



**Karolinska
Institutet**

Department of Women's and Children's Health

Antimicrobial and Xenobiotic Defence in the Mammalian Testis

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska
Institutet offentligen försvaras i Skandiasalen, Astrid Lindgrens
Barnsjukhus, Plan 1, Karolinska Sjukhuset

Fredagen den 15 juni, 2012, kl 09.00

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Stockholm 2012

ABSTRACT

Different mechanisms exist in the mammalian testis to protect the germ cells from autoimmune attack, invading microbes, and xenobiotic induced toxicity, which would otherwise be deleterious to the preservation of fertility. The general aim of this thesis was to study these testicular defence mechanisms, including the structural building blocks of the blood– testis barrier (BTB), antimicrobial peptides, proinflammatory cytokines and ATP-binding cassette (ABC) transporter proteins.

Coxsackie and Adenovirus Receptor (CAR) is a cell adhesion molecule present in tight junctions of epithelial cells. We found that CAR was expressed in male germ cells in the human, the rat and the mouse testis, with a localization corresponding to the acrosomal structure of the elongated spermatids as well as in mature spermatozoa. CAR co-localized and co-immunoprecipitated with JAM-C in the mouse testis, suggesting that CAR may function in germ cell differentiation and polarization, similar to JAM-C.

Interleukin-18 (IL-18) is a proinflammatory cytokine that contributes to host defence in epithelial barrier tissues. We found that IL-18, the IL-18 receptor and the interleukin-1 β converting enzyme (ICE) was expressed in the rat testis throughout postnatal development. IL-18 protein and messenger ribonucleic acid (mRNA) were mainly localized in meiotic and post-meiotic germ cells. Only Pro-IL-18 was detected in interstitial fluid and in testicular cell extracts, suggesting that IL-18 normally is in its non-active form in the healthy testis, but may become activated during testicular infection. Recombinant IL-18 stimulated spermatogonial proliferation and thus may act as a growth factor during patho-physiological conditions in the testis.

The nuclear protein High mobility group box chromosomal protein-1 (HMGB1) does also have extracellular immune-functions, including cytokine stimulation and direct antimicrobial activity. We found that HMGB1 was expressed in the nucleus and in the cytoplasm of Sertoli cells in the human and rat testis. HMGB1 protein was also present in interstitial fluid collected from non-treated rat testis, indicating extracellular release. HMGB1 purified from human and rat testis demonstrated strong and direct antibacterial activity and thus may act as an antimicrobial peptide in the seminiferous epithelium, contributing to the protection of the developing germ cells against invading pathogens.

The ABC transporter family is responsible for active transport of substrates across membranes. They are located in barrier tissues such as the BTB and the blood– brain barrier (BBB) and protect against uptake of xenobiotics. We found that testes from immature (6-day-old) rats accumulated significantly higher levels of the ABC transporter substrate and anticancer drug doxorubicin, compared to the testes from 16- and 24-day old rats. This correlated with a significantly lower level of testicular expression of ABC transporters compared to 16- and 24-day-old rats. Thus, lack of a mature ABC transporter efflux system may render the immature testis more susceptible to xenobiotic-induced toxicity.

The studies described here support the view that the mammalian testis has evolved several defence mechanisms to preserve fertility.

ISBN 978-91-7457-762-4