GENETICS

Gene profiles identify malignant pheochromocytomas

Differential expression of a small number of genes could help clinicians to distinguish between benign and malignant pheochromocytomas with high diagnostic accuracy, according to a report published in the *Annals of Surgery*.

Pheochromocytomas comprise a heterogeneous group of rare, catecholamine-secreting tumors. The need to distinguish malignant pheochromocytomas from their benign counterparts is critical for successful management of the disease. Unfortunately, however, histopathologic criteria have so far proven unreliable; as a consequence, the development of novel diagnostic tools has become an active area of biomedical research.

The steps involved in the malignant transformation of pheochromocytomas are poorly understood. Insoo Suh (University of California, San Francisco) and colleagues aimed to uncover the molecular mechanisms that underpin this process by exploiting microarray technology to perform a genome-wide expression profiling study. This powerful technique allows researchers to simultaneously analyze the expression of thousands of genes in a single biological sample. The raw data are then used to create a database that can be 'mined' using sophisticated bioinformatics software to determine patterns or associations of gene expression.

Suh *et al.* analyzed the gene expression profiles of 58 pheochromocytomas, 13 of which had been classified as malignant owing to the presence of metastases in the lymph nodes or at distant sites. Benign tumors were classified on the basis of biochemical cure after surgical removal of a localized lesion (mean follow-up 5.6 years).

The researchers performed a supervised cluster analysis of the microarray data, which demonstrated that many genes are differentially expressed between benign and malignant pheochromocytomas. The expression of 26 of these genes was validated by quantitative real-time PCR.

In addition, a gene-ontology analysis was undertaken to determine the potential functions of the differentially expressed genes. Eight functional groups were identified and included genes involved in signal transduction, transcription, protein synthesis, protein transport, ion transport, chemotaxis, smooth-muscle contraction and electron transport.

Suh *et al.* next performed a gene-set-enrichment analysis that identified 20 sets of genes whose expression was enriched in malignant tumors and 14 gene sets that were differentially expressed in benign lesions. When used in combination, a subset of these genes (*CFC1*, *ESYT2* [formerly *FAM62B*], *HOMER1*, *LRRN3*, *TBX3*, *ADAMTS9*) displayed high accuracy for diagnosis of malignant pheochromocytomas.

In addition to providing insight into the process of malignant transformation, the identification of genes characteristic of malignant pheochromocytomas might have important clinical implications. In future, patients could potentially be treated according to their 'malignancy-risk' gene-expression profile.

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Original article Suh, I. *et al.* Candidate genes associated with malignant pheochromocytomas by genome-wide expression profiling. *Ann. Surg.* **250**, 983–990 (2009)