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Molecular characterization of a metastatic neuroendocrine cell cancer arising in the prostates of transgenic mice.

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Abstract

The features and functions of prostatic neuroendocrine (NE) cells remain ill-defined. Neuroendocrine differentiation (NED) in adenocarcinoma of the human prostate (CaP) is associated with more aggressive disease, but the underlying mediators are poorly understood. We examined these issues in transgenic mice that utilize regulatory elements from the cryptdin-2 gene (Defcr2) to express simian virus 40 large T antigen (TAg) in prostatic NE cells. CR2-TAg mice develop prostatic intraepithelial neoplasia at 8 weeks of age, 1 week after the onset of TAg expression. An invasive phase follows 2-4 weeks later, with lymph node, liver, lung, brain, and bone metastases appearing within 16 weeks. DNA microarray studies revealed 122 mRNAs that were increased >/=2-fold in duplicate assays of 16-week-old CR2-TAg versus normal prostates. Thirty two transcripts encode proteins associated with neurons and endocrine cells (e.g. basic helix loop helix, SRY-related high mobility group box and sine-oculis homeobox transcription factors, Hu RNA-binding proteins, **neuronatin**, Racgap1, collapsin response mediator protein-1, synaptotagmin-1, proprotein convertase, and secretogranins). Follow-up studies of candidate mediators and biomarkers of differentiation/growth in the microarray data set involved real time quantitative reverse transcriptase-PCR assays of laser capture microdissected NE cells from CR2-TAg prostates plus liver metastases, and immunohistochemical comparisons of transgenic mouse prostates and 35 human CaP samples. Our findings include (a) expression of the bHLH mouse achaete-scute homolog (mASH1) in normal and CR2-TAg NE cells and foci of NED in human CaP, (b) glutamic acid decarboxylase and its product (gamma-aminobutyric acid) in neoplastic NE cells juxtaposed next to cohorts of normal gamma-aminobutyric acid receptor expressing secretory cells (a potential route for paracrine interactions between these two epithelial lineages), and (c) aromatic l-amino-acid decarboxylase, but not its dopamine/serotonin products, in CR2-TAg NE cells and NED. These results underscore the value of CR2-TAg mice for characterizing normal NE cell biology and tumorigenesis.

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