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Oral Presentations

O-9
The correlation between varicocele and unfolded protein response occurred in ER stress

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Background: Excessive reactive oxygen species generation plays a crucial role in male infertility, especially varicocele. One of the most cardinal pathways that defend cells against this destructive situation is the unfolded protein response (the so-called UPR/ER stress response). The UPR/ER is triggered by aggregation of unfolded/misfolded proteins in the Endoplasmic Reticulum (ER) lumen, leading to detach ER chaperons from ER membrane including inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6), and the PKR-like endoplasmic reticulum kinase (PERK). In the face of stress conditions, BiP is detached from membrane sensors and the three mentioned proteins are transiently activated to modify cell survival signals. Eventually, should the stress condition prolong, apoptosis is prompted by specific inducers such as the Jun-kinase/caspase-3 pathway.

Objective: The assessment of UPR/ER pathways in a VCL-induced rat model to find out the plausible role of UPR/ER stress response in varicocele condition.

Materials and Methods: Varicocele induction was surgically performed on ten 8-wk-old adult male Wistar rats, as varicocele group, and ten rats were considered as a control-sham group. After conducting sperm function tests, the expression of BiP, Caspase-3, Bax, Bak, Bim, Bcl2, XBP1, and NRF2 using Real-time PCR, and expression of p-JNK, CHOP, and NRF2 using Western blot were assessed. The data between the two groups were compared with the Independent *t* test, and p-value lower than 0.05 was considered statistically significant between the two groups.

Results: To assess the activation of UPR/ER pathways in VCL testis, the BiP/GRP78/HSAP5 protein level was evaluated, and no difference in the expression of BiP in VCL testis tissue compared with control group was indicated. By prolonging UPR response, IRE1 pathway induces apoptosis by activation of ER-associated protein degradation pathway (ERAD), which is accomplished by XBP1s, and stimulation of JNK/p-JNK pathway by downregulation of Bcl2 and upregulation of Bax and Bak, leading to activation of Caspase-3. Increased level of XBP1s mRNA, phospho-JNK ($p = 0.04$) and caspase-3 transcript (4.84 ± 0.64 versus 1.14 ± 0.14, $p = 0:03$) in the VCL testis tissue, was a sign of activation of the JNK pathway.

Conclusion: Ample evidence has shown that in the UPR/ER stress response, the first pathway to be activated is PERK, then ATF6, and finally IRE1. As CHOP and NRF2 protein content were no higher in VCL testicular extracts compared to control testis, it is clear that late apoptosis pathway, PERK/ATF4/NRF2/CHOP, has not activated. Activation of the p-JNK-induced Caspase-3 apoptotic signal is also suggested that we are in the late stages of the UPR/ER stress response. The UPR/ER response is certainly activated in the VCL testis by activation of the IRE1/JNK pathway.

Key words: *Varicocele, Endoplasmic reticulum stress, Unfolded protein response, ROS.*

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