

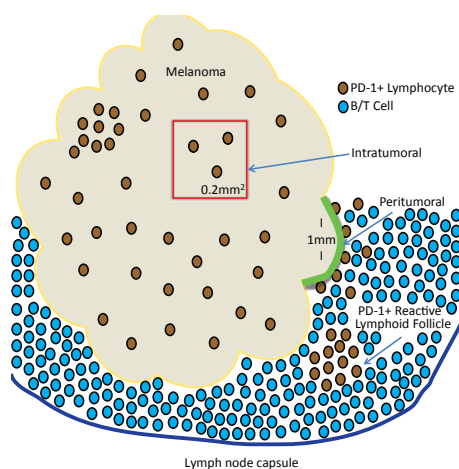
INSIDE THE USCAP JOURNALS

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MODERN PATHOLOGY

Immune correlates in melanoma sentinel lymph node metastases

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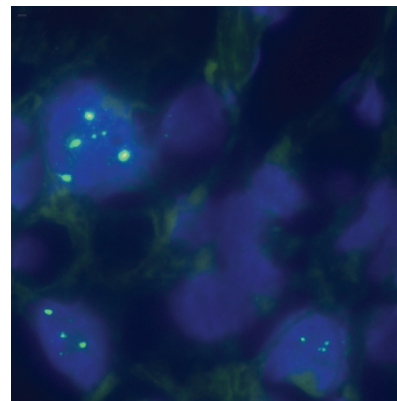


Kakavand and colleagues characterized the immune environment of sentinel lymph nodes from patients with early-stage melanoma. These patients have variable 5-year survival rates of 39–70%, predicted to some degree by tumor burden and number of lymph nodes involved. The effects of local antitumor response and the potential applicability of immune checkpoint inhibitors in this early setting are unknown. Checkpoint inhibitors can show remarkable efficacy in patients with unresectable late-stage metastatic melanoma. Significant positive correlation with recurrence-free and overall survival was seen with the numbers of CD3⁺, CD4⁺, and CD8⁺ tumor-infiltrating lymphocytes. Negative correlations were seen with the number of peritumoral PD-1⁺ lymphocytes. Tumoral PD-L1 expression was noted in 43% of cases but lacked correlation with outcome. This study suggests prognostic significance of lymphocytic infiltrates in melanoma sentinel lymph node metastases and indicates that adjuvant checkpoint inhibitor therapy may be considered in patients with early-stage metastatic disease.

Telomeres and ATRX expression in sarcoma

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On the basis of their cytogenetic profiles, sarcomas can be broadly characterized as either simple (often bearing recurrent chromosomal translocation) or complex karyotype tumors. Alternative lengthening of telomeres

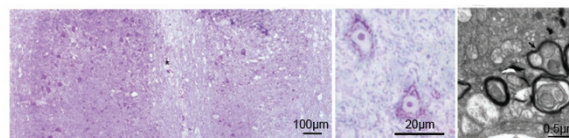


(ALT), a common method of telomere maintenance in sarcoma, is often associated with loss of ATRX or DAXX protein. Liao *et al* found that ALT is very common in complex karyotype sarcoma, such as undifferentiated pleomorphic sarcoma (UPS; 65%) and myxofibrosarcoma (MFS; 76%), but ATRX (or DAXX) loss was seen in half of the UPS cases with ALT and only one of the MFS cases with ALT. Clearly other mechanisms exist. Although often not of the complex karyotype, dedifferentiated liposarcomas commonly show ALT (45%); this is explained mostly by ATRX loss (93%). ALT and ATRX loss was seen in only a few cases of the translocation sarcomas tested as well as in gastrointestinal stromal tumors and epithelioid sarcoma.

LABORATORY INVESTIGATION

G-CSF limits neural tissue damage after spinal cord injury

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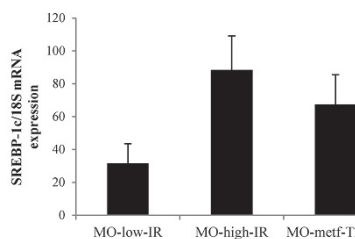


Using a mouse spinal cord hemisection model, Guo *et al* studied the effects of granulocyte colony-stimulating factor (G-CSF). Neural damage is associated with a progressive cascade of secondary injuries associated with apoptosis. G-CSF is known to inhibit apoptosis in neutrophils, and its receptor is also expressed in central nervous system cells. There is emerging evidence that G-CSF may have neuroprotective effects. The authors' results suggest that the presence of G-CSF promotes autophagy after spinal neuronal injury at the expense of the apoptosis and thus decreases the extent of local

damage. When autophagy is inhibited during G-CSF exposure, apoptosis increases with associated increased spinal injury. The mechanism for this appears to be G-CSF-mediated inhibition of the nuclear factor- κ B pathway. This increase in autophagy in response to G-CSF is rapid, and activation of the pathway may have therapeutic applications.

