Pheochromocytoma in rats with multiple endocrine neoplasia (MENX) shares gene expression patterns with human pheochromocytoma.

Abstract:

Pheochromocytomas are rare neoplasias of neural crest origin arising from chromaffin cells of the adrenal medulla and sympathetic ganglia (extra-adrenal pheochromocytoma). Pheochromocytoma that develop in rats homozygous for a loss-of-function mutation in p27Kip1 (MENX syndrome) show a clear progression from hyperplasia to tumor, offering the possibility to gain insight into tumor pathobiology. We compared the gene-expression signatures of both adrenomedullary hyperplasia and pheochromocytoma with normal rat adrenal medulla. Hyperplasia and tumor show very similar transcriptome profiles, indicating early determination of the tumorigenic signature. Overrepresentation of developmentally regulated neural genes was a feature of the rat lesions. Quantitative RT-PCR validated the up-regulation of 11 genes, including some involved in neural development: Cdkn2a, Cdkn2c, Neurod1, Gal, Bmp7, and Phox2a. Overexpression of these genes precedes histological changes in affected adrenal glands. Their presence at early stages of tumorigenesis indicates they are not acquired during progression and may be a result of the lack of functional p27Kip1. Adrenal and extra-adrenal pheochromocytoma development
clearly follows diverged molecular pathways in MENX rats. To correlate these findings to human pheochromocytoma, we studied nine genes overexpressed in the rat lesions in 46 sporadic and familial human pheochromocytomas. The expression of GAL, DGKH, BMP7, PHOX2A, L1CAM, TCTE1, EBF3, SOX4, and HASH1 was up-regulated, although with different frequencies. Immunohistochemical staining detected high L1CAM expression selectively in 27 human pheochromocytomas but not in 140 nonchromaffin neuroendocrine tumors. These studies reveal clues to the molecular pathways involved in rat and human pheochromocytoma and identify previously unexplored biomarkers for clinical use.

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