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MODERN PATHOLOGY

Methylation in rhabdomyosarcoma

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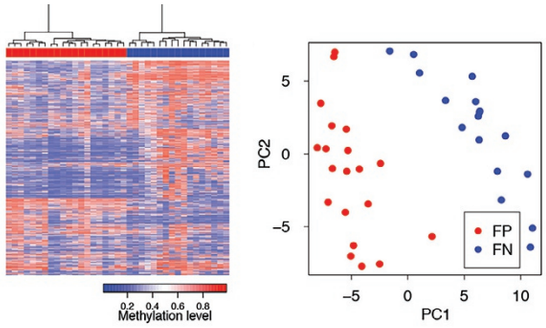

Rhabdomyosarcoma shows distinct skeletal-muscle type differentiation and can be broadly characterized into gene fusion–positive cases (*PAX3-FOXO1* or *PAX7-FOXO1*, most commonly) and those that lack such a fusion. Sun *et al* examined the methylation profiles of rhabdomyosarcoma tumors, rhabdomyosarcoma cell lines, and normal tissues. Fusion-negative cases had substantially higher levels of methylation than the fusion-positive cases, which were much more similar to the methylation patterns of normal skeletal muscle or bone marrow. PAX3-FOXO1 binding sites were enriched in genes that were differentially expressed and methylated between the fusion-positive and -negative cases, suggesting a role for methylation in target gene regulation. An 11-gene DNA methylation signature was established that could classify fusion-positive and -negative cases. A better understanding of the methylation patterns of rhabdomyosarcoma is likely to advance our knowledge of tumor biology and may suggest novel treatments.

Correlation of lung molecular type and immune factors

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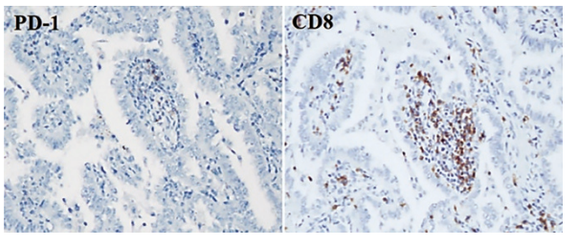

Immunotherapies targeting the programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) axis have shown efficacy in a variety of tumors, including in the lung. Koh *et al* demonstrated that both PD-L1 and PD-L2 are expressed in about 60% of tumors, with a high degree of correlation in expression. PD-L1 expression was significantly elevated in cases of nodal metastasis, smokers, poorly differentiated tumors, and histologic subtypes with solid and micropapillary patterns. Expression was correlated with *ALK* translocation and epidermal growth factor receptor (EGFR) expression (but not mutation) and mesenchymal-epithelial transition (MET) factor. The numbers of $CD8^+$ and $PD\text{-}1^+$ lymphocytes were higher in smokers and associated with poorer disease-free survival. Although it is not clear that expression of $PD\text{-}1^+$, $PD\text{-}L1^+$, and $CD8^+$ lymphocytes correlated with clinical response to immune checkpoint inhibitors, these factors appear to correlate with different lung cancer types and etiologies, and there may be prognostic value to these markers as well.

LABORATORY INVESTIGATION

Gene fusion detection in benign fibrous histiocytoma

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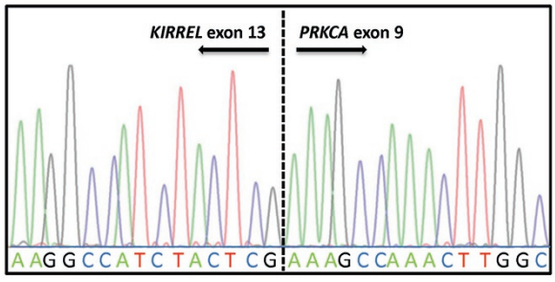

It has recently been noted that gene fusions in benign fibrous histiocytomas involve *PRKCB, PRKCD* (protein kinase C genes) and *ALK*. *ALK* translocation was uniquely seen in the epithelioid form. Walther and colleagues examined a variety of benign fibrous histiocytoma subtypes for the gene rearrangements in a series of multiple histologic and clinical subgroups of benign fibrous histiocytoma. They confirmed the presence of *PRKCB* or *PRKCD* translocations in a minority of traditional, epithelioid (mutually exclusive of *ALK* rearrangements), cellular (by RNAseq), and deep fibrous histiocytomas. Rearrangements were not seen in aneurysmal, atypical, or metastatic lesions. However, given the low prevalence of the rearrangements, the numbers in these latter

categories are underpowered. Using RNAseq, the authors demonstrated a KIRREL-PRKCA fusion transcript involving a new member of the PKC family. This study raises the following questions: (i) what alternative translocations or mechanisms drive fusion-negative tumorigenesis and (ii) are there clinically relevant differences between fusion-positive and -negative cases?

