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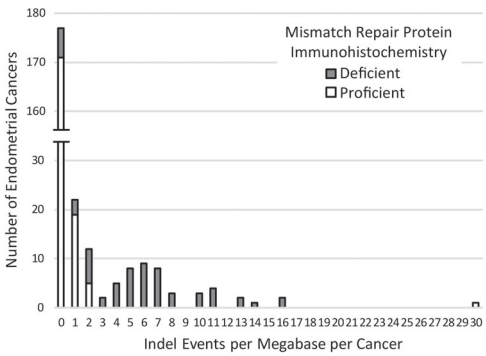
MODERN PATHOLOGY

Detection of mismatch repair deficiency by sequencing

doi:10.1038/s41379-018-0125-4

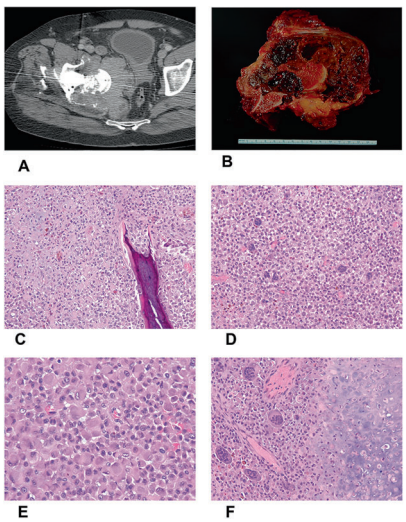


Insertion and deletion mutations in mononucleotide repeats are a molecular signature of mismatch repair deficiency, which can be used as a biomarker of immunotherapy response of Lynch syndrome–associated endometrial cancers as well as those with sporadic microsatellite instability. Dong et al. compared their sequencing results to tumors identified by immunohistochemistry (IHC) expression patterns for loss of MLH1, MSH2, MSH6, and PMS2 and classified 259 endometrial cancers as mismatch repair deficient, proficient, or intermediate, with an overall concordance between the two methods. Sequencing through their algorithm provided 94% concordance with IHC, but the authors note that IHC will remain the most cost-effective method for identifying mismatch repair deficiency in endometrial cancers until targeted next-generation sequencing is in wide use for clinical cancer care. At that point, with gene panels of appropriate size, obtaining actionable information including determination of mismatch repair deficiency would potentially lead to increased clinical benefit relative to sequencing cost.

Synovial nature of malignant tenosynovial giant cell tumors

doi:10.1038/s41379-018-0129-0

Al-Ibraheemi et al. examined the features of ten well-characterized malignant tenosynovial giant cell tumors. Immunohistochemistry (IHC) revealed heterogeneous admixtures of cells and even the production of relatively mature cartilage in places. IHC also showed small nests of tenosynovial giant cell tumor surrounded by fibrosarcoma-like spindle cell production. The team propose that the malignant cells in these tumors are derived from clusterin-positive large mononuclear cells found in benign tenosynovial giant cell tumor and the normal synovium. *CSF1* rearrangements and

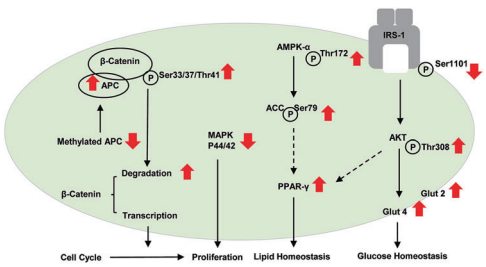


CSF1 overexpression suggest a role for inhibitors of CSF1 and CSFR1 in the treatment of patients with the disease. The team concluded that their data support a synovial origin of these tumors, a finding that could influence future research and have therapeutic implications.

LABORATORY INVESTIGATION

Effects of aspirin in obesity prevention in females

doi:10.1038/s41374-018-0144-2



Zhou et al. created a high-risk model of obesity and non-alcoholic fatty acid liver disease using mouse offspring with over-nutrition in utero. The offspring were fed a high-fat diet and diethylnitrosamine to induce obesity. Mice in one group were then given low-dose aspirin for 12 weeks. Female mice that received aspirin treatment, unlike the male mice, showed less body weight gain, reversed glucose intolerance, and depressed hepatic lipid accumulation. Once the underlying pathways were analyzed, the investigators found that while both the male and female mice had higher levels of hepatic PPAR-γ, only the female mice showed resensitized

insulin/Akt signaling and overactivated AMPK signaling. There were also sex-specific changes in liver expression of cell-cycle genes and alternate epigenetic and post-translational regulation of Wnt signaling. The finding that the effects of aspirin were different between male and female mice in this model may indicate a need for gender-specific approaches to dealing with obesity and non-alcoholic fatty acid liver disease.

