Gynecological Endocrinology

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Ovarian and reproductive disease modelling using stem cell technology

We combine human stem cell technology to unravel the original of signaling pathways in reproductive disease and in early embryonic development. As a putative mediator of inhibin signaling in the ovary we originally identified an E3 ubiquitin ligase for inhibin B receptor, EULIR, which is now renamed as HECTD1. In order to study its function, we generated a new mutant mouse model using the gene trap strategy. Homozygous mutant mice resulted in a early embryonic lethality, displaying severe growth retardation, abnormal placental development and defective of neural tube closure (e.g. spina bifida). Hectd1 expression is detected in specific cell populations of multiple tissues (Fig. 1), is regulated by insulin and by heat and hypoxia. E3 ligase activity of Hectd1 regulates the protein level of Iqgap1 through ubiquitination and mediates the dynamics of focal complexes including the recruitment of paxillin and actinin. Loss of Hectd1 resulted in accelerated cell spreading but impaired directionality of migration and reduced β-catenin localization at adherens junctions, suggesting a molecular mechanism in which Hectd1 regulated the cell-cell contact and cell movements during neural tube development. In addition, we found that Hectd1 is a novel centrosome protein (Fig. 2) and it regulates centrosome duplication and disjunction. Hectd1 interacts with numbers of proteins in Y2H and MS assays, suggesting the eminant role of this gene in many basic cellular actions.

Within the frame of the Swiss Center of Applied Human Toxicology (SCAHT) we established a novel *in vitro* assay based on differentiating human embryonic stem cells (hESC) for testing early neurodevelopmental toxicity, focusing to stages corresponding to the formation of the neural tube and the generation and proliferation of the neural precursors. This model was setup as a proof of principle aiming at demonstrating that hESC can be used for developmental toxicity testing. We have confirmed the validity and reliability of our assay by analyzing the effect of three neuroteratogens: valproic acid (VPA), cyclopamine (CPA) and nicotine and two control compounds, the hepatotoxic but non-embryotoxic compound theophylline and the neutral compound saccharin, on four independent hESC lines. We have shown that our assay allows the specific identification of neurodevelopmental toxicants, can identify a developmentally toxic effect independently of effect on cell viability, allows an estimation of the toxic dose coherent with *in vivo* data, can distinguish effects of toxicants with different mode of action and different outputs *in vivo*, but does not allow to recognize, and therefore to predict, a particular *in vivo* defect. To determine the correct readout(s), we questioned the capacity of our system to recognize/predict a neural tube defect (NTD). We found that immunocytochemistry analysis cannot be used to reveal differential effects of VPA vs non NTD-inducing toxicants. However, we have selected a number of other markers, specifically and transiently expressed in rosette cells, whose expression can be quantified by RT-PCR. Dose/response experiments have been performed and analyses are ongoing to identify those with the optimal differential expression among the toxicants evaluated.

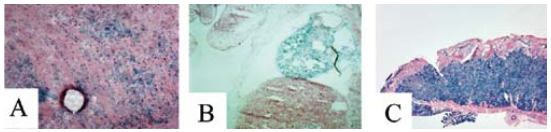

Fig. 1: Expression of Hectd1 in brain (A), embryonic heart at E13.5 (B) and placenta (C, E16.5).

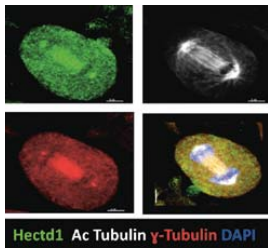

Fig. 2: Hectd1 is a novel centrosome protein

Selected Publications

Jia, Z., Gao, S., M'Rabet, N., De Geyter, C., Zhang, H. (2014) Sp1 is necessary for gene activation of Adamts17 by estrogen. Journal of Cellular Biochemistry, 115: 1829–1839.

Sterthaus O, Feutz AC, Zhang H, Pletscher F, Bruder E, Miny P, Lezzi G, De Geyter M, De Geyter C. Gene expression profiles of similarly derived human embryonic stem cell lines correlate with their distinct propensity to exit stemness and their different differentiation behavior in culture. Cell Reprogram. 2014 Jun;16(3):185–95

De Geyter C, M'Rabet N, De Geyter J, Zürcher S, Moffat R, Bösch N, Zhang H, Heinimann K. Similar prevalence of expanded CGG repeat lengths in the fragile X mental retardation I gene among infertile women and among women with proven fertility: a prospective study. Genet Med. 2014 May;16(5):374–8