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MODERN PATHOLOGY

Not all Merkel cell carcinomas are created equal

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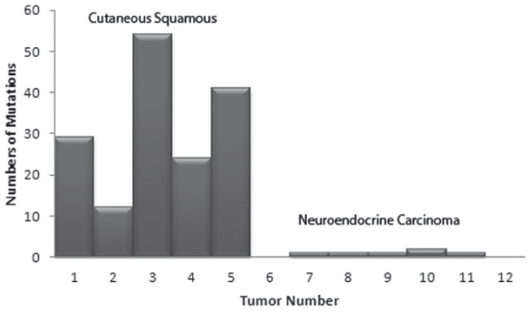

Merkel cell carcinomas, which are associated with clonally integrated Merkel cell polyoma virus, show strong expression of retinoblastoma 1 (RB1) protein and low p53 expression. The rare polyomavirus-negative forms lose expression of RB1 while gaining expression of p53, indicating divergent molecular pathogenesis. Using immunohistochemistry and focused next-generation sequencing. Pulitzer *et al* explored a series of Merkel cell carcinomas that exhibited distinct squamous differentiation (combined tumors) as well as traditional Merkel cell carcinomas. Combined Merkel cell carcinomas are not associated with viral integration, and in this study they showed a higher mutational load along with potential UV signature *RB1* and *TP53* mutations that generally lead to protein loss and overexpression, respectively. *NOTCH1* mutations were also identified. This genomic study further establishes an independent pathogenic mechanism for Merkel cell carcinoma with squamous features; accordingly, the authors suggest that the terminology of cutaneous squamous and neuroendocrine carcinoma be employed.

Maintaining telomeres in liposarcoma

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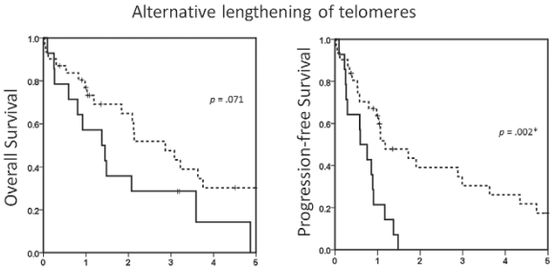
Sarcomas generally seem to maintain their telomere length via alternative lengthening of the telomere pathway rather than though telomerase activation. In Lee and colleagues' study, dedifferentiated and pleomorphic liposarcomas showed loss of α-thalassemia/mental retardation syndrome X-linked (ATRX) while this protein was maintained. This mechanism, which had previously been demonstrated



in pancreatic endocrine neoplasms and glioma, can also be mediated by loss of death domain–associated protein 6 (DAXX). Loss of DAXX is uncommon in liposarcoma. The correlation of loss of ATRX or DAXX expression with alternative lengthening of telomeres was 100%, suggesting an association worthy of further investigation to confirm causality. Alternative telomere lengthening was also a poor prognostic predictor in dedifferentiated liposarcoma. These studies provide deeper insight into the molecular mechanism of alternative lengthening of telomeres in pleomorphic and dedifferentiated liposarcoma.

LABORATORY INVESTIGATION

Insights into hepatic encephalopathy

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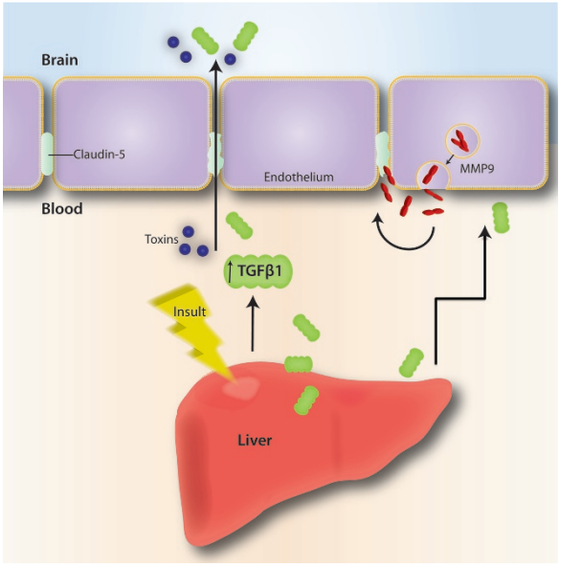

Acute liver failure can lead to hepatic encephalopathy associated with vasogenic brain edema, which is evidence of a compromised blood–brain barrier that can allow entry of neurotoxins. Impaired liver function allows toxins to persist

and circulate in the blood and diffuse into the brain. This is believed to be mediated by matrix metalloproteinase 9 (MMP9) activity and downregulation of tight-junction proteins. Noting an increase in transforming growth factor-β1 (TGF-β1) circulating in the blood following liver damage, McMillin *et al* used a mouse model and cell culture to demonstrate that treatment with recombinant TGFβ-1 leads to increased brain vascular permeability. This was associated with increased MMP9 expression and repression of claudin-5 expression; the latter is important for maintaining tight junctions. Pharmacologic inhibition of SMAD3, an immediate downstream mediator of TGF-β1 signaling, blocked the effects of TGF-β1 treatment, suggesting that inhibition of this pathway may have therapeutic efficacy.

