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MODERN PATHOLOGY

SMARCA4-deficient undifferentiated uterine sarcoma

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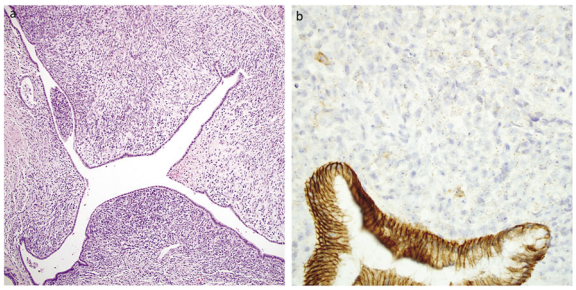

Kolin et al. describe a distinct group of uterine cancers with features like those of *SMARCA4*-mutated small-cell carcinoma of the ovary, hypercalcemic type. In the cases examined, sheets of prominently large, atypical epithelioid cells with rhabdoid morphology were seen, indistinguishable from those in the ovarian cancer model. The ovarian and uterine points of origin for these cancers are sites of distinct preliminary symptoms, namely, abdominal pain or swelling as opposed to a cervical mass or vaginal bleeding. The tumors studied were characterized by extensive lymphovascular invasion, extrauterine spread, and marked infiltrative growth as well as by their aggression, with a median survival of 7 months; all study patients were deceased. The authors propose that these newly identified features be used to distinguish SMARCA4-deficient uterine sarcoma from other gynecological cancers with similar features. Correct diagnosis will be crucial for improved prognostic results as well as exploration of potential targeted therapy such as EZH2 inhibitors and anti-PD-1 immunotherapy.

ZBTB46 as a biomarker of dendritic-derived neoplasms

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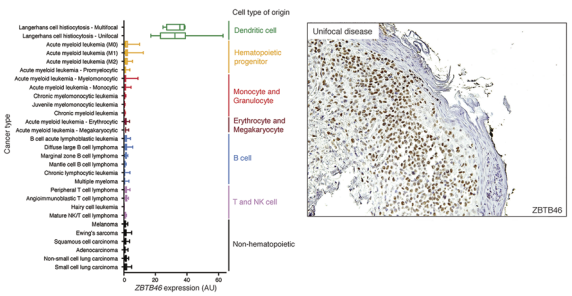
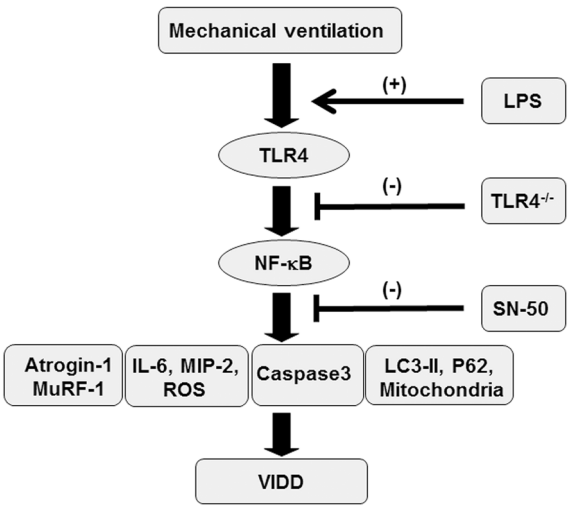


Satpathy et al. explored the use of a zinc finger and BTB domain–containing transcription factor, ZBTB46, which is expressed by dendritic cells and committed dendritic cell precursors but not other myeloid cell types. The group demonstrated expression of ZBTB46 in Langerhans cell histiocytosis and histiocytic sarcoma, but it was absent in Erdheim–Chester disease and other neoplasms. The team developed an anti-human ZBTB46 antibody for assessing expression in clinical samples. All of the Langerhans cell histiocytosis cases exhibited strong nuclear staining. In addition, staining was present in all tissues of these patients, indicating that disease site did not influence staining. The results of the same assay in related but distinct disorders showed no ZBTB46 expression. In seeking to determine whether ZBTB46 is a biomarker for malignant cells in indeterminate cell histiocytosis, the authors found positive staining in two of three samples, which suggests that more investigation into the pathogenesis of this disease is necessary.

LABORATORY INVESTIGATION

The TLR4/NF-κB pathway in VIDD

doi:10.1038/s41374-018-0081-0

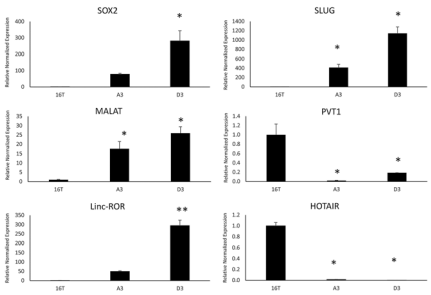


Diaphragm weakness has been shown to correlate with poor outcomes in critically ill patients with ventilator-induced diaphragm dysfunction (VIDD) due to inactivity and infection. Investigating mechanisms that regulate VIDD, Li et al. hypothesized a link between mechanical stretch, diaphragmatic structural damage, free radicals, muscle proteolysis, and autophagy of the diaphragm via the TLR4/NF-κB pathway. The group analyzed protein expression patterns along with physiological patterns such as disorganized myofibrils, disrupted mitochondria,

and myonuclear apoptosis, in response to mechanical ventilation with endotoxemia, which aggravated VIDD. Pharmacologic inhibition of the NF-κB pathway using SN50 and/or TLR4 homozygous knockouts attenuated these responses. A better understanding of these pathophysiologic mechanisms is necessary for identifying and perfecting a potential approach to supporting patients on mechanical ventilation.

