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MODERN PATHOLOGY

Histopathology of proliferative leukoplakia

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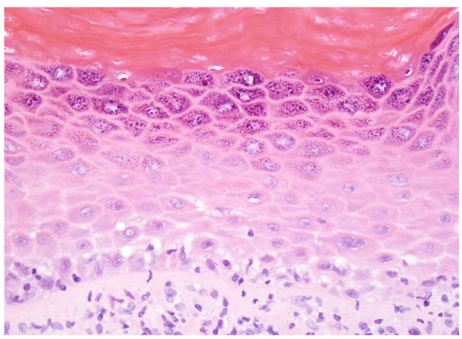

Alabdulaaly et al. characterized the histopathologic features of proliferative leukoplakia from initial/early biopsies and correlated these with malignant transformation in a multicenter retrospective study. The biopsies were evaluated for various histopathologic features. Cases that lacked unequivocal features of dysplasia, termed "hyperkeratosis/parakeratosis not reactive", amounted to 31% of the samples. The most common diagnosis was oral epithelial dysplasia (54%). Almost half (48%) of patients developed carcinoma, and the mortality rate was 12% throughout the study, with malignant transformation occurring in 3.7% of cases. The group now seek additional sampling with longer follow-up periods in order to enhance their data to better support the development of targeted therapeutics for proliferative leukoplakia.

Genomic profiling of *EWSR1/FUS::CREB* translocation tumors

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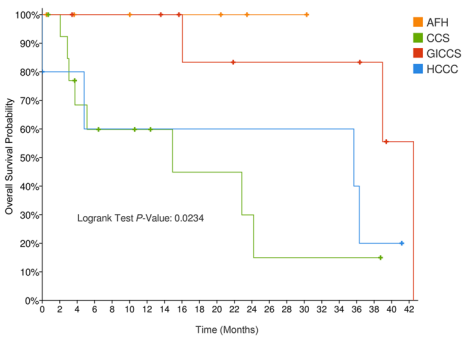

Seeking a better understanding of the mechanisms of the clinicopathologic spectrum of *EWSR1/FUS::CREB* translocation-associated tumors, Dermawan et al. performed a comprehensive genomic analysis across a large cohort of tumor types. The distribution of fusion partners (*ATF1*, *CREB1*, and *CREM*) along with exon involvement was significantly different across tumor types. *CDKN2A/B* homozygous deletions were recurrent in angiomatoid fibrous histiocytoma and restricted to metastatic cases. A sarcoma methylation classifier was able to accurately match 100% of clear cell sarcoma cases to the correct methylation class; however, it was suboptimal when applied to other histologies. The group conclude that their profiling reveals fusion transcript variant heterogeneity resulting in prognostically significant secondary recurrent genetic alterations.

LABORATORY INVESTIGATION

Analysis of DNA copy number aberrations in soft tissue and bone tumors

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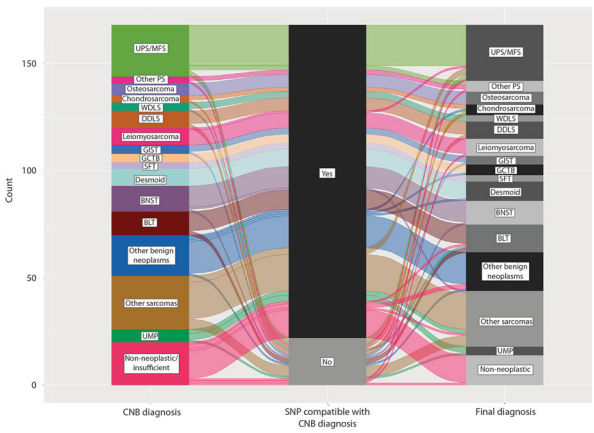

Management of patients with soft tissue and bone tumors (STBTs) often utilizes preoperative core needle biopsies. Köster et al. evaluated the feasibility of single-nucleotide polymorphism array analysis in diagnostics of DNA copy number aberrations (CNAs) in samples from 171 patients. Analysis was successful in 98% of the samples, and diagnostics were comparable in 87% of core needle biopsy samples. For 43 of 171 patients, there were corresponding samples from surgery that were also analyzed, and in 33 of those the two cognate samples clustered together. The group demonstrated that the analysis is feasible, but one drawback was the inability to determine whether a sample lacking CNAs was representative of the tumor population. There was,

however, diagnostic agreement where the CNAs supported the morphological diagnosis, and sometimes informed diagnosis as well.