EBV linked to inhibition of DNA damage repair

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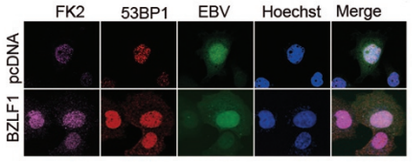

The Epstein-Barr virus (EBV) is associated with several human disease states, including malignant transformation. The immediate-early viral protein BZLF1 mediates the switch from the latent to the lytic form. The lytic form of EBV is linked to malignant transformation such as is seen in nasopharyngeal carcinoma, but the mechanism is not understood. Using a nasopharyngeal carcinoma cell line model, Yang *et al* demonstrated that BZLF1 disrupts the RNF8-53BP1 pathway critical for repair of DNA double-strand breaks and induction of the G2/M checkpoint in response to DNA damage. This suggests a pathogenetic mechanism whereby EBV in its lytic phase can prevent repair of DNA damage and thus allow acceleration of DNA mutation accumulation, which can promote carcinogenesis.

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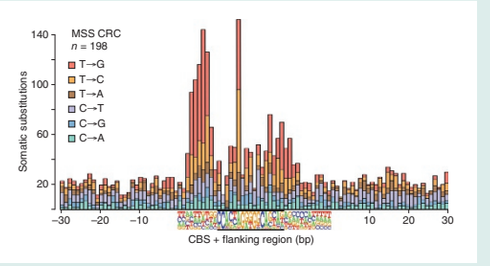
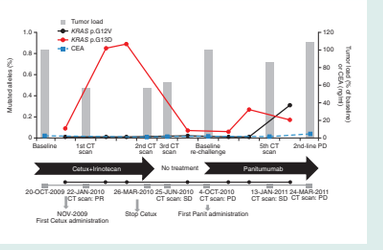
Cohesin binding site mutations common in cancer



The role of noncoding DNA is largely unexplored in cancer. Cohesin, a protein, is present in almost all active gene enhancer regions, where it associates with transcription factors. It is frequently colocalized with the CTCF (CCCTC-binding factor) protein and influences genomic instability, gene expression, and epigenetic homeostasis. Various cohesin subunits have been found to be mutated in cancer, but the consensus enhancer binding sites for cohesin and CTCF have been little explored. In a study reported in *Nature Genetics,* Katainen and colleagues integrated whole-genome sequencing with chromatin immunoprecipitation sequencing to identify widespread point mutations in CTCF/cohesin binding sites. Analysis of other cancer genomes showed that such mutations were not limited to colorectal carcinoma. Additional work to examine the functional consequences of these mutations in various enhancer sites will be of great interest.

Nature Genetics 2015;47: 818–821; doi:10.1038/ng.3335

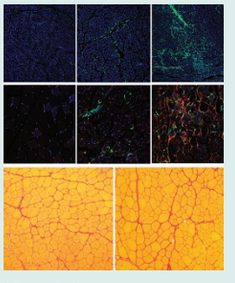
A liquid biopsy for genomic monitoring



Molecular profiling of colorectal carcinomas from tumor samples is now routine. This analysis represents a single point in time, and tumor heterogeneity can affect the ability to detect subclones. As reported in *Nature Medicine,* Siravegna *et al* examined circulating tumor DNA and tracked clonal evolution during treatment with epidermal growth factor receptor (EGFR)-inhibiting antibodies. Acquired resistance to EGFR inhibition was associated with detection of genetic alteration in several genes, including: *KRAS, NRAS, MET, ERBB2, FLT3, EGFR,* and *MAP2K1*. Interestingly, they found that mutated *KRAS* clones ebb and flow with EGFR withdrawal and reintroduction and that such changes correlate with patient benefit from multiple drug challenges. This study provides insight into the dynamic and adaptive nature of the colorectal carcinoma genome as it responds to treatment and evolves according. If made clinically robust, such a system might offer value in the management of patients with colorectal cancer and others..

Nature Medicine, published online 1 June 2015; doi:10.1038/nm.3870

Pharmacologic modulation of tissue healing



When tissue is acutely injured, healing follows a spectrum from full regeneration to fibrosis with organ-function compromise. Although several stromal cells and factors are known to be involved in wound healing, the role of the inflammatory infiltrate in the balance between restoration and fibrosis is unknown. In *Nature Medicine,* Lemos *et al* report that interactions between multipotent mesenchymal stem cells and infiltrating inflammatory cells in damaged skeletal muscle help establish this balance. Specifically, infiltrating macrophages can express tumor necrosis factor, which directly induces apoptosis in the fibro-/adipogenic precursor cells that can give rise to fibrosis and fosters additional muscle regeneration. With more chronic damage, however, secretion of transforming growth factor-β1 (TGF-β1) predominates and not only prevents apoptosis of the fibro-/adipogenic precursors but also induces their differentiation to matrix-producing cells with elaboration of fibrosis. In the authors' mouse model, nilotinib, a tyrosine kinase inhibitor, blocked the effects of TGF-β1 signaling and reduced fibrosis.

Nature Medicine, published online 8 June 2015; doi:10.1038/nm.3869