EMT in tumorigenesis and metastasis in thyroid cancer

doi:10.1038/s41374-018-0065-0



Treatment resistance, multipotent capability, and tumorigenesis in thyroid cancer are thought to involve the presence of cancer stem-like cells (CSCs) and their role in epithelial–mesenchymal transition (EMT). Using two in vitro models, Hardin et al. explored the role of exosomes in transferring non-coding RNAs and long-non-coding RNAs (lncRNAs) to distinct cell populations. In the first method, EMT was induced in a papillary thyroid carcinoma cell line by TGFβ1 treatment and exosomes were isolated and cultured with naïve papillary thyroid carcinoma cells and examined for EMT induction. Alternatively, exosomes were isolated from a CSC clonal line and cultured with normal thyroid cells and examined for EMT induction. While several EMT effectors, such as SLUG and SOX2, were observed in both models, EMT induction was observed only in the CSC model (along with transfer of linc-ROR), which is therefore proposed as being key to effecting EMT. Targeting CSCs, their exosomes, and/or the lncRNAs with targeted therapeutics could modulate metastatic capacity in thyroid tumors.

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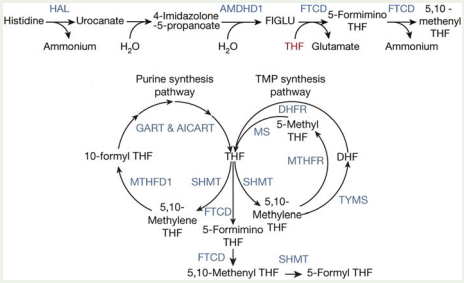
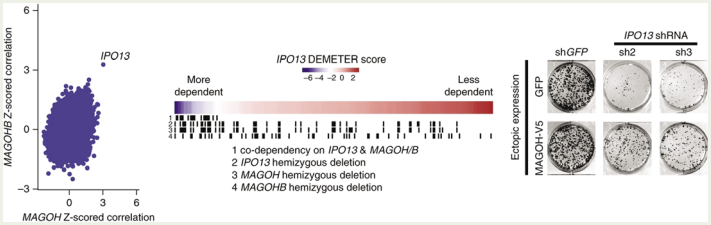
Histidine supplementation to allow reduced dosing of methotrexate

Using a CRISPR-Cas9-based screen, Kanarek et al. sought to identify genes involved in the response of cancer cells to methotrexate. The drug is widely used despite potential toxicity that can lead to discontinuation of treatment. The screening identified *FTCD*, which encodes an enzyme involved in the catabolism of histidine. The team showed that depletion of the histidine degradation pathway (by expression of *FTCD* or reduced expression of histidine ammonia lyase (HAL), the rate-limiting enzyme in the histidine degradation pathway) resulted in decreased sensitivity to methotrexate by reducing the concentration of tetrahydrofolate and inhibiting nucleotide synthesis. Dietary supplementation with histidine enhanced sensitivity of leukemia xenografts to methotrexate by enhancing depletion of tetrahydrofolate within tumor cells. HAL therefore becomes a potentially predictive marker for sensitivity in these patients and could influence therapeutic strategies. Perhaps the most significant finding is the potential for histidine supplementation in methotrexate-treated patients to reduce dosing and thus enhance clinical benefit.



Nature 2018;559:632–636; doi:10.1038/s41586-018-0316-7

Gene dependencies of chromosome loss in cancer

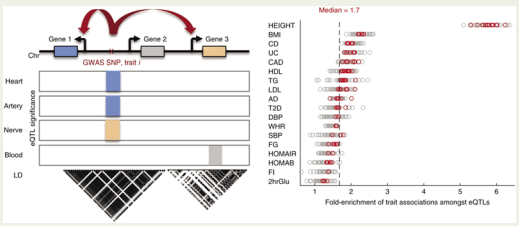


Genome-scale short hairpin RNA was assessed using CRISPR screening on hundreds of cancer cell lines to identify *MAGOH* and *MAGOHB*, core members of the splicing-dependent exon junction complex. In cases of chromosome 1p loss, inhibition of *MAGOHB* in the setting of *MAGOH* depletion compromises viability by perturbing alternative splicing and RNA surveillance. *IPO13*, an importin-β receptor that mediates nuclear import of the MAGOH/B-Y14 heterodimer, is highly dependent on both *MAGOH* and *MAGOHB*. These results implicate the *MAGOHB–IPO13* axis in cancers with chromosome 1p loss. IPO13 has small-molecule inhibitors designed against it; antisense/RNAi-based approaches as well as targeted protein degradation may prove to be useful in targeting some of these dependencies across cancers with any chromosome-arm deletion. Understanding the gene dependencies of broader chromosomal loss may thus enable effect targeting of aneuploidy.

Nature Genetics 2018;50:937–943; doi:10.1038/s41588-018-0155-3

Gene expression and heritable traits

Seeking out trait-associated loci leads to correlation with expression quantitative loci (eQTLs) across several known traits (e.g., metabolic and cardiovascular traits) in relevant pathogenic tissues. The set of eQTLs explains the traits' heritability, from 38.0 ± 27% for body mass index (BMI) to 78.2 ± 15.2% for Alzheimer's disease. A distinction can made between the traits associated with tissue-shared eQTLs and tissue-specific ones such as blood pressure, indicating the importance of broad sampling of tissues. The group also assessed eQTLs as a mechanism for discovery of new trait associations and genes and were able to enrich for trait association in height and BMI as well as Crohn's disease. Integrating prior biological knowledge with eQTL analyses in relevant tissues, the authors proposed and replicated multiple potentially causal genes and novel trait associations.



Nature Genetics 2018;50:956–967; doi:10.1038/s41588-018-0154-4