Invited paper

TRANSCRIPTIONAL PROFILING OF GENES INVOLVED IN REPRODUCTIVE IMMUNOLOGY OF FARM ANIMALS

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Abstract

It is now well established that interactions between the immune and reproductive system have important consequences for fertility and reproductive health. Pattern recognition receptors (PRRs) are one of the key components of innate immune recognition in vertebrate species. One of the best studied members of PRRs innate immune system is the family of Toll-like receptors (TLRs), which is a family of conserved transmembrane proteins recognizing conserved molecular motifs in a broad range of bacteria, viruses, fungi and parasites. In this review the role of TLR genes in the reproductive immunology of tract of farm animal species will be discussed.

Key words: *embryos, gametes, gene expression, reproductive organs, toll-like receptors*

Introduction

Many studies have reported on the involvement of TLRs in the interactions between the immune and reproductive system, as well as on the involvement of TLRs in the physiology of reproduction in various vertebrate species (Fazeli et al., 2005; Andersen et al., 2006; Itoh et al., 2006; Soboll et al., 2006; Herath et al., 2007). Furthermore, microbial invasion presents a threat to the health of male reproductive organs that can affect fertility (Dejucq et al., 2001; Com et al., 2003; Palladino et al., 2003). Various pathogens are able to infect the male reproductive tract in vertebrates, resulting in reproductive dysfunction and endocrine disorders. Microbial infection of the testis and epididymis can have as a consequence orchitis or epididymal inflammation, leading to transient or permanent sterility (Dejucq et al., 2001; Hall et al., 2002; Com et al., 2003; Rodrigues et al., 2008). Protection of the male reproductive organs from invading microorganisms is therefore an essential aspect of reproductive physiology.

During the last years, pattern recognition receptors (PRRs) have been identified as one of the key components of innate immune recognition in vertebrate species, providing the first line of defense against potential pathogens (Akira et al., 2001; Brownlie and Allan 2010). One of the members of PRRs, the family of Toll-like receptors (TLRs), has been reported to be expressed in the reproductive organs in various vertebrate female species and thus have been implicated in many aspects of reproductive physiology and pathology, providing evidence to suggest that TLRs may function to affect fertility (Fazeli et al., 2005; Andersen et al., 2006; Shimada et al., 2006; Soboll et al., 2006; Herath et al., 2007; Ozoe et al., 2009;

Michailidis et al., 2010; 2011). However, mechanisms of antimicrobial protection of male reproductive organs mediated by TLRs have not been studied extensively.

Male reproductive tract

It has been reported that rat male reproductive organs, including testis, epididymis and vas deferens express TLRs1-11 (Palladino et al., 2007), while mouse Sertoli cells express TLRs2-5 at relatively high levels and TLR6, 7 and 13 at lower levels and do not express TLR1 and TLR8-12 (Riccioli et al., 2006; Starace et al., 2008). Adult human testis also expresses TLR2 and 4 at high levels and TLR5 and 6 at lower levels (Nishimura and Naito, 2005).

Bacterial and viral infections of the male reproductive organs can cause orchitis, epididymitis, and epididymo-orchitis, as well as obstructions of the reproductive tract, which can result in compromising movement of spermatozoa through the excurrent ductal system, contributing significantly to impaired fertility (Palladino et al., 2003; Bhushan et al., 2009). Protection of male reproductive tissues, such as testis and epididymis from microbial invasion is therefore an emerging aspect of research in reproductive physiology.

In recent years, research on antimicrobial protection of male reproductive organs and spermatozoa have indicated the crucial role of the innate immune system in controlling microbial infections of the male genital tract. As innate immune system competence is of critical importance in preventing microbial penetration, a growing number of known or putative antimicrobial defense systems have been reported to be present in the testis of various vertebrate species. In particular, a number of antimicrobial peptides, such as defensins, eppin, human cationic antimicrobial protein 18, and lipopolysaccharide binding protein (Com at al., 2003; Palladino et al., 2003), have been detected in the male reproductive tract and spermatozoa of various vertebrates. In addition to their roles in innate immunity of male reproductive organs, antimicrobial peptides, such as members of the b-defensin family have been reported to play roles not only in innate immunity but also in male fertility, sperm survival in male reproductive tract, and sperm-egg interaction in mammals (Com et al., 2003; Palladino et al., 2003).

