Transcriptional Basis of Idiopathic Central Hypogonadism in Isolated Congenital Cryptorchidism with Defective Mini-Puberty

Hadziselimovic Faruk 1, Gegenschatz-Schmid Katharina 1, Verkauskas Gilydas 1, Demougin Philippe 2, Stadler Michael B. 3, Bilis Vytautas 3, Malcius Dalius 3, Dasevicius Dalius 3

Objective: Cryptorchidism represents the most common cause of non-obstructive azoospermia in man [Fedder et al., 2004]. Large prospective study showed that despite successful surgery infertility develops if due to defective mini-puberty the transformation of Ad spermatagonia was compromised (high infertility risk group; HIR) [Hadziselimovic, and Hoecht, 2008]. Incidence of a high infertility risk subgroup was reported to be as high as 47% [Bilis et al., 2015]. The available molecular data favors LH deficiency with EGR4 as a master regulator to be responsible for infertility development [Hadziselimovic et al., 2009]. The study objective was to explore the causative role of isolated congenital cryptorchidism in azoospermia in the context of our previously published GeneChip data by utilizing whole-genome RNA profiling of testicular biopsies and DNA strand-specific RNA-sequencing [Hadziselimovic et al., 2009, 2011].

Method: Fifteen cryptorchid patients, aged 7 months to 5 years, were selected based on histological results. During surgery, testicular tissue biopsies were collected and split in half for histological examination and RNA-sequencing. Utilizing semi-thin sections, seven were classified as high infertility risk (HIR) and eight as low infertility risk (LIR) group.

Results: Our previous independent study analyzing differentially expressed genes involved in germ cell and in the hypothalamus-pituitary-testicular axis development (using oligonucleotide microarray technology) reported 59 down-regulated genes in the HIR versus LIR group [Hadziselimovic et al., 2009, 2011]. The differential gene expression analyses conducted in this study confirmed 57 of these gene targets. Observed multiple differences in gene expression between high and low infertility risk group underscores the importance of an intact hypothalamic-pituitary-testicular axis during the period of mini-puberty. The important new finding was a decreased PROK2, CHD7, FGFR1 and SPRY4 genes expression in the HIR group (Fig.1). Furthermore, decreased signaling of five mediators of GnRHR gene, DLX2, DLX3, MSXI, NR4A1 and LHX3 genes and two LH-promoter regulating genes EGR4 and PITX1 gene were also observed in the high infertility risk group. Thus, insufficient gene expression directly involved in the modulation of αGSU and LHβ expression implies a direct effect on LH secretion and provides a plausible explanation for the reduced LH levels measured in HIR patients [Hadziselimovic et al., 1979, Verkauskas et al., 2016].

Conclusion: Presented molecular data strongly supports the theory that insufficient PROK2/CHD7/FGFR1/SPRY4 genes signal together with reduced EGR4/PITX1 genes expression is responsible for deficient LH secretion during mini-puberty, and thus resulting in azoospermia or infertility development (Fig. 2).

References:

Nothing to declare