NEW INSIGHTS INTO THE GENETICS OF PHEOCHROMOCYTOMAS

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Pheochromocytomas are neuroendocrine tumors that may be either sporadic or manifestation of a familial cancer syndromes. In recent years new data have been obtained on the genetics of pheochromocytoma, implicating many genes and signaling pathways.

Succinate dehydrogenase (SDH) is a complex II in the mitochondrial respiratory chain. Two subunits of this protein are especially interesting in pheochromocytoma, the one encoded with *SDHB*, and the one encoded with *SDHD* gene. Germline mutations in *SDHB* and *SDHD* genes have been found to be responsible for susceptibility to pheochromocytoma. Germline mutations in the *ret* protooncogene are very frequent (95%) in syndrome-associated pheochromocytomas. Mutations in the *VHL* and loss of the wild-type allele of *NF1* tumor suppressor genes have also been implicated in syndrome-associated pheochromocytomas. On the other hand, the genetic basis of sporadic pheochromocytoma is unclear, and much work is still required to determine the final list of genes involved. Although it was suspected that the *ret* protooncogene may also be involved in sporadic pheochromocytoma, only about 8% of cases show *ret* mutation. The mutations of the *VHL* and *NF1* genes are also uncommon.

Our research on sporadic pheochromocytoma showed that point mutations of *k-ras* were frequent findings, namely 88.9% of pheochromocytomas harbored activating *k-ras* mutations in codon 12. The k-Ras and c-Myc protein expression was up-regulated. Moderate up-regulation of k-Ras, was observed in 61.5% of samples, while strong expression was not present. Increased levels of Myc protein were detected in 92.3% of cases. Strong upregulation was observed in 6 pheochromocytoma samples and also in the investigated lymph node metastasis (53.8%). Five out of 10 samples with activating *k-ras* mutation had upregulated levels of both k-Ras and c-Myc.

Our investigations on adenomatous polyposis coli, (APC) and E-cadherin (CDH1) tumor suppressor genes in sporadic pheochromocytomas detected samples with allelic imbalance of the APC and CDH1 genes. Interestingly, another type of genomic instability — microsatellite instability (MSI) of the E-cadherin gene was detected in 30.8% of pheochromocytomas. MSI indicates that mismatch repair may be targeted in pheochromocytoma cells.

We also analyzed sporadic pheochromocytomas for the activating point mutations in *Ret* gene, and for loss of heterozygosity (LOH) in *NF1*, *p53*, *BRCA1*, *nm23-H1*, *SDHB* and *SDHD* tumor suppressor genes. The results showed that changes were confined to *ret* oncogene (15%), while *NF1*, *p53*, *BRCA1*, *nm23-H1* were not targeted in phaeochromocytoma sample. The analysis showed two cases with LOHs of *SDHB* gene and one case with LOH of *SDHD*.

Our findings may contribute to better understanding of pheochromocytomas genetic profile.