Prostaglandins in semen compromise the immune response against sexually transmitted pathogens ☆

F. Remes Lenicov, A. Varese, A. Merlotti, J. Geffner, A. Ceballos *

Instituto de Investigaciones Biomédicas en Retrovirus y SIDA (INBIRS), Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires C1121ABG, Argentina

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ABSTRACT

Seminal plasma is not just a spermatozoa carrier. It induces the expression of inflammatory cytokines and chemokines and a massive infiltration of neutrophils, monocytes and dendritic cells in the female genital mucosa after coitus, enabling the innate immune system to fight against sexually transmitted pathogens. However, exposure to seminal plasma not only turns on an inflammatory response but also induces regulatory mechanisms that allow the fetus (a semiallograft) to grow and develop in the uterus. In mouse models it has been shown that seminal plasma induces the expansion of regulatory T cells specific to seminal Ags in the receptive partner, thus promoting tolerance to paternal alloantigens and avoiding allogeneic fetal rejection. These mechanisms appear to be mainly induced by prostaglandins of the E series (PGE) and TGF-β, which are present at huge concentrations in the seminal plasma. Moreover, we have recently shown that exposure to seminal plasma induces the differentiation of dendritic cells into a tolerogenic profile through a mechanism dependent on the activation of the prostanoid receptors EP2 and EP4 by seminal PGE.

Our hypothesis proposes that this tolerogenic response induced by seminal PGE, while promoting fertility by inducing tolerance toward paternal alloantigens, might also compromise the development of the adaptive immune response against sexually transmitted pathogens in the receptive partner.

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Background

Semen contains a large array of components such as carbohydrates, lipids, peptides, proteins, cytokines, and chemokines, produced from the testis, epididymis, and accessory glands. A number of these components bear immunosuppressive activity, like prostaglandins, TGF-β and other cytokines, polyamines, prostasomes and complement-inhibiting proteins [1–4]. In particular, huge concentrations of TGF-β and prostaglandins of the E series (PGE) are found in normal human semen [5–7]. PGE in semen include PGE1, PGE2 and their 19-OH-derivatives in concentrations exceeding 700 μg/ml [5,6].

It is well known that semen deposition onto the female genital mucosa triggers a strong inflammatory response. This inflammatory response has been described in mice, pigs, rabbits and humans [8–11]. Studies performed by Sharkey and coworkers in ectocervi-cal epithelial cells showed that seminal plasma stimulates the production of a variety of inflammatory cytokines and chemokines such as IL-8, MCP-1, IL-6, and GM-CSF [12]. Seminal plasma also induced the expression of cyclooxygenase-2, the rate-limiting enzyme for prostanoid synthesis, in human vaginal and cervical epithelial cells [12,13]. Moreover, Berlier and coworkers reported that seminal plasma promotes the attraction of Langerhans cells via the stimulation of CCL20 secretion by vaginal epithelial cells [14]. Consistent with these observations, serial analysis of human cervical samples revealed that semen deposition promotes the massive infiltration of the cervix by neutrophils, monocytes, and dendritic cells (DCs) through a mechanism dependent on TGF-β [7,10]. What is the meaning of this inflammatory response induced by semen? We don't know the answer to this question. Inflammation might induce a dual action on the receptive mucosa. It might induce the local recruitment of innate immune effectors to fight against sexually transmitted pathogens. Moreover, it might favor the implantation of the embryo, a process which has been shown to require the expression of inflammatory cytokines in the pre-implantation uterus [15].

The actions mediated by semen at the female genital mucosa are not restricted to the induction of an acute inflammatory response. In apparent contradiction, semen also induces a strong

tolerogenic response. This response appears to be required for the survival of spermatozoa in the female reproductive tract and also to avoid allogeneic fetal rejection. In this regard, Robertson and coworkers showed that seminal fluid delivered at coitus causes the expansion of a CD4(+) FOXP3(+) regulatory T cell population (Tregs), which subsequently home to the uterus, thus preventing embryo rejection by the maternal-allospecific immune response [16,17]. Notably, this tolerogenic response occurs even in the absence of conception, thus suggesting a critical role for seminal fluid as an inducer of Tregs [18]. In fact, a strict requirement of Treg expansion during pregnancy has been clearly demonstrated in mice, since depletion of Tregs induces resorption of the embryos in allogeneic matings [19,20]. More importantly, maternal-fetal tolerance is dependent on peripheral, but not thymic (natural) Tregs [21]. Generation of peripheral Tregs requires the activation of conventional naive CD4+ T cells by tolerogenic DCs, which express a semimature phenotype and drive the differentiation of Tregs in a microenvironment characterized by the absence of inflammatory cytokines and the presence of high concentrations of TGF-β and IL-10 [22,23]. The mechanisms underlying the ability of semen to promote a regulatory T cell-response remain poorly defined.

