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Cytokines in the male reproductive tract and their role in infertility disorders

Monika Fraczek, Maciej Kurpisz*

Department of Reproductive Biology and Stem Cells, Institute of Human Genetics, Polish Academy of Sciences, Poznan, Poland

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ABSTRACT

Cell integration between the immune and reproductive systems is the basis for normal male reproductive physiology. Cytokines are a part of the autocrine/paracrine network operating in the male reproductive tract. At the same time, immunological reactions occurring *via* cytokines appear to be both beneficial and/or risk factors for male fertility. As the cytokines are produced by a whole spectrum of cells in all compartments of the male genital tract, they can also be involved in a variety of andrological disorders. The monitoring of cytokines and other immune factors in seminal plasma may offer a chance to better understand the mechanisms leading to sub-/infertility. In this review, we present insights into cytokine interplay in some of the pathological conditions associated with male reproduction.

1. Introduction

The nature, origin, and role of cytokines in the male reproductive tract are still under investigation. On the one hand, they are intrinsically involved in normal reproductive physiology, and in this respect, cytokines constitute natural components of the seminal plasma. On the other hand, cytokine local or systemic perturbations underline the pathophysiology of sperm function, and in a number of pathological conditions cytokines can appear in large concentrations in semen. A variety of cytokines, chemokines, and growth factors were shown to be present in human semen, such as: interleukins (IL-1α and -1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-11, IL-12, IL-13, IL-17, IL-18, IL-23); tumor necrosis factors (TNFα); TNF-related apoptosis-inducing ligand (TRAIL); soluble receptors and antagonists (IL1RA, sR IL-2, sR IL-6, TNF-R1, TNF-R2); granulocyte and macrophage colony-stimulating factors (GM-CSF, G-CSF, M-CSF); interferons (IFN-γ); chemokines (IL-8); macrophage inflammatory proteins (MIP-1α, MIP-1β); transforming growth factors (TGFα, TGFβ); monocyte chemotactic and activating factor (MCAF); hepatocyte growth factor (HGF) (Maegawa et al., 2002; Politch et al., 2007; Seshadri et al., 2009). In the male reproductive tract, the cytokines and other immune regulatory factors are mainly produced in the testis by somatic cells, including Leydig and Sertoli cells, and are involved in the regulation of spermatogenesis and other testicular cell functions (Cudicini et al., 1997). However, some studies indicated that their local production took place in the secondary sex glands irrespective of spermatogenesis; namely, the epididymis, the prostate gland, and even the seminal vesicles (Huleihel and Lunenfeld, 2004; Matalliotakis et al., 1998; Friebe et al., 2003; Seshadri et al., 2009). Cytokines and other immune regulatory factors are released by various immune cells present in the male genital tract, including macrophages, monocytes, lymphocytes, dendritic cells, and also in response to foreign antigens and pathogens in addition to chronic inflammation (Ochsendorf, 1999).

* Corresponding author at: Department of Reproductive Biology and Stem Cells, Institute of Human Genetics, Polish Academy of Sciences, Strzeszynska 32, 60-479 Poznan, Poland. Tel.: +48 61 6579 212; fax: +48 61 8233 235.
E-mail addresses: framon@man.poznan.pl (M. Fraczek), kurpimac@man.poznan.pl (M. Kurpisz).

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Recently, seminal dendritic cells turned out to be involved in a secretion of the proinflammatory cytokines, including IL-23, TNF-α, and TRAIL (Duan et al., 2014). In contrast, other authors showed that during the inflammatory process, activated dendritic cells produce rather low amounts of inflammatory cytokines such as IL-12, IL-1β, TNF-α, and IL-6, but demonstrate a high ability to produce anti-inflammatory immune factors such as IL-10 and TGF-β (Remes Lenicov et al., 2012). Little is known of the production of cytokines by the germ cells. However, some years ago, the production and secretion of bioactive IL-1 and IL-6 by human ejaculated spermatozoa were reported (Huleihel et al., 2000a,b).