IL-34 and PTPRZ-dependent mechanisms limit arthritis

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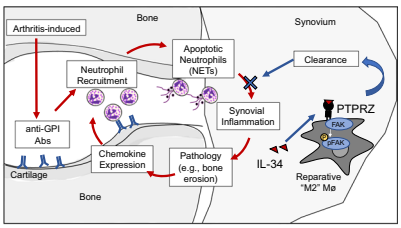

Because IL-34, a macrophage growth factor, is elevated in patients with rheumatoid arthritis (RA), it is considered a therapeutic target. González-Sánchez et al. unexpectedly found that inflammatory arthritis induced in IL-34 knockout mice and in mice lacking the newly identified IL-34 receptor protein-tyrosine phosphatase, receptor type zeta (PTPRZ), was more severe in both groups. Through macrophage-mediated mechanisms, IL-34 and PTPRZ-dependent events limited apoptotic neutrophil-rich synovial inflammation and joint destruction. These findings counter the assumption that IL-34 is harmful in RA, and may fuel further studies toward design of a therapeutic approach for this illness. Moreover, the findings demonstrate that overexpression of a molecule does not necessarily indicate that it promotes pathology—rather, it may limit tissue destruction.

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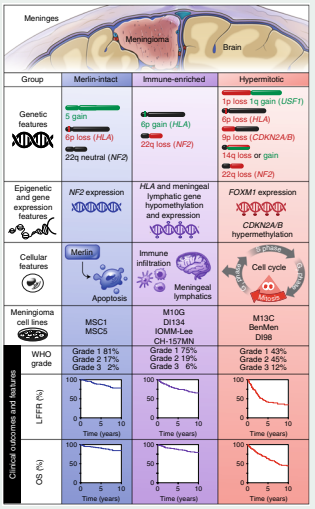
DNA methylation reveals three groups of meningioma

Choudhury et al. explored meningioma biology, seeking information to spur therapeutic development. Using DNA methylation profiling of 565 meningiomas integrated with additional systemic and single-cell approaches, they divided meningiomas into three DNA methylation groups with distinct clinical outcomes, biological drivers, and therapeutic vulnerabilities. Merlin-intact meningiomas (34%) had the best outcomes, and *NF2*/Merlin might regulate susceptibility to cytotoxic therapies. Immune-enriched meningiomas (38%) showed intermediate outcomes, with immune infiltration. Hypermitotic meningiomas (28%) had the poorest outcomes and were distinguished by convergent mechanisms driving the cell cycle along with resistance to cytotoxic therapeutics. The group demonstrated that cytostatic cell cycle inhibitors attenuated meningioma growth in each model tested, from cell culture to patients.



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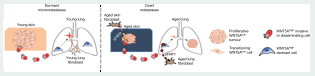
Age is crucial in emergence from melanoma dormancy

Metastasis from primary tumor is facilitated by disseminated cancer cells seeding distal tissues. However, tumor dormancy is possible, allowing years to pass between dissemination and overt metastasis development. Fane et al., in a melanoma model, show that the lung microenvironment facilitates a permissive niche for outgrowth of dormant disseminated cells, whereas skin suppresses melanoma growth but drives dissemination. According to the phenotypic switching model, the melanoma cells flip between a proliferative state and an invasive one. WNT5A was an activator of dormancy in disseminated melanoma cells within the lung, but its impact could be reversed with age-induced reprogramming of lung fibroblasts pushing the cells into metastatic outgrowth. Age-induced changes in these dormant niches seem to promote reactivation and metastasis in the lung.



Nature 2022;606:396–405; https://doi.org/10.1038/s41586-022-04774-2

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