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MODERN PATHOLOGY

Dendritic cell sarcoma genomics

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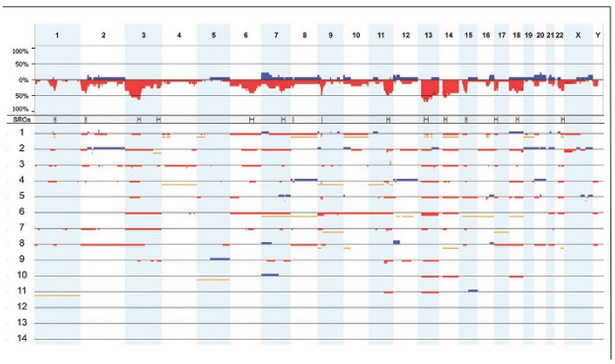

Using molecular inversion probe array analysis, Andersen *et al* identified abnormal genomic profiles in 11 of 14 cases of follicular dendritic cell sarcoma. Alterations were observed in 45% to 91% of chromosomal regions across the 11 samples. Many of the alterations overlap with those seen in other cancers, suggesting an active role for them in the pathogenesis of the disease. Homozygous deletions in tumor suppressor genes *CDKN2A*, *RB1*, *BIRC3*, and *CYLD* form the basis of the hypothesis that follicular dendritic cell sarcoma may be tumor suppressor–driven at the somatic copy-number level. These findings will need to be investigated further to identify potential novel therapeutic strategies for follicular dendritic cell sarcoma now that more is known about the molecular and cellular pathways that drive its development.

Suppressor driver in sporadic lymphangioleiomyomatosis

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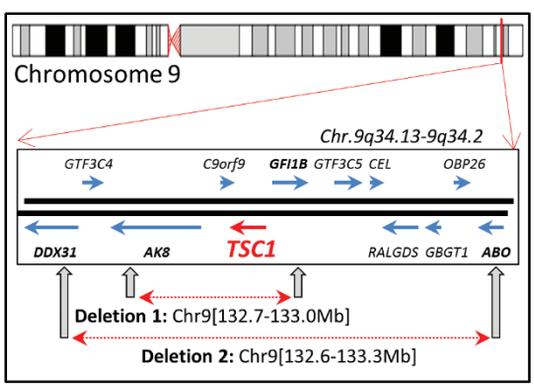

Because of the migratory/invasive properties of the smooth muscle–like lymphangioleiomyomatosis cells in sporadic lymphangioleiomyomatosis, it is characterized by many as a low-grade malignancy. Murphy *et al* used mate pair sequencing to define structural variations with laser capture–microdissected enriched cell populations from five patients. The resulting mutation panel demonstrated characteristic *TSC2* driver mutations in three of the cases, and one case contained two different size deletions encompassing the entire *TSC1* locus. Beyond these molecular aberrations, other structure arrangements were seen in some of the tumors, but none of these were recurrent. Somatic structural rearrangements are now identified in, and provide a novel method of, genomic characterization of these tumors. This might lead to advances in defining cases and aid investigation into additional pathological mechanisms of this rare disease. Identifying specific molecular targets such as this one could offer researchers additional therapeutic strategies.

LABORATORY INVESTIGATION

Membrane MUC1 glycoform analysis

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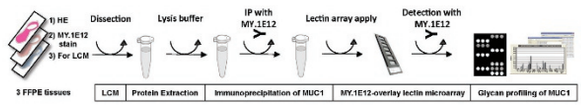

Matsuda *et al* developed a potentially feasible method for differential glycoform analysis of an endogenous tumor–associated glycoprotein MUC1 via an antibody-overlay lectin microarray. Anti-MUC1 antibody MY.1E12 was used to recognize a specific MUC1 glycosylation isoform, and positive staining areas were selected using laser capture microdissection followed by optimized lectin microarray analysis. The approach provided the group with a method for investigating novel glycodynamics, such as *O*-glycome analysis in biology, as well as diseases related to many membrane proteins, including MUC1. This shows promise for distinguishing between sometimes challenging differential diagnosis with limited samples, such as for cholangiocarcinoma and pancreatic ductal adenocarcinoma, with significant implications for surgical management, chemotherapy, and prognosis. The tool could also facilitate study of how the glycosylation of tumors affects their development and behavior.

