epithelium might be lower and its responsiveness to

insults correspondingly higher [27]. Studies have shown that even in the cervix there are regional differences, with the endocervix (higher up in the FRT) having a greater response to foreign stimuli [29]. Perhaps this robust response is due to the fact that the upper cervical region sees fewer foreign stimuli than the lower region and stands poised to provide a more effective response to stop colonization of the upper cervix [29].

Factors that are released by epithelial cells in a basolateral direction in response to apical exposure to semen also orchestrate reproductive inflammatory/tolerance events by influencing local immune cells [30]. For example, the transition of uterine natural killer cells (uNK) from a cytotoxic to a "helper" phenotype is essential to fetal development [31], insofar as having uNKs recognize fetal development as "self," or non-foreign, and therefore not attacking the developing fetus through induced tolerance. During embryogenesis, uNK cells release IFN-γ to aid in angiogenesis and vascularization of the uterus in order to support the developing fetus [31,32]. Although it remains controversial, the shift in uNK phenotype leading to tolerance may be induced by IL-15 and IL-7 [33]. Release of IL-15 from the epithelium is increased 22-fold in the subepithelial space as early 4 h post-semen exposure [34]. As mentioned previously, the combination of IL-15 and TGF-β increases T-cell switching to a T_{reg} phenotype, further contributing to key events that initiate fetal tolerance [13]. Interestingly, the number of T_{regs} and uNK cells present in the uterus are higher relative to the peripheral blood, implicating the intensive role these cell types play in local reproductive immunity [35]. The shift from inflammation to tolerance in the FRT during semen exposure has been likened to the changes that occur in the tumor microenvironment, both of which provide protection from immune clearance and allow cells to proliferate in a similar manner [36]. Combined, the activity of the reproductive epithelium added to the effects of factors contained in semen creates a biphasic local immune response that is key to clearing excess sperm and essential to developing tolerance to the nascent fetus in the FRT during reproduction.

In the context of pathogen transmission, the same factors that are important to reproduction may also contribute to susceptibility to sexually transmitted infections (STIs). When CD4+ T cells were incubated directly in seminal plasma, there was an observed increase in CCR5 surface expression, resulting in preferential R5 infection in the presence of human immunodeficiency virus type 1 (HIV-1) [37]. There is also evidence that the same type 2 responses that are responsible for tolerance of sperm may also protect the virus from clearance. Prostaglandins in semen that drive a local type 2 response, as described previously, may also inhibit IL-12 release and upregulate IL-10 production by DCs, possibly reducing the capacity for clearance of virus [15]. Combined with the data demonstrating that IL-7 -which is increased in the seminal fluid of HIV-1-infected males and also released by the epi-

thelium after semen exposure-can enhance HIV-1 transmission to T cells in cervicovaginal explants [38], these findings further highlight the potential effects of combined factors from both seminal fluid and the reproductive epithelium in directly modulating transmission of HIV-1, as well as other STD pathogens.

Future directions

Studies that strive for a better understanding of the interplay between seminal factors and the FRT will provide new insights into reproductive biology as well as failures in reproduction attributable to disease or infection. Such studies will also give rise to the development of new model systems in which critical aspects of this important interplay can be readily manipulated and studied. For example, *in vitro* studies using a simple model consisting of semen and cervicovaginal epithelial cells may attribute a failure to modulate key innate immune responses in a timely manner to decreased concentrations of TGF-β in seminal plasma. Such information could be the catalyst for the development of new drugs that effectively treat infertility. This review highlights the importance of the major constituents of semen and provides the first stepping stones toward future experiments of this nature.

Outside of reproduction, immunomodulatory factors in semen may also affect key events that influence the transmission of STD pathogens, such as HIV-1, resulting in an increased or decreased risk of male-to-female transmission. Having greater knowledge about the dynamics of biologically active factors in semen will increase our understanding of not only reproductive biology, but also STD pathogen transmission. More detailed information about the role of semen in modulating the risk of pathogen transmission will likely reveal new strategies for preventing STD acquisition by women. For example, a greater understanding of seminal factors that result in FRT inflammation and the chemotaxis of HIV-1-susceptible immune cells to the cervicovaginal epithelium may provide a path toward the development of next generation topical microbicides that reduce semen-associated immune cell recruitment and reduce the risk of male-to-female HIV-1 transmission. It is our hope that this review will also serve as a supporting resource for these types of studies.

Conclusions

Semen is a biologically active fluid capable of orchestrating and influencing immune responses within the FRT. Some of the numerous agents in semen that profoundly affect the immunological environment of the FRT include cytokines, chemokines, growth factors, and other biologically active molecules. These components disrupt the normal immune response of the female, which may leave her susceptible to further complications. Although the MRT is highly compartmentalized, semen composition can be influenced by reproductive tract disease and conditions outside the MRT, resulting in changes in concentration of key seminal compo-

nents that are important in guiding reproductive processes in the FRT. Significant changes in factors present in semen may result in infertility or reproductive dysfunction. Similarly, indirect changes induced by semen, such as the release of factors by the epithelium or changes in immune cell populations, may also influence the delicate pro-inflammatory and anti-inflammatory phases of reproduction.

Additional files

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Table S4
Supplementary Table S5

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	SK	KS	BW	FCK
Research concept and design	✓	✓	✓	✓
Collection and/or assembly of data	✓	✓	--	--
Data analysis and interpretation	--	--	--	--
Writing the article	✓	✓	--	--
Critical revision of the article	✓	✓	✓	✓
Final approval of article	--	--	✓	✓
Statistical analysis	--	--	--	--

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