Comparison of global gene expression profiles of microdissected human foetal Leydig cells with their normal and hyperplastic adult equivalents - DTU Orbit (09/11/2017)

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STUDY QUESTION: Do human adult Leydig cells (ALCs) within hyperplastic micronodules display characteristics of foetal LCs (FLCs)?SUMMARY ANSWER: The gene expression profiles of FLCs and all ALC subgroups were clearly different, but there were no significant differences in expressed genes between the normally clustered and hyperplastic ALCs.WHAT IS KNOWN ALREADY: LCs are the primary androgen producing cells in males throughout development and appear in chronologically distinct populations; FLCs, neonatal LCs and ALCs. ALCs are responsible for progression through puberty and for maintenance of reproductive functions in adulthood. In patients with reproductive problems, such as infertility or testicular cancer, and especially in men with high gonadotrophin levels, LC function is often impaired, and LCs may cluster abnormally into hyperplastic micronodules (defined as clusters of > 15 LCs in a cross-section).STUDY DESIGN, SIZE, DURATION: A genome-wide microarray study of LCs microdissected from human foetal and adult tissue samples (n = 12). Additional tissue specimens (n = 15) were used for validation of the mRNA expression data at the protein level.PARTICIPANTS/MATERIALS, SETTING, METHODS: Frozen human tissue samples were used for the microarray study, including morphologically normal foetal (gestational week 10-11) testis samples, and adult testis specimens with normal LC distribution, LC micronodules or LC micronodules adjacent to hCG-producing testicular germ cell tumours. Transcriptome profiling was performed on Agilent whole human genome microarray 4 x 44 K chips. Microarray data pre-processing and statistical analysis were performed using the limma R/Bioconductor package in the R software, and differentially expressed genes were further analysed for gene set enrichment using the DAVID Bioinformatics software. Selected genes were studied at the protein level by immunohistochemistry.MAIN RESULTS AND THE ROLE OF CHANCE: The transcriptomes of FLCs and ALCs differed significantly from each other, whereas the profiles of the normally clustered and hyperplastic ALCs were similar despite morphological heterogeneity. The study revealed several genes not known previously to be expressed in LCs during early development, including sulfotransferase family 2A member 1 (SULT2A1), WNT1-inducible signalling pathway protein 2 (WISP2), hydroxyprostaglandin dehydrogenase (HPGD) and insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1), whose expression changes were validated at the protein level.LARGE SCALE DATA: The transcriptomic data are deposited in ArrayExpress (accession code E-MTAB-5453).LIMITATIONS, REASONS FOR CAUTION: The small number of biological replicates and the necessity of RNA amplification due to the scarcity of human tissues, especially foetal specimens, are the main limitations of the study. Heterogeneous subpopulations of LCs within micronodules were not discriminated during microdissection and might have affected the expression profiling. The study was constrained by the lack of availability of truly normal controls. Testis samples used as 'controls' displayed complete spermatogenesis and were from patients with germ cell neoplasia but with undetectable hCG and normal hormone levels.WIDER IMPLICATIONS OF THE FINDINGS: The changes in LC morphology and function observed in patients with reproductive disorders possibly reflect subtle changes in the expression of many genes rather than regulatory changes of single genes or pathways. The study provides new insights into the development and maturation of human LCs by the identification of a number of potential functional markers for FLC and ALC.

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