FBXW7 regulation of ENO1 in colon cancer

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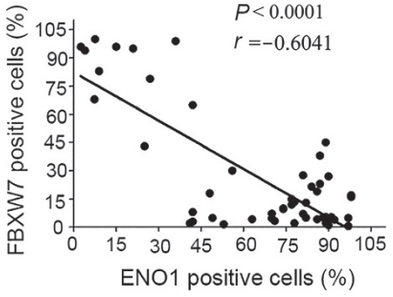

FBXW7 (encoding F-box and WD40 domain protein 7) is a tumor suppressor that is known to be mutated and inactivated in a variety of human cancers, but its mechanism of action is poorly understood. Its normal function could be mediating the destruction of proteins relevant to cancer. Zhan and colleagues now demonstrate a connection between FBXW7 and enolase 1 (encoded by *ENO1*). Enolase 1 is integral to glycolysis but is overexpressed in various cancers and thought to act as an oncogene and perhaps participate in the Warburg effect. ENO1 and FBXW7 expression are inversely correlated in several cell lines and tissues. In addition, FBXW7 physically binds ENO1 and targets it for ubiquitin-mediated destruction. In doing so, it suppresses the genes regulated by ENO1 expression. This work provides insight into a regulatory pathway of ENO1 and suggests a potential mechanism of action of FBXW7.

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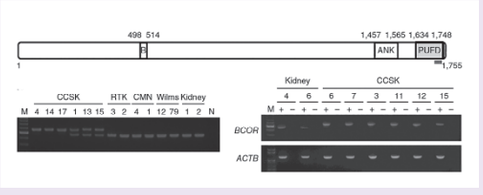
ATM variants confer gastric cancer risk

Gastric cancer is a worldwide scourge, but it has been more studied in Asian populations, among whom the prevalence is higher. In a study reported in *Nature Genetics*, Helgason *et al* performed a genome-wide association study (GWAS) in a large Icelandic cohort (2,500 population-based cases and 205,652 controls). They discovered that three rare loss-of-function (stop-gain or nonsense) mutations in *ATM* confer a significant risk for gastric cancer (hazard ratio: 4.74). There was also associated risk for both pancreatic and prostate cancer (odds ratios: 3.81 and 2.18, respectively). *ATM* is critical for the DNA damage response. Germ-line alterations in this gene (either homozygous or compound heterozygous) cause the ataxia telangiectasia syndrome and probably increase the risk of cancer (breast, colorectal, gastric and pancreatic) in heterozygous carriers. Only some of the GWAS findings in Asian population were replicated here suggesting genetic diversity. The strength of GWAS in the Icelandic population is the significant founder effects, which enable detection of rare alleles.

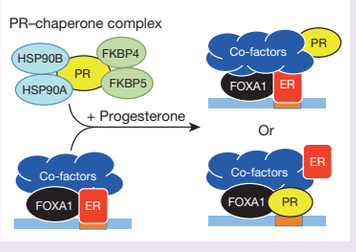
Nature Genetics 2015;47:906–910; doi:10.1038/ng.3342

BCOR duplications in clear-cell sarcoma of the kidney



Clear-cell sarcoma of the kidney (CCSK) is a pediatric renal malignancy that ranks second in incidence after Wilms tumor. The genetic derangements that underlie CCSK are largely unknown, although *YWHAE-NUTM2* gene fusions are seen (12%). As reported in *Nature Genetics*, Ueno-Yokohata and colleagues identified internal tandem repeats in the *BCOR* gene in all cases studied (20/20). These were absent in other pediatric renal tumors ($n = 193$). This group had previously demonstrated hypermethylation in CCSK, and, because of the connection between hypermethylation and histone modifications or marks, they studied *BCOR*. The gene was both hypomethylated and overexpressed. *BCOR* (BCL6 corepressor) encodes a component of the polycomb repressive complex-1, which has a role in the histone modification that regulates gene expression. The partial *BCOR* duplication involves the extreme C-terminus, and this mutated allele appears to be preferentially expressed and promotes anchorage-independent growth when expressed in a cell-line model. Because of its overexpression, immunohistochemical detection of BCOR may aid in diagnosis.

Nature Genetics 2015;47:861–863; doi:10.1038/ng.3338



Progesterone receptor and ERα in breast cancer

Progesterone receptor (PR) is a breast cancer biomarker that has been correlated with estrogen receptor-α (ERα) function and prognosis. PR expression is induced by ERα. Mohammed *et al* report in *Nature* that PR associates directly with ERα in a ligand-dependent fashion in which it functions to modulate ERα chromatin binding, resulting in a gene expression pattern associated with a good outcome. Progesterone administration inhibited the growth promotion associated with estrogen-stimulated ERα in cell lines and breast tumor explants and augmented the antiproliferative effects of ERα antagonists. Copy-number loss of *PGR*, the gene encoding PR, is common in breast cancer and probably represents a type of tumor progression given that shedding of PR allows ERα to induce gene expression more conducive to aggressive behavior. These critical insights into the function of PR can help explain the prognostic value of these markers and have therapeutic implications.

Nature 2015;523:313–317; doi:10.1038/nature14583