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Reproductive System and Sexual Disorders: Current Research

Commentary

The Impact of TNF and Nitric oxide in the Suppression of Spermatogonial Cell Growth

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ABOUT THE STUDY

The network of somatic, immunological, and germ cell connections in the testis is disrupted during an inflammatory phase, resulting in organ failure. Spermatogenesis impairment is related with decreased spermatogonia proliferation, an increase in the number of immune cells, and a higher level of pro-inflammatory cytokines in testicular biopsies from infertile men. In models of testicular injury and in human testis with maturation arrest, TNF-TNFR and Nitric Oxide (NO)-NO synthase systems are up-regulated. The goal of this study was to see if the TNF-TNFR system and NO affected the function of spermatogonia in the inflamed testis. Using flow cytometry, we investigated the influence of TNF and NO on GC-1 spermatogonia cell cycle progression and mortality. TNFR1 and TNFR2 were found in GC-1 cells (immunofluorescence). TNF (10 and 50 ng/ml) and DETA-Nonoate (0.5 and 2 mM), a NO releaser, increased the proportion of cells in S-phase and decreased the proportion in G1, triggering cell death. TNF did not cause oxidative stress, unlike NO, because N-acetyl-L-cysteine (2.5 and 5.0 mM) prevented NO-induced cell cycle arrest and death. GC-1 spermatogonia overcame NO-induced cell cycle arrest but not TNF, since spermatogonia proceeded through the cell cycle when NO was removed. We believe that TNF and NO may contribute to spermatogenesis dysfunction by inhibiting the spermatogonia population from functioning properly. TNF and NO disrupted the spermatogonia cell cycle, causing GC-1 to stall in the S phase [1]. Spermatogenesis is a complicated, coordinated process that requires spermatogonia proliferation and differentiation, meiotic division of spermatocytes, and spermatid differentiation to produce high-quality sperm. Growth factors and cytokines generated by Sertoli cells, peritubular myoid cells, Leydig cells, as well as macrophages, endothelial cells, and substances transported in systemic circulation, all influence spermatogonial proliferation. Immune cells, lymphocytes, macrophages, mast cells, and dendritic cells are generally rare in the testicular interstitial compartment of a healthy man's testis. To facilitate spermatogenesis, the typical testis maintains a balance toward a tolerogenic immunological microenvironment. When a pathogenic state arises, testicular immune cells normally activate, resulting in testicular function impairment. In fact, nearly 30% of testicular biopsies from infertile individuals exhibited asymptomatic localized inflammatory lesions [2,3].

Infections, chemical noxae, or physical causes (genital trauma, vasectomy) can all cause testicular inflammation (orchitis), although most instances are idiopathic. Testicular biopsies from azoospermic individuals usually demonstrate a reduction in the number of proliferating spermatogonia as well as spermatogonial stem cells. In the chronically inflamed testis of infertile individuals, an increased number of cells expressing IL-6, TNF, IL-23, and inducible nitric oxide synthase (iNOS), among other variables, was seen. However, the functional relationship between inflammation and spermatogonia pathology remains unknown. It is widely recognised that pro-inflammatory chemicals such as TNF and NO may disrupt the cell cycle progression of several somatic cell types, resulting in anti-proliferative and apoptotic consequences. Our general hypothesis is that elevated inflammatory mediators in diseased testis hinder spermatogenesis.

In this study, we believe that the inflammatory mediators TNF and NO halt cell cycle progression and/or promote spermatogonia death. To test this idea, we wanted to look at how TNF and NO affect spermatogonia growth and mortality, using the GC-1 spermatogonia cell line as a model. Spermatogonial stem cells (SSCs) support spermatogenesis by balancing self-renewal and differentiation to create progenitor spermatogonia dedicated to sperm formation. We performed single-cell RNA velocity investigations and confirmed the results *in vivo* to characterise the regulatory logic between SSCs and progenitors.

Through mitogen-activated protein kinase (MAPK)/AKT signalling, a predominate quiescent SSC population generates a small minority of cell-cycle-activated SSCs. Activated SSCs generate early progenitors, and mTORC1 inhibition promotes activated SSC accumulation, which is consistent with a blockage to progenitor production. Inhibiting mTORC1 decreases transcription in spermatogonia and particularly changes insulin growth factor (IGF) signalling in early progenitors. Following mTORC1 suppression, Tex14/testes do not accumulate activated SSCs, demonstrating that steady-state mTORC1 signalling promotes

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promotes activated SSCs to create progenitor clones. These findings support a concept of SSC self-renewal based on interconversion between active and quiescent SSCs, as well as mTORC1-dependent differentiation initiation. from stem cells to progenitor clones. The methylation of histone H3 lysine 9 (H3K9) is continually controlled by methyltransferases and demethylases [4,5].

After birth, prospermatogonia develop into differentiating or undifferentiated spermatogonia in spermatogenesis. The epigenetic control of the prospermatogonia to spermatogonia transition, on the other hand, is mainly unknown. We discovered that perinatal prospermatogonia contain exceptionally low levels of di-methylated H3K9 (H3K9me2) and that the H3K9 demethylases JMJD1A and JMJD1B catalyse H3K9me2 demethylation. Male germ cells were completely lost during puberty when JMJD1A and JMJD1B were depleted in the embryonic germline, demonstrating that H3K9me2 demethylation is required for male germline preservation. Germ cells lacking JMJD1A/JMJD1B were unable to develop into functional spermatogonia. Through JMJD1 isozymes, multiple spermatogonial stem cell maintenance genes were activated. We hypothesise that H3K9 demethylation is important for spermatogonia formation during the prospermatogonia-to-spermatogonia transition. In conclusion, JMJD1A/JMJD1B-mediated H3K9me2 demethylation enhances the differentiation of prospermatogonia into functional spermatogonia by creating appropriate gene expression profiles.

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