Nerve-derived TRPV4 augments epithelial stem cell proliferation via NGF

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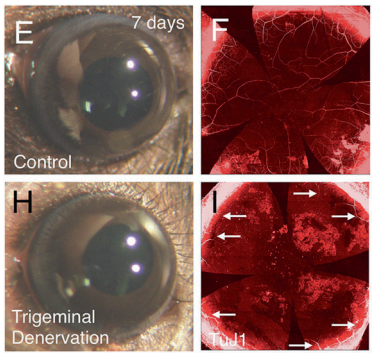

Modulation of stem cell activity by nerves is critical during tissue repair and regeneration as well as in cancer development and growth. However, the mechanisms involved in this process are not understood. Corneal sensory nerves play a key role in epithelial cell proliferation; their absence results in the degenerative disease neurotrophic keratopathy. Okada et al. used a mouse model of neurotrophic keratopathy with compromised epithelial wound healing to investigate the mechanisms that underlie epithelial cell proliferation. They found that low expression of transient receptor potential vanilloid 4 (TRPV4) was associated with impaired corneal epithelial wound healing. Overexpression of TRPV4 rescues epithelial impairment and elevates expression levels of nerve growth factor (NGF). Topical application of NGF improves corneal epithelial wound healing. Thus, corneal sensory nerves mediate epithelial wound healing via TRPV4-mediated elevation of NGF. The US Food and Drug Administration recently approved NGF for treatment of neurotrophic keratopathy.

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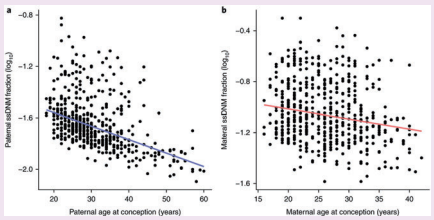
Transmission of de novo mutations in families

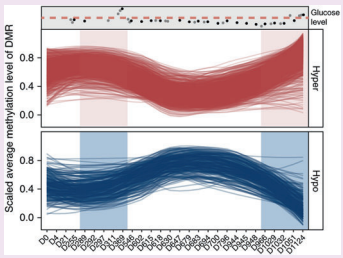
From a sample of 1007 sibling pairs from 251 families, Jónsson et al. identified 878 de novo mutations shared between siblings (ssDNMs) at 448 genomic sites. They demonstrated a decrease in both paternal and maternal ssDNMs, but that this effect was weaker in mothers than in fathers. Mothers accumulated a high proportion of C>G variants, and there was a lower maternal ssDNM fraction in these regions compared with outside. The authors demonstrated that sex differences in germ cell development were responsible for parent-of-origin effects on the type and location of ssDNMs. Their discovery of two DNM transmissions with paternal somatic mosaicism led to their launch of a recurrence calculator for researchers seeking to explore the impact of these DNMs in their own populations and to study the relationship between germline and somatic mosaicism to further elucidate clinical significance with regard to DNM control of rare diseases.



Nature Genetics 2018;50:1674–1680; doi:10.1038/s41588-018-0259-9

Are DNA methylation changes a disease signature?

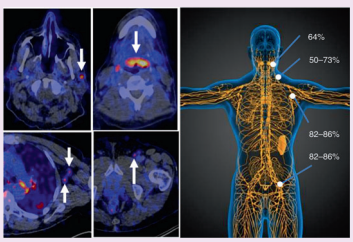
The control of genomics can influence downstream factors as significantly as mutations in the genes themselves. Epigenomics is thus an exciting field in the exploration of precision personal medicine. Assessing whole-genome DNA methylation and the transcriptome of peripheral blood mononuclear cells from a healthy volunteer over a 36-month period, Chen et al. identified 28 methylome and 57 transcriptome datasets. DNA methylomic changes were shown to be associated with glucose-level alteration around 80–90 days before clinically detectable glucose elevation. However, it was under conditions such as viral infection that the transcriptome was altered. A deeper examination of allele-specific differentially methylated regions showed them to be generally stable and not randomly distributed; they tended to correlate with the number of genes on a chromosome. While more analysis is required, the authors show that RNA expression and DNA methylation changes are associated with disease signatures and could be predictive, preceding clinical symptoms.



Nature Medicine 2018;24:930–1939; doi:10.1038/s41591-018-0237-x

PET scan as a noninvasive predictive marker of response to PD-L1 blockade

Identifying patients who will benefit from a treatment is a critical element of clinical decision making, but current methods are incomplete or inexact. They may not account for patients who do not express particular markers but do receive clinical benefit. Developing noninvasive methods for identifying such patients is an ongoing goal of research into targeted therapeutics. Bensch et al. sought to validate a first-in-human method of using PET imaging with antibodies to PD-L1 to select patients in whom PD-L1 blockade will be beneficial. Using zirconium-89-labeled atezolizumab (anti-PD-L1 antibody), the group scanned 22 patients across three tumor types prior to initiation of therapy. While the PET signal showed several distinct patterns, it was better correlated with response compared with immunohistochemistry or RNA sequencing. These very encouraging results will likely spur further assay development in this area.



Nature Medicine 2018;24:1852–1858; doi:10.1038/s41591-018-0255-8