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Review article

Seminal plasma proteomes and sperm fertility

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ABSTRACT

During ejaculation, the spermatozoa are transported by the seminal plasma, a fluid resulting from secretions originating mainly from the prostate and the seminal vesicles in mammals. The interaction of the seminal plasma with spermatozoa induces binding of seminal proteins onto the sperm surface and membrane remodeling potentially impacting the sperm transport, survival and fertilizing ability in the female genital tract. The seminal plasma also contains peptides and proteins involved in the inflammatory and immune response of the female tract. Therefore the seminal plasma proteome has been investigated in a large range of taxa, including mammals, birds, fishes and insect species. The association of the seminal plasma with semen preservation or fertility identified proteic markers of seminal plasma function in domestic species. This review summarizes the current knowledge in seminal plasma proteomes and proteic markers of sperm preservation in animal species.

1. Introduction

From the testis to the cauda of the epididymis, the spermatozoa undergo biochemical and functional modifications which lead to the acquisition of the fertilizing ability. During the ejaculation and their deposit in the female genital tract, the spermatozoa are transported by a biological complex fluid, the seminal plasma. The seminal plasma is the result of secretions from several organs from the male genital tract, the epididymis, the prostate, the seminal vesicles and the bulbo-urethral glands (Maxwell et al., 2007).

The duration of contact between spermatozoa and seminal plasma is very short, several minutes at the maximum, as the spermatozoa will rapidly migrate from their site of deposition, generally the vagina, toward the uterus through the cervix. The acquisition of the motility and the fertilizing ability taking place during the epididymal maturation, it could be thought that the seminal plasma has mainly a function of sperm transport without any other major biological role. However, the complexity of the seminal plasma composition, especially in proteins but also other families of molecules such as sugars and lipids, combined with the interaction of its compounds with the sperm surface, suggests a biological function (Rodríguez-Martínez et al., 2011). Moreover, apart from the direct impact on spermatozoa, the seminal plasma plays an indirect role on reproduction through the activation of inflammatory and immune mechanisms in the female (Bromfield, 2014; Schjenken and Robertson, 2014; Rath et al., 2016). However, the real role of seminal plasma in reproduction remains a question (Rodríguez-Martínez et al., 2011; Bedford, 2015; Bromfield, 2016; Sullivan and Mieusset, 2016).

To better understand the potential role of seminal plasma interaction with spermatozoa at ejaculation, a parallel could be made with epididymal maturation. Epididymal sperm maturation consists in a progressive acquisition of mobility and zona pellucida binding as sperm transit along the epididymis (Cornwall, 2009; Dacheux and Dacheux, 2013; Sullivan and Mieusset, 2016). It is accepted that this sperm maturation is not linked to an autonomous maturation of the sperm cell but the result of mechanisms

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associated to the activity of epididymal tubule (Cooper, 1998; Dacheux et al., 2012). The epididymis is composed of three anatomical regions, the caput, corpus and cauda, being subdivided in a variable number of zones depending on the author and the species (Domeniconi et al., 2016). Using a microcannulation method of the epididymal tubule, the luminal fluid and the spermatozoa were obtained for up to 10 epididymal segments in several species such as the human, the pig, the sheep and the horse (Syntin et al., 1996; Dacheux et al., 2012). This precisely regionalized characterization of luminal and sperm protein profiles showed the lost or modifications of testicular membrane proteins as well as binding of proteins originating from epididymal secretions (Cornwall, 2014; Dacheux et al., 2016; Gadella, 2017).

The comparison of transcriptomic and protein secretion activities in the different epididymal regions showed a strong activity mainly located in the proximal and distal caput (Belleannee et al., 2011; Guyonnet et al., 2011; Belleannee et al., 2012). However, the acquisition of mobility and zona binding does not occur in the caput but in the corpus and the cauda. Therefore, it seems there is a time dissociation between sperm surface proteome maturation and functional maturation. During ejaculation, several proteins from seminal origin, also integrate the sperm membrane. Therefore, considering the sperm membrane proteome, epididymal maturation and interaction with seminal plasma proteins can be considered as a continuous process of differentiation. If the functional result of the epididymal maturation such as the mobility or the zona binding can be rather easily experimentally shown, demonstrating an actual biological role of seminal plasma is made difficult by the fact that the interaction of spermatozoa with the seminal plasma will have functional consequences difficult to experimentally assess such as the sperm transit and the survival in the female genital tract (Hung and Suarez, 2010; Rickard et al., 2014). Therefore, similarly as for epididymal maturation, there may be a temporal and spatial dissociation between the biochemical modification of spermatozoa induced by interaction with seminal plasma in the male tract and the functional consequences occurring in the female genital tract, such as in the oviduct, hours or days later (Suarez, 2008; Rodriguez-Martinez et al., 2009).