Cytokine expression is interconnected with multiple factors, including steroid hormones, the redox system, and prostaglandins (Ochsendorf, 1999; Huleihel and Lunenfeld, 2004). However, the final participation of cytokines in the regulation of fertility is dependent upon their concentrations, the expression of cytokine inhibitors, their receptors and/or soluble counterparts (Huleihel et al., 1996; Lazaros et al., 2012). There is growing evidence that a genetic background such as the cytokine gene polymorphisms is associated with altered levels of their production. It is possible that different variations in cytokine/receptor/receptor antagonist genes might also contribute to the final clinical outcomes with regard to male infertility (Shoskes et al., 2002; Jaiswal et al., 2013; Zalata et al., 2013). Although some studies indicated the lack of any connection between the cytokine levels and semen quality (Comhaire et al., 1994; Papadimas et al., 2002; Friebe et al., 2003), a number of authors showed a negative correlation between cytokine levels in the semen and standard semen quality parameters such as sperm concentration (Paradisi et al., 1997; Furuya et al., 2003; Sanocka et al., 2003; Matalliotakis et al., 2006), motility (Gruschwitz et al., 1996; Paradisi et al., 1997; Koçak et al., 2002; Sanocka et al., 2003; Matalliotakis et al., 2006), viability (Kopa et al., 2005), morphology (Paradisi et al., 1997; Furuya et al., 2003), and viscosity (Castiglione et al., 2013). In the case of sperm motility, this is confirmed by several *in vitro* studies, in which the inhibitory effect of some recombinant cytokines was also found (Hill et al., 1987; Eisermann et al., 1989; Perdichizzi et al., 2007). In turn, some investigators suggested that the cytokines detected in semen are associated rather with the incidence of leukocytospermia than seminological abnormalities (Maegawa et al., 2002; Eggert-Kruse et al., 2007).

It is well known that cytokines do not act in isolation, but rather within a network. In this respect, the toxicity of one cytokine to spermatozoa can be increased in the presence of the others. One such classical example may be IL-12. The IL-12 levels correlate positively with the total sperm count and normal morphology, suggesting that this interleukin might play a certain biological role in male fertility/infertility (Naz and Evans, 1998). In turn, IL-12 in combination with IL-18 may be critically dangerous for sperm membranes and DNA integrity under *in vitro* conditions (Fraczek et al., 2008, 2013). Independent groups of authors observed some *in vivo* correlations among various proinflammatory cytokine levels in seminal fluid (Hussenet et al., 1993; Papadimas et al., 2002; Sanocka et al., 2003; Matalliotakis et al., 2006; Qian et al., 2011). Elsewhere, the increase in proinflammatory cytokine levels with a concomitant decrease in anti-inflammatory cytokines in the semen of infertile men was also documented (Camejo, 2003). Presumably, the interactions among the numerous immune factors create a specific micro-pattern of cytokines related to different subgroups of sub-/infertile men with direct clinical implications (Seshadri et al., 2011).

2. Cytokines and male genital tract inflammation/infection

It is known that the inflammatory process in the male genitourinary tract may limit fertility through testis damage, obstruction of the reproductive tract, and may affect the biological function of mature gametes. In particular, orchitis and epididymo-orchitis are relevant co-factors in human subfertility/infertility. The secretion of cytokines is one of the first signals from the innate host defense to combat genital tract inflammation/infection. Additionally, the chemokines facilitate the inflammatory reactions to cause chemoattraction of the leukocytes to the site of inflammation/infection (Lotti and Maggi, 2013). Studies using experimental models of autoimmune orchitis show that the initial phase of inflammation/infection involves recruitment of the immune cells, followed by their activation and increased production of proinflammatory cytokines such as TNF-α, IFN-γ, IL-6, IL-12, IL-17, and IL-23 (Jacobo et al., 2011; Naito et al., 2012; Qu et al., 2013). Acting on adherens and tight junction molecules, the complex network of proinflammatory cytokines affects blood–testis barrier permeability, entering the seminiferous tubules and inducing apoptosis of germ cells (Jacobo et al., 2011). Thus created, an immunopathological microenvironment destroys the physiological immunosuppressive privileged status of the human testis. During chronic, asymptomatic testicular inflammation, these processes are responsible for the disruption of tolerance and the induction of an autoimmune inflammatory response against spermatic antigens. However, the development of autoimmune/inflammatory disorders with male infertility risk also depends on the genetic predisposition for inflammatory response (Shoskes et al., 2002). Although high levels of cytokines can be recorded in autoimmune diseases related to the reproductive organs, the current literature does not report a relationship between circulating cytokine levels in the blood and shedding cytokine levels to seminal plasma during systemic autoimmune disorders.

Inflammation/infection of the male urogenital tract is associated with important biochemical changes in seminal plasma in addition to alterations in the spermatozoa function, reducing their fertilizing potential. Generated by infiltrating leukocytes, cytokines are one of the key mediators of inflammatory process kinetics in the male urogenital tract (Fraczek and Kurpisz, 2007). It is suggested that the proinflammatory cytokines released during semen inflammation/infection might modulate the activity of the pro-oxidative and antioxidative systems to the advantage of the oxidative stress responsible for permanent peroxidative damage to spermatozoa, with consequences for their fertilizing potential (Rajasekaran et al., 1995; Omu et al.,