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MODERN PATHOLOGY

Mutations in colorectal neuroendocrine carcinomas

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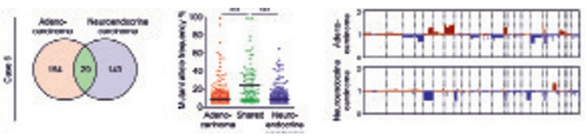

Neuroendocrine carcinomas (NECs) of the colorectum appear to share many genetic alterations with colorectal adenocarcinomas. In fact, many neuroendocrine carcinomas show adjacent glandular adenomatous or adenocarcinomatous components. No definitive genetic data have been collected regarding the molecular derangements characteristic of neuroendocrine carcinomas. Using analyses of 15 colorectal NECs, Woischke *et al* investigated the shared genetic alterations and the three mutations with the highest allele frequencies: *TP53*, *KRAS*, and *APC*. The finding of identical *KRAS* mutations in both glandular and NEC components suggests a clonal origin to both types of tumor, with yet-to-be-explored independent additional mutational evolution of the two components after clonal divergence. The relatively small proportion of shared mutations between the neuroendocrine and glandular components suggests an early divergence. The group proposes that, with increasing understanding of the molecular biology of these tumors, a distinct classification may better support accurate characterization and clinical management of these neoplasms in the future.

Low-grade triple-negative breast neoplasia

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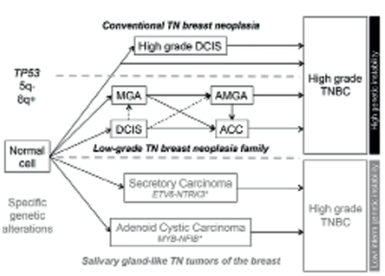

Acinic cell carcinoma is an indolent invasive breast cancer, and microglandular adenosis is a neoplastic proliferation. Geyer and colleagues assessed somatic mutations, insertions, deletions, and copy number alterations in acinic cell breast carcinoma. Using triple-negative breast cancer tissue as a model, the group identified *TP53* as the sole highly recurrently mutated gene in microglandular adenosis (75%) and acinic cell carcinoma (88%). They propose that microglandular adenoses/atypical microglandular adenoses and acinic cell carcinomas may constitute a spectrum of low-grade triple-negative breast cancers. They developed an evolutionary model of triple-negative breast neoplasms, with varying characteristic *TP53* mutations distinguishing two groups of triple-negative breast cancer: low-grade, which rarely metastasizes (represented by acinic cell and microglandular adenosis) and high-grade, which may evolve from the low-grade form. They conclude that more research is needed to determine how the low-grade cancer progresses to the high-grade, and the implications for breast cancer care.

LABORATORY INVESTIGATION

CD68, an immunomarker with a day job

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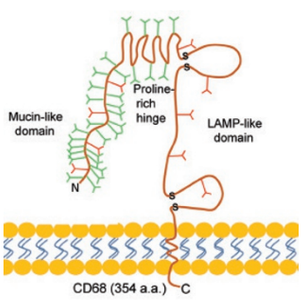

Chistiakov *et al* reviewed the use of CD68 as a cytochemical marker in histochemical analysis of inflammation, cancer, and other immunohistopathological conditions. They note that the function of CD68 has been little investigated, but its preferential location within late endosomes suggests a role in peptide transport/antigen processing. The group assessed the role of CD68 in osteoclast development, in which macrophage colony-stimulating factor and nuclear factor-κB were shown to induce CD68 expression. In cancer, CD68 was shown to be expressed in metastatic tumor cells. Tumor cells can widely express immune markers to escape macrophage-mediated phagocytosis and cell-damaging effects from cytotoxic $CD8^+$ T cells during invasion of a normal, non–tumor tissue environment. The research has enabled the group to identify new roles for CD68 outside its

established use as a macrophage marker in histology. Its role in immunity is intriguing, but there much remains to be investigated.

