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IDENTIFICATION OF PROGNOSTICALLY RELEVANT SUBSETS OF COLORECTAL CARCINOMAS BASED ON CLUSTERING ANALYSIS OF PATHOLOGIC AND MOLECULAR DATA

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During the last decade, research about colorectal cancer (CRC) classification assessed a wide range of potential prognostic biomarkers but ignored the robust clinical significance of pathologic predictors. In this study, unsupervised hierarchical clustering analysis was used to investigate the possibility of identifying prognostically relevant groups of CRCs by integrating both pathologic and molecular factors.Unsupervised hierarchical clustering analysis was done by using 17 markers of putative prognostic significance in 129 CRCs and survival analysis was done by Kaplan-Meier method.Three prognostically relevant subsets of CRCs were identified by clustering analysis (p=0.0006). The efficacy of the individual clustering predictors was evaluated by X2 test or Fisher's exact test. We found that the following markers showed significant differences between the three groups: tumor location, histologic type, grade, pT stage, macroscopic growth, invasive tumor pattern, neuroinvasion, angioinvasion, lymphoinvasion, presence of fibrosis, lymphoid infiltrate, MSI and 5q, 17p, 18q LOH status, BRAF mutation and MGMT methylation status.Our study suggests that unsupervised hierarchical clustering analysis of pathologic and molecular data identifies three prognostically relevant subsets of CRCs and that a more accurate classification of CRCs should combine pathologic and molecular predictors in order to improve our understanding of the disease and the selection of optimal therapy.

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ACTIVITY AND GENOMIC EXPRESSION OF ENZYMES CONTRIBUTING TO THE MRS CHOLINE PROFILE OF OVARY CANCER CELLS

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Aberrant phosphatidylcholine (PC) metabolism in cancer cells point to novel biomarkers of tumor diagnosis and may represent the target of newly designed anti-cancer therapies. Two- to 3.5-fold [illegible] (EONT) (E Iorio et al. Cancer Res 2005; 65:9369-7[illegible] This study investigates activities and genom[illegible] expression of enzymes responsible for PC[illegible] accumulation in EOC cells.**Methods.** Human EOC ce[illegible] lines: OVCAR3, IGROV1, SKOV3, CABA 1. EONT: cel[illegible] from normal ovary surface epithelium (OSE), and no[illegible] tumoral, immortalized cell variants (IOSE, hTERT[illegible] Enzymatic activities were measured by using MRS based assays at 9.4T and 16.4T. Microarray-base[illegible] gene expression analysis was performed usin[illegible] Affymetrix HG-U133Plus2 platform on EOC and EONT focusing on expression of genes involved in cholin[illegible] metabolism.**Results.** In the Kennedy pathway ar[illegible] average 20-fold increase was found in the activity o[illegible] choline kinase (chok) in EOC vs. EONT cells In catabolic pathways, the activity of PC-specific phospholipase C (PC-plc) strikingly increased (up to 17x). The activity of phospholipase D (pld) and glycerophosphocholine-phosphodiesterase (GPC-pd) only increased 2-4x in some (but not all) EOC cells. Genomic analyses on enzymes of the Kennedy pathway showed: 10x chokα upregulation in cancer cells, associated with practically unaltered chokβ expression: 30% decrease in cytidylyltransferase CCT1α and a 38% increase in CCT1β and 40% increase in cholinephosphotranferase CPT1. The overall expression of pld family genes decreased by about 20%. Real-time PCR will be performed on genes involved in choline metabolism to validate the microarray data results. Regarding PC-plc, for which no genomic information is as yet available, MRS analyses confirmed its role in modulating the PCho profile in cells exposed to PC-plc inhibitor. **Conclusions.** Major contributions to PCho accumulation in EOC cells are identified in up-regulation/activation of chokα and increase in PC-plc activity. Emerging knowledge on selective genomic/biochemical regulation of PC-cycle enzymes may open novel ways to targeted anticancer therapies in EOC.

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CLAUDIN IMMUNOHISTOCHEMICAL EXPRESSION PATTERN IS SPECIFIC FOR SOLID-PSEUDOPAPILLARY TUMOR AND PANCREATIC ENDOCRINE TUMOR

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Background. Solid-pseudopapillary tumor (SPT) of the pancreas is a rare neoplasm with indolent biological behavior usually cured by surgery. However, the distinction between SPT and pancreatic endocrine tumors (PET) can be difficult both at imaging and cytological-histological level. The cell-cell adhesion proteins E-cadherin and ß-catenin have been shown to be involved in SPT, where they are both dislocated from their normal location on the cell membrane, possibly driven by ß-catenin mutations. Claudins are cell-cell adhesion proteins essential for the formation of tight [illegible]