Genetic Markers for Gestational Trophoblastic Disease

Annie NY Cheung

Department of Pathology, The University of Hong Kong

Gestational trophoblastic diseases (GTD) is a heterogeneous group of diseases arise from the placental trophoblasts. It encompasses hydatidiform moles (HM), invasive mole, choriocarcinoma, placental site trophoblastic tumour and epithelioid trophoblastic tumour. The latter three are frank malignant tumours whilst HM can be considered as abnormal conceptuses capable of developing malignant disease requiring chemotherapy in 15% to 30% of cases. The pathogenesis concerning GTD remains unanswered questions and few biological parameters, except serial HCG assays, have been found useful in predicting the progress of HM to malignant disease.

It is believed that HM are chromosomally abnormal androgenetic pregnancies arising either with all their nuclear DNA being paternally derived transmitted only from the spermatozoa to an anuclear "empty ovum" or allowing an extra chromosomal load of paternal origin. We have demonstrated that chromosome in situ hybridization and fluorescent microsatellite genotyping after microdissection can assist in histological diagnosis of this disease.

We have demonstrated in our previous studies that telomerase and apoptotic activities in HM were associated with the development of malignant disease. The telomerase activity was assessed by the telomeric repeat amplification protocol (TRAP) assay while the apoptotic activity was evaluated by the terminal deoxynucleotidyl transferase (TdT)-mediated deoxyuridine triphosphate (dUTP) nick end labeling (TUNEL) method and M30 Cytodeath immunohistochemistry. HM with high telomerase activity and low apoptotic index are more likely to develop aggressive disease requiring chemotherapy.

The differential expression of genes in HM that subsequently developed GTN was compared with HM that spontaneously regressed, using the AtlasTM Human Apoptosis Array, Suppression Subtractive Hybridization (SSH) combined with cDNA microarray. As confirmed by quantitative RNA expression and immunohistochemical study in correlation with clinical data, Mcl-1 and Insulin-like growth factor binding protein 1 (IGFBP1) have been found to be potentially useful markers for predicting the clinical behavior.

Promoter hypermethylation of several tumour suppressor genes has been documented by methylation specific PCR in HM, though at a frequency lower than choriocarcinoma. In particular promoter hypermethylation of p16 alone, or combined with E-cadherin, was significantly correlated to such development of persistent disease, suggesting a possible role in patient management.

In conclusion, application of ancillary laboratory techniques identifies potential genetic markers that may predict clinical behaviour of GTD and facilitate patient management.