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Prenatal exposure to endocrine disruptors induces trans-generational deregulation of microRNAs involved in the development of male primordial germ cells

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Human epidemiological studies have showed that the risk of developing diseases in adulthood could be related to disorders that have their origin during embryogenesis and the fetal life. In this sense a clear example of the "fetal origins of disease" in human are some forms of testicular cancer. In male germ cell tumors have their origin on undifferentiated primordial germ cells (PGCs)-gonocyte which maintaining the undifferentiated state in the adult testis may cause carcinoma in situ and neoplasia. Testicular tumors are the most common solid cancers in men aged 15–40 years from developed countries, constituting 2% of all human malignancies. In mammals, germ cell differentiation initiates in the early embryonic period as PGCs. After specification, the PGCs migrate to the gonad (at around 10.5dpc in the mouse), at which time they are highly proliferative and have the ability to form either the male (spermatogenic) or female (oogenic) germ lines. Experimental evidence suggests that male-female germ cell fate is strongly influenced by the surrounding cellular micro-environment as well as external environmental factors like endocrine disruptors. Endocrine disruptors EDs are described by World Health Organization (WHO) as an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations. Over 150 different contaminants have been detected in various tissues and fluids of the US human population, some as bisphenol A (BPA) and phthalates in nearly the entire population. Recent studies, from the host laboratory, showed that the effects of each ED produce specific alterations of gene signatures, this phenomena was non-dependent to the concentration of the toxicant or developmental period of exposition, being detected in adult mice that were only exposed at the very early window of development. Evidences in animal models suggest that EDs may affect not only the exposed individual but also the offspring and subsequent generations. In the mechanisms of trans generational effects could also be involved changes in DNA methylation and deregulation of small non-coding RNAs including microRNAs (miRNAs), as has been recently reported. miRNAs are non-coding single-stranded RNAs of 20-25 nucleotides in length acting as negative post-transcriptional regulators of mRNAs and consequently modulating the level of the corresponding proteins. miRNA are implied in the regulation of pre-implantation development stem cell and PGC development, differentiation and tumor malignancy. Consequently, this complex homeostasis of gene regulation can be altered by the EDs. For example, these effects can be detected as apoptosis in PGCs and disruption of differentiation, but the molecular pathways are not well defined. The effects of EDs on germ cells can also be observed at cytogenetic level, affecting processes as meiosis. Meiosis is the reduction division of the genome that produces haploid cells. In males initiate in pubertal period but in females the process begins during fetal life and only ends if fertilization of oocytes occurs at metaphase II stage. Recent studies demonstrated that the exposure during fetal development to a wide knows ED: BPA, induceaneuploidies. Aneuploidy is defined as abnormal number of chromosome, as a consequence of non-disjunction during meiosis I, and is classically consider as one of the main causes of abortion during 1st trimester.

Biography

Miguel Angel Brieno-Enriquez received his medical degree from Autonomous University of San Luis Potosi, Mexico, and his PhD from Autonomous University of Barcelona, Spain. His research includes the study of molecular and cytogenetic effects of endocrine disrupting chemicals on humanfetal oocytes. During the last two years, he was working as Postdoctoral Researcher at the Laboratory of Molecular Biology of Gametogenesis CIB-CSIC, Madrid, Spain. His work in these years focused on the role of small RNAs in gonadal development as well as the effects of endocrine disruptors on miRNA profile in mouse primordial germ cells. Nowadays, he is working as Post-doctoral Researcher in Cornell University.

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