Differentiation of human embryonic stem cells into multiple lineages - a toxicogenomic platform for developmental toxicity.

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Published on 23 Oct 2010

The differentiation of human embryonic stem cells (hESC) into multiple organotypic cells has great potential in developmental biology and regenerative medicine. In recent years mouse embryonic stem cells were used for in vitro toxicity studies, in particular developmental toxicity studies. We combined hESCs with toxicogenomics for the construction of a developmental toxicity platform. hESCs were randomly differentiated into multiple lineages such as endoderm, ectoderm and mesoderm and challenged with thalidomide at sublethal doses. To identify significant toxicity markers, microarray analysis was performed with Illumina HumanHT-12 v3 Expression BeadChip. We could identify 40 significantly upregulated and 407 significantly downregulated genes (P<0.05) in day 14 Thalidomide treated samples compared to day 14 untreated samples. Among these transcripts, we found that germ line markers expressed on day 14 were down regulated when challenged with thalidomide. Gene ontology enrichment analysis reveals thalidomide treatment downregulated organ development, anatomical structure development, multicellular organismal development and circulatory system development in biological process. Shortlisted developmental markers were further validated with real time quantitative PCR (RT-qPCR) in independent experiments. To validate these markers a similar experiment was carried out with penicillin as a control compound where no changes were observed in the expression level. Further more, to study the interspecies differences, a similar experiment was carried out with CGR8 mouse embryonic stem cells. Interestingly we found a battery (Markers shortlisted in hESC study) of markers was significantly repressed with thalidomide at sublethal concentration in RT-qPCR studies. Thus, the multilineage differentiation of pluripotent stem cells combined with transcriptioanal profiling of developmental markers may be a strong tool for the developmental toxicity platform.