Jejunal lipogenesis in morbid obesity with insulin resistance

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Type 2 diabetes is often associated with dyslipidemia, an important risk factor for atherosclerosis. Intestinal *de novo* lipogenesis and lipoprotein synthesis can be seen in this setting, but the role of insulin resistance and signaling in this process in the setting of morbid obesity has not been explored. Using messenger RNA (mRNA) extracted from jejunal samples obtained during bariatric surgery, Gutierrez-Repiso *et al* investigated the expression of genes involved in lipogenesis and lipoprotein synthesis in three groups: individuals with low insulin resistance, individuals with high insulin resistance, and type 2 diabetes patients treated with metformin. The jejunum of individuals with high insulin resistance showed decreased mRNA expression of genes involved in *de novo* fatty acid synthesis and increased expression of genes involved in lipoprotein synthesis. This effect was attenuated in individuals treated with metformin. The findings suggest a role for jejunal lipoprotein synthesis in the dyslipidemia of type 2 diabetes.

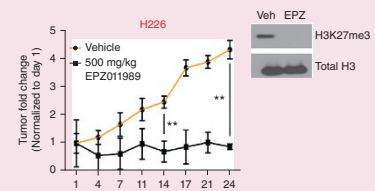
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Loss of BAP1 leads to EZH2-dependent transformation

BAP1 (BRCA associated protein 1) is a tumor suppressor that is lost in certain malignancies, including uveal melanoma, mesothelioma, and cholangiocarcinoma. BAP1 interacts with ASXL1 to form a polycomb deubiquitinase complex that catalyzes monoubiquitin removal from histone H2A lysine 119 and thus regulates gene expression. Interestingly, the *BAP1* and *ASXL1* genes are mutated in distinct cancers in mutually exclusive fashion suggesting regulation of differing pro-oncogenic pathways. In a study reported in *Nature Medicine*, LaFave *et al* demonstrated in a transgenic mouse model that *Bap1* loss leads to increased levels of histone H3 lysine trimethylation. This led to elevated expression of enhancer of zest 2 polycomb repressive complex 2 subunit (*Ezh2*) and thus to increased repression of polycomb repressive complex 2 (PRC2) targets. Mesothelial cells that lack BAP1 are sensitive to pharmacologic EZH2 inhibition. This relationship between BAP1 and EZH2 suggests a therapeutic avenue, but it must be demonstrated in additional cancer types.

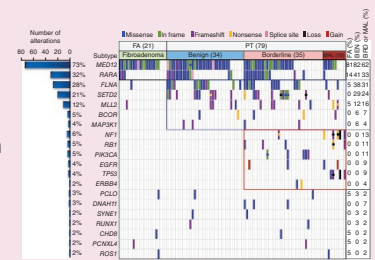
Nature Medicine, published online 5 October 2015; doi:10.1038/nm.3947



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Genomics of breast fibroepithelial neoplasia

Breast fibroepithelial neoplasia ranges from benign fibroadenomas to phyllodes to borderline and malignant phyllodes tumors. As recently described in *Nature Genetics*, Tan *et al* confirmed the previously demonstrated *MED12* mutations in both fibroadenomas ($n = 100$, targeted sequencing) and phyllodes tumors ($n = 22$ exomes). *RARA* mutations were common in both groups and coexistent with *MED12* mutations rather than mutually exclusive.

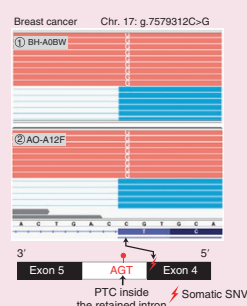


The *RARA* mutations clustered in the encoded

ligand binding domain and functionally suppressed *RARA*-mediated transcriptional activation, probably by enhancing *RARA* interactions with transcriptional corepressors. *MED12* and *RARA* mutations appeared to facilitate fibroepithelial tumorigenesis. Phyllodes tumors of all types—benign, borderline, and malignant—had additional mutations in *FLNA*, *SETD2*, and *KMT2D*. For the borderline and malignant phyllodes tumors, mutations in more classic proto-oncogenes and tumor suppressors such as *PIK3CA*, *EGFR*, *NF1*, *RB1* and *TP53* were noted. These results suggest molecular progression across the tumor spectrum and may have therapeutic implications.

Nature Genetics, published online 5 October 2015; doi:10.1038/ng.3409*

Intron retention in tumor suppressor inactivation



Loss of tumor-suppressor-gene expression is important in many cancers. Jung *et al*, in a study reported in *Nature Genetics*, examined the mechanisms of this loss. They noted that substantial numbers of mutations in cancer result from aberrant splicing. Somatic single-nucleotide variants (SNVs) have been well characterized in cancer exomes, but their association with abnormal RNA splicing is relatively unexplored. Through coordinated examination of exome and RNA sequencing data across more than 1,800 cancer cases, the authors identified ~900 exonic SNVs that disrupt splicing. No fewer than 163 SNVs—interestingly, including 31 synonymous substitutions—were shown to result in either intron retention or exon skipping in an allele-specific fashion. Approximately 70% of these SNVs occurred at the last base of exons, adjacent to the splice site. The vast majority of the retained introns led to a premature termination codon, resulting in nonsense-related decay or predicted protein truncation. This study has clear implications for molecular diagnostics.

Nature Genetics, published online 5 October 2015; doi:10.1038/ng.3414

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