Apart from antimicrobial peptides, during the last years the discovery of Toll-like revealed the significant role of pattern recognition receptors in the innate immune system (Akira et al., 2001). TLRs recognize a range of microbial molecular patterns and generate intra-cellular signals through nuclear factor-kB (NFKB) dependent pathways to induce chemokine and cytokine expression that activate a range of host responses (Zarember and Godowski, 2002). As interactions between the immune and reproductive systems have important consequences for fertility and reproduction, there is increasing evidence that many of these interactions involve the family of Toll-like receptors (Girling and Hedger, 2007). Although their function in the male reproductive tract has not yet been studied extensively, there is increasing evidence that the innate defense system of the testis hinges on recognition of bacterial products by members of the TLR family and TLRs play a role in testicular steroidogenesis and spermatogenesis during normal function, as well as in testicular pathology (Girling and Hedger, 2007; Bhusham et al., 2009). Previous studies have reported that in the testis, TLRs are found in immune cells such as macrophages and dentritic cells, as well as in testicular somatic cells and also in the germ cells (Bhushan et al., 2009). Messenger RNA for TLRs was abundantly expressed in the testis (Palladino et al., 2007), expression of TLR1-9 was detected in human testis (Nishimura and Naito, 2005), while various types of TLRs were expressed in testicular Sertoli cells (Riccioli et al., 2006; Wu et al., 2008).

Bacterial and viral infections of the male reproductive organs are one of the most serious causes of infertility in males as they can cause orchitis, epididymitis, and epididymo-orchitis, as well as obstructions of the reproductive tract, which can result in compromising movement of spermatozoa through the excurrent ductal system, contributing significantly to impaired fertility (Palladino et al., 2003; Bhushan et al., 2009). Protection of male reproductive organs, from microbial invasion is therefore an emerging aspect of research in reproductive physiology.

Although some studies have reported on the testis, there have been relatively few studies on inflammatory signaling in the epididymal epithelium or on the effects of systemic inflammation on epididymal function. However, it is well established that immune responses within the testis, where sperm develop, and immune responses in the epididymis, where mature sperm concentrate and mature, are very different and the immune functions of the epididymis have largely been underestimated (Hedger, 2011; Meinhardt and Hedger, 2011). Intraepithelial lymphocytes and other immunocompetent cells have been observed in the epididymis (Da Silva et al., 2011; Meinhardt and Hedger, 2011), but the precise nature of these cells and their immunological properties remain to be elucidated. Surprisingly, one of the most understudied aspects of epididymal physiology is its interaction with the immune system (Hedger and Hales, 2006; Da Silva et al., 2011). The epididymal mucosal system must protect autoantigen-coated spermatozoa from destruction by the immune system as well as invading pathogens. Because of the role of the epididymis in sperm maturation and storage it is critical that the epithelium of the male reproductive tract be protected from a variety of pathogens that can invade the tract including pathogens that cause sexually transmitted diseases (Palladino et al., 2007). Previous studies have reported on the role of host defense peptides and proteins such as defensins and TLRs in protecting the epididymis and therefore both spermatozoa and the epididymal epithelium from microbes, as well as on motility and fertility in different mammalian species (Frohlich et al., 2001; Avellar et al., 2004; Yenugu et al., 2006; Palladino et al., 2003; 2007; Lin et al., 2008).

Female reproductive tract

TLRs have been reported to be expressed in the reproductive organs of various female species and have been implicated in critical aspects of ovarian, endometrial and placental function (Fazeli et al., 2005; Girling and Hedger, 2007; Michailidis et al., 2010 and 2011). Several studies have reported on the role that TLRs play in the maintenance of the immune system in the reproductive organs in many vertebrate species. Members of the TLR family were expressed in the ovary and granulosa and cumulus cells in mouse, as well as in cattle, pig, chicken, sheep and human ovaries, providing evidence to suggest that they may function to affect fertility (Fazeli et al., 2005; Rodriguez-Martinez et al., 2005; Alvarez et al., 2006; Shimada et al., 2006; Herath et al., 2007; Shimada et al., 2008). A number of studies have also reported the presence of TLR family members in the uterine, vaginal tissues and oviductal stromal fibroblasts in the female reproductive tract (Soboll et al., 2006; Fazeli et al., 2005; Andersen et al., 2006; Itoh et al., 2006).

Conclusion

Collectively, members of the TLR family are abundantly expressed in the ovary, oviduct, testis, epididymis and embryos during embryonic development, their mRNA abundance is developmentally regulated during sexual maturation and that certain TLRs are significantly induced in the male and female reproductive tract response to various infections. These findings suggest that TLRs are important for innate immunity of the reproductive organs and embryos and suggest that a TLR mediated immune system exists in the reproductive organs and that it probably plays a role in the recognition of pathogens, and in the initiation of immune response to protect the gametes for successful fertilization, and in preventing microbial pathogens from being incorporated into the embryos. Increased knowledge about TLRs may result in the identification of breeds that are more resistant to colonization of pathogens, which will be very important as farm animals are important reservoir of zoonotic pathogens harmful to humans and provide an important food source.

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