Dendritic cells are unique in their ability to stimulate naive T cells, to start the adaptive immune response and to induce the differentiation of CD4+ T cells into different profiles including Tregs [24]. Looking for the mechanisms underlying the ability of semen to promote a tolerogenic T cell response, we have recently analyzed whether seminal fluid influences the functional profile of DCs. We reported that exposure to seminal plasma skews the differentiation of DCs into a tolerogenic profile [25]. The presence of seminal plasma during the differentiation of monocytes into DCs, even when employed at dilutions as high as $1:10^5$, induced the development of DCs with a phenotype characterized by the absence of CD1a, the presence of CD14, and their inability to acquire a full mature phenotype upon activation by inflammatory stimulus such as LPS, TNF-α or CD40 ligand. Moreover, upon activation by LPS, these DCs produced low amounts of the inflammatory cytokines IL-1β, TNF-α, IL-6, and IL-12p70 and high amounts of IL-10 and TGF-β. Furthermore, they showed an enhanced ability to induce the expansion of CD25+ FOXP3+ regulatory T cells. Importantly, we also demonstrated that seminal PGE play a major role in determining the tolerogenic profile of DCs. In fact, the inhibition of the prostanoid receptors EP2 and EP4 almost completely prevented the tolerogenic effect induced by seminal plasma on the phenotype and function of DCs [25]. Whether semen might be able to induce the development of tolerogenic DCs at the receptive mucosa *in vivo*, remains to be determined. Supporting this scenario, however, a large body of evidence suggests that semen might actually interact with DCs at the female genital mucosa. Not only there is a massive postcoital recruitment of DC precursors to the genital mucosa (i.e., inflammatory monocytes [26]), but also the induction of microabrasions in the genital epithelium occurring during sexual intercourse might enable semen to effectively influence the local course of DC differentiation [27,28].

Hypothesis

By inducing a tolerogenic environment at the receptive mucosa, seminal PGE does not only suppress the host-immune response against paternal alloantigens favoring reproduction, but also compromises the ability of the receptive partner to mount an effective adaptive immune response against sexually transmitted pathogens. Our hypothesis suggests that the presence of PGE in human seminal plasma may promote the spread of sexually-transmitted pathogens by inducing the differentiation of DCs into a tolerogenic

profile, driving the activation and expansion of Tregs directed to pathogen-associated antigens.

Hypothesis testing

In order to test this hypothesis, it should be determined whether *in vivo* exposure of vaginal mucosa to PGE actually results in the induction of tolerogenic DCs, the infiltration of the mucosa by Tregs, and the spreading of sexually-transmitted pathogens. The immune deviation induced by seminal PGE cannot be studied by lowering semen PGE levels, since using cyclooxygenase inhibitors has been shown to reduce PGE concentrations in semen only partially [29]. We believe that our hypothesis could be tested instead by determining the effect induced by PGE in an animal model of sexually-transmitted infection, such as HSV-2 in the mouse. This model may allow the study of the phenotype of DCs and CD4+ T cells found at the genital mucosa, as well as the course of the HSV-2 infection, following vaginal inoculation of HSV-2 in the presence of mouse seminal plasma supplemented with different amounts of PGE2.

Clinical implications

Sexually-transmitted infections are highly prevalent and represent an important cause of morbidity and mortality worldwide. Our hypothesis proposes that PGE in semen promotes immunological tolerance to sexually transmitted pathogens in the receptive partner. Understanding the influence exerted by seminal PGE on the mucosal immune response might result in the development of innovative approaches to prevent the spreading of sexually transmitted diseases.

Conflict of interest statement

The authors have no conflicting financial interests. The sponsors have not participated in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

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