Covalently deposited dyes for immunohistochemistry

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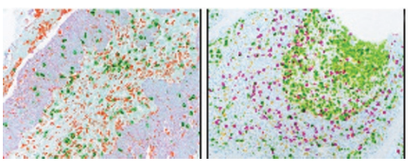

Day *et al* used a multiplex analysis of biomarkers using reporter dyes with spectral properties that enable discrimination of signals. The broad absorbance of chromogens used for immunohistochemistry make them difficult to combine. Fluorescent signals are narrower and can be combined, but they are not suitable for light microscopy. The researchers synthesized and characterized a family of tyramide chromogens and assessed their deposition *in situ* using covalent deposition of selected dyes conjugated with tyramine. The ability to mix the new chromogens and generate new colors enabled them to seek out multiple biomarkers in a single assay on a single tissue section. The narrow absorbance bands made it possible to easily distinguish colocalized biomarkers from individual biomarkers. This technique will have interesting applications in translational research, but perhaps also in the clinical world because traditional morphologic topology of histology sections is better visualized with light than with fluorescent microscopy.

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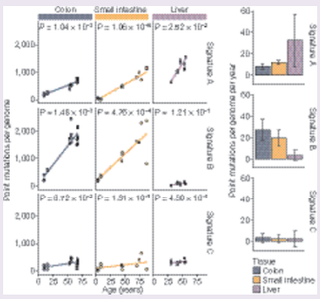
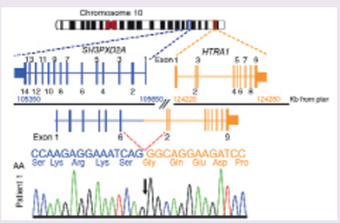
Mutation accumulation in adult stem cells



Blokzijl *et al* sought to evaluate the unavoidable random mutations that arise during DNA replication in human adult stem cells and the mutations' relationship to cancer risk. After assessing genome-wide mutation patterns in adult stem cells of various tissues from human donors aged 3 to 87 years, the researchers noted a positive correlation between the number of somatic point mutations and the age of the donor. Two known signatures of mutations were investigated. Signature A was shown in their data set to correlate with the linear trend, indicating that mutations with that signature accumulate with age, whereas signature B showed no such correlation. Because the cells from many different donors were analyzed without controlling for lifestyle or gender, the similarities in point-mutation rate and mutation spectrum led the group to conclude that environmental risk factors for mutation had a minimal effect on the mutational landscape in this context.

Nature 2016; 538:260–264; doi:10.1038/nature19768

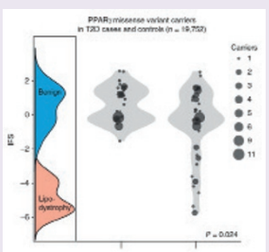
Schwannoma genomics



Agnihotri *et al* identified genomic aberrations common to sporadic schwannomas. The lack of understanding of the mechanisms by which these tumors progress makes residual and radiation-treated schwannomas a clinical challenge. The group identified not only the expected recurrent mutations in *NF2* but also aberrations in the chromatin-modifying genes *ARID1A*, *ARID1B*, and *DDR1*. Most schwannomas (76%) were associated with 22q deletion or *NF2* mutations, which in their turn were observed in significantly higher proportions in vestibular schwannomas than in spinal schwannomas. A novel *SH3PXD2A-HTRA1* gene fusion was identified in 10% of cases. This is transcribed to mRNA and translated to a protein that leads to increased ERK pathway activity. The findings expand the genomic understanding of schwannomas beyond *NF2* inactivation and provides additional insights into their pathogenesis.

Nature Genetics 2016; 48:1339–1348; doi:10.1038/ng.3688

PPARG variant classification



Majithia *et al* sought to classify the functional differences between every 9,595 variants of *PPARG* (encoding the peroxisome proliferator–activated receptor γ). It is known that approximately 1 in 500 people harbor missense variants of *PPARG*, the majority of which have no functional impact. By generating a library of all the possible single–amino acid permutations for expression in human macrophages, the authors developed a pooled functional assay of all the protein variants. In diabetes patients the assays successfully discriminated between nonpathogenic variants and the Pro12Ala variant linked to diabetes predisposition. Five of six variants identified in patients with familial lipodystrophy 3 were classified as pathogenic, resulting in defective protein. Conventional predictor models of mutation deleteriousness were unable to distinguish between pathogenic and benign variants. This new model will support molecular diagnostics through a Web application developed by the authors, allowing wide and efficient sharing of this information.

Nature Genetics, doi:10.1038/ng.3700

Emma Judson contributed to these reviews.