If the demonstration of the biological role of the seminal plasma proteome in the physiology of the spermatozoa is still complex, it is however possible now to precisely characterize the sperm and seminal plasma proteomes, using high resolution mass spectrometry methodologies. However, the growing body of information from these proteomes, up to several thousands of proteins for a single species, is often too complex to use in itself to understand the sperm physiology. The comparison of these proteomes with physiological and pathological properties of spermatozoa could allow the identification of markers of semen pathology, and as it is the case generally for pathologies, provide us valuable information about the processes occurring during normal reproduction. This review will focus on seminal plasma proteomes available and the identification of sperm functional markers originating from seminal plasma.

2. Seminal plasma proteomes

In a growing number of animal species, the seminal plasma proteomes are investigated concomitantly with the sperm proteomes using protein separation methods associated to protein identification through mass spectrometry.

In the majority of mammalian species, the seminal plasma is a mix from secretions from the epididymis, the prostate, the seminal vesicle and the bulbo-urethral glands. This multi -organ origin concurs to the complexity of the seminal proteome. However there are notable exceptions like dogs and camelids devoid of seminal vesicles (Merket, 1990; Fowler, 1999). On the other hand, the seminal plasma of pigs is mainly constituted of seminal vesicle secretions (Davies et al., 1975).

The dog seminal plasma proteome shows a markedly unbalanced composition. If high resolution mass spectrometry associated to fractionation of the ejaculate during collection (presemen, sperm rich fraction and prostatic fraction) and SDS-PAGE protein separation revealed a moderate diversity with the identification of 268 proteins (Aquino-Cortez et al., 2017), the arginine esterase, the major secretory product of the canine prostate, and the lactoferrin are the quantitatively major proteins of the dog seminal plasma (Chapdelaine et al., 1984; Kikuchi et al., 2003).

The proteome of the camel seminal plasma was investigated using 2D-PAGE / MALDI TOF (Kumar et al., 2012) and 2D-LC/MS-MS (Druart et al., 2013) and provided only a short list of around 20 proteins, probably because of limited information available about the genome of camelids. The camelid seminal plasma also shows an unbalanced composition with one single protein, the beta-Nerve Growth Factor, constituting 47%and 25% of the total amount of proteins in respectively, the alpaca and the camel seminal plasma (Druart et al., 2013). The ovulation in camelids is triggered by the mating and the deposition of seminal plasma in the female genital tract (Vaughan and Tibary, 2006; Skidmore, 2011). The beta-Nerve Growth Factor was shown to be the seminal component responsible for the ovulation inducing activity of semen (Kershaw-Young et al., 2012; Ratto et al., 2012). The camelid semen also shows an unusually high viscosity for mammalian species. This viscosity was shown to linked to the presence of high amounts of mucins (Kershaw-Young and Maxwell, 2012), high molecular weight glycosylated proteins involved in the viscosity of mucus, such as cervical and pulmonary mucus.

Apart from exceptions like dogs and camelids, most of the mammalian species show a seminal plasma composition mainly linked to prostatic and seminal vesicles secretions. The most comprehensive today analysis of seminal plasma proteome was made in human species with the identification of more than 2000 proteins) (Batruch et al., 2011; Rolland et al., 2012; Milardi et al., 2013; Gilany et al., 2015).

In ram, analysis of seminal plasma by GeLC-MS/MS has allowed the identification of more than 700 proteins, showing a high abundance of Binder of Sperm Proteins (BSP1, BSP5), members of the spermadhesin family (SPADH1, SPADH2, bodhesin2) and newly identified proteins like liver enriched gene 1 (LEG1/C6orf58) with unknown reproductive function (Soleilhavoup et al., 2014). The comparison of the proteomes of epididymal and ejaculated ram spermatozoa revealed moderate changes induced by seminal plasma interaction such as binding of BSPs, LEG1 and EDIL3 (epidermal growth factor-like repeats and discoidin I-like domains 3)