EMMPRIN expression in ALCL

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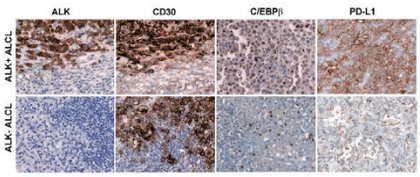

C/EBPβ, a transcription factor constitutively overexpressed in ALK$^+$ anaplastic large-cell lymphoma (ALCL) cells, is known to have roles in adipogenesis, myelomonocytic development, metabolism, inflammation, and cellular proliferation. Using a knockdown cell line and 115 patient samples, expression of CD147 (EMMPRIN) was shown to be strong to moderate in all cases of ALK$^+$ ALCL, whereas in ALK$^-$ ALCLC cases expression was weak. Twenty-two cases (ALK$^+$ and ALK$^-$) were also stained for PD-L1. Of the 22, all 10 ALK$^+$ cases and 2 of the 12 ALK$^-$ cases showed strong expression of PDL-1; the remaining 10 ALK$^-$ cases showed weak expression. This followed through from their cell line model to the patient cases, suggesting a possible immunosuppressive role for C/EBPβ in ALK$^+$ ALCL. The group hypothesizes that CD147 expression in ALK$^-$ ALCL could, through C/EBPβ, promote invasiveness through induction of matrix metalloproteinase production via the C/EBPβ target gene *S100A9*. Further investigation is warranted.

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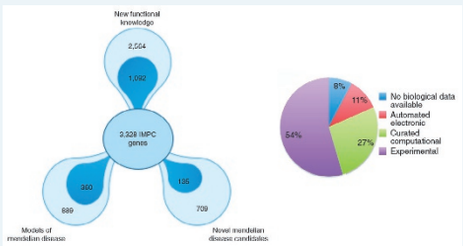
Functional models of the "ignorome"



Revolutionary advances in next-generation sequencing have greatly expanded the identification of genes, leaving the challenge, addressed by Meehan *et al*, of determining the functions and pathobiological mechanisms of these genes. By creating a genome- and phenome-wide catalog of gene function based on characterization of new knockout-mouse strains, the International Mouse Phenotyping Consortium (IMPC) identified what may be the first models of type C Bernard-Soulier, Bardet-Biedl-5, and Gordon Holmes syndromes. The IMPC focused on diseases for which a transgenic mouse model had not been produced, the phenotypes of these strains providing deep insights into the functions of the "ignorome"—the name sometimes given to this class of genes for which functional information is so scarce. The IMPC has established a tool that greatly increases our knowledge of mammalian gene function. When paired with the existing identification of functional variants and disease sequencing, this work holds exciting possibilities for the human disease research community.

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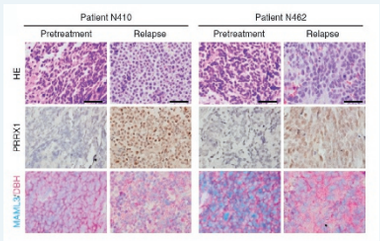
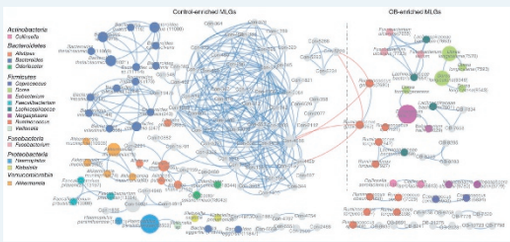
Mesenchymal and adrenergic states in neuroblastoma



In diseases such as neuroblastoma for which few gene mutations have been identified, the search for epigenetic factors controlling gene activity is a logical next step. Van Groningen *et al* explored and compared the clinical relevance of mesenchymal versus adrenergic cells *in vitro* and found that the former were more resistant to standard-of-care chemotherapy, the usual treatment for newly diagnosed neuroblastoma. Comparing pre- and posttreatment biopsy tissue showed enrichment for PRRX1$^+$ cells following therapy, inducing a transition to the mesenchymal state, although *PRRX1* expression did not correlate with prognosis. The group demonstrated that intratumoral heterogeneity is not a random process but is caused by master regulators of these two phenotypes, and that the plasticity between them, along with the relative resistance of mesenchymal state neuroblastoma cells to standard therapy, might indicate the promise of targeted therapy directed toward the mesenchymal state cell lineage.

Nature Genetics 2017;49:1261–1266; doi:10.1038/ng.3899

Gut microbiome, serum metabolome and obesity



Liu *et al* performed a metagenome-wide association study along with serum metabolomics profiling in lean and obese young Chinese individuals. The group identified a specific bacterium, *Bacteroides thetaiotaomicron*, which was markedly less abundant in obese individuals and inversely correlated with serum glutamate concentration. *B. thetaiotaomicron* can be a dominant bacterial species residing in the human gut. In a mouse model, gavage with live *B. thetaiotaomicron* significantly lowered total and inguinal fat mass and increased lean body mass of conventionally raised mice on normal chow. Furthermore, it alleviated body weight gain and adiposity of mice fed a high-fat diet. The antiobesity effect of *B. thetaiotaomicron* may require a specific intestinal microenvironment, as the bacterium has also been reported to increase body fat content in germ-free mice. The group acknowledges the need for wider study groups to fully elucidate these connections and potentially identify an obesity intervention.

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Emma Judson contributed to these reviews.