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Tumor progression in aberrant karyotypic human embryonic stem cells derived from long term suboptimal culture

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Human embryonic stem (hES) cells have the developmental potential to form derivatives of all three embryonic germ layers and indefinitely proliferate and pay an importanct role in regenerative medicine and cell replacement therapy. Recently, some reports indicated that during long term culture the HES cells acquired genomic alterations from chromosome to gene level, which are similar to those occurred in the human tumorgenesis and raise concerns again about the safety of future clinical use of the cultured HES cells. Here, in our laboratory we reported one human embryonic stem cells, *ch*HES-3 was established in kunmingbai mouse embryonic fibroblast feeder cells with high density. In the modified Thomson serum-free culture the cell acquired karyotypic change from the simplity to complexity. In earlier stage (P34) the duplication appeared in 1p32-p36, the mltichromosome complex rearrangeand in intermediate stage (P44-99) and tumor-like multikaryotype chimera in the later (P142-198) were acquired. The results of FACS showed that the percentage of S phase increased and apoptosis ratio dercreased with the karyotype complexity. Teratoma formation experiments *in vivo* and pathological report showed the normal karyotypic HES cells formed relative mature teratoma, the *ch*HES3-p96 cells formed malignant immtrure grade three teratoma. and teratoma included some primary neur-tube construction. The gene expression profiles of normal, aberrant karyotypic HES cells and embryonal carcinoma cells were analysed by gene chip. We found that the expression profiles of oncogene, suppress tumor genes and genes related with aopotosis had tendency to EC with complexity and compared with the normal karyotypic HES cells, the activating Wnt pathway gene up-regulated and the suppressing gene down-regulated in the aberrant karyotypic HES cells. The species and abundance of the wnt gene family had obvious difference in difference batch mouse embryonic fibroblast feeder cells. The results above all showed that HES might appear adaption karyotypic change in the suboptimal culture condition, and the adaption HES cells had more stronger power of self renewal and anti-apopotosis and could form malignant teratoma compared with the normal HES cells. The change of the gene expression profiles indicated that the transformation HES cells had a tendency to progression to malignant cells, and Wnt family members expressed in the feeder cells might have involved in it.

***Keywords*:** human embryonic stem cell, aberrant karyotype, Wnt pathway

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