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INSIDE THE USCAP JOURNALS

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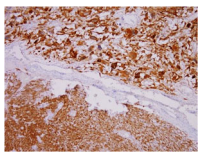
MODERN PATHOLOGY

Pan-TRK immunohistochemistry as a screening tool

https://doi.org/10.1038/s41379-021-01005-3



Tsai et al. describe seven ultra-rare cases of adult *NTRK*-rearranged spindle-cell neoplasms of the viscera. Identification of such cases is critical given their excellent response to *NTRK*-targeting inhibitors. However, correct diagnosis of these neoplasms—including those with unusual cardiac and pleural locations and heterologous differentiation—requires awareness of their ever-expanding clinicopathologic and genetic spectrum in order to prompt confirmatory molecular diagnostics. Using RNA sequencing, fluorescence in situ hybridization, RT-PCR, and immunohistochemistry, the authors characterized visceral mesenchymal tumors harboring *TPM3-NTRK1* (uterine cervix ($N = 2$), pleura, prostate), *LMNA-NTRK1* (lung), *SQSTM1-NTRK3* (heart), and *NTRK3* rearrangement with an unknown fusion partner (colon/mesocolon). Among these, abrupt high-grade transformation into pleomorphic liposarcoma was found in one cervical tumor and the pleural tumor contained intermixed rhabdomyoblasts. As identified by whole-exome sequencing, the former *TPM3-NTRK1*-positive cervical tumor also harbored a *TP53* splicing mutation limited to its heterologous liposarcomatous component. The importance of acknowledging *NTRK*-rearranged sarcoma as a histologic mimic of malignant triton tumor is underscored.

Factors affecting efficacy of anti-HER2 therapies in endometrial cancer

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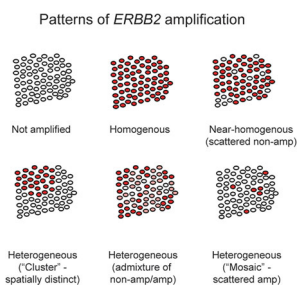

HER2 has been established as a therapeutic biomarker in advanced or recurrent endometrial serous carcinoma. In clinical next-generation-sequencing analyses of over 2000 endometrial carcinomas across all histologic subtypes, Ross et al. characterized the clinicopathologic and molecular features of *HER2*-amplified cases. Almost all *HER2*-amplified endometrial carcinomas were of high-grade histology with co-existing *TP53* mutation but were not restricted to serous histology. Intratumor heterogeneity in HER2 expression, as shown by immunohistochemistry, was common and correlated with genetic heterogeneity by fluorescence in situ hybridization. These results have important implications for HER2 testing in endometrial cancer. Intratumor heterogeneity, p53 dysregulation, and concurrent genetic alterations in *PIK3CA* and *ERBB3* in this cancer type may potentially impact the efficacy of anti-HER2 therapies.

LABORATORY INVESTIGATION

Epigenetic dysfunction in pathogenesis of malignant glioma

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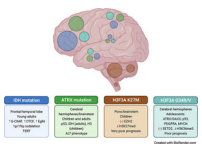

Dharmaiah and Huse review the literature on epigenetic dysregulation events that have been identified as drivers for glioma development. With the identification of such biomarkers, diagnostic neuropathology of diffuse gliomas is not restricted to histomorphological characteristics. *IDH* mutation, *ATRX* mutation, *H3F3A* K27M, and *H3F3A* G34R/V are the hallmark molecular alterations in malignant glioma, each with various mechanisms. They are typically associated with glioma in different areas of the brain, but they all provide a tool for glioma classification and are potential targets for therapeutics. DNA methylation in conjunction with the use of highly recurrent biomarkers such as *IDH1/2* mutation and 1p/19q codeletion, prevents erroneous classification of diffuse gliomas as other central nervous system entities. The impact of these discoveries on tumor biology has not been fully explored. This review discusses how the findings informed the 2021 WHO Central Nervous System Tumor classification.

Assessing multiplexed mass spectrometry as a tool in diagnostics

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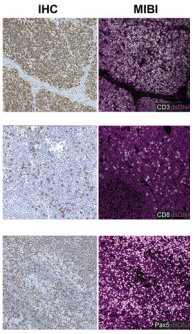

Liu et al. sought to validate concordance between multiplexed ion beam imaging by time-of-flight (MIBI-TOF) mass spectrometry imaging (capable of imaging dozens of proteins in the same tissue section) and single-plex immunohistochemistry over 12 days using a 16-marker staining panel. Samples included disease-free tonsil, lymph node, thymus, and spleen in addition to several types of carcinomas, sarcomas, and central nervous system lesions. Working across 12 serial sections of a tissue microarray of 21 samples, the group assessed concordance on the pixel level and saw concordance in both staining intensity and frequency. CD20 staining in positive regions of tonsil and lymph node in all images was verified to be membrane-localized and enriched in follicles. Correlation was also seen across eight cell populations, in which cell frequencies were measured across serial sections. MIBI-TOF technology can generate quantitative analysis in the clinic that could aid in diagnostics as well as in therapeutic selection.

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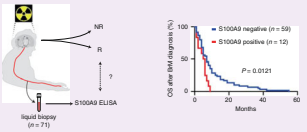
S100A9/RAGE as a biomarker of resistance to whole-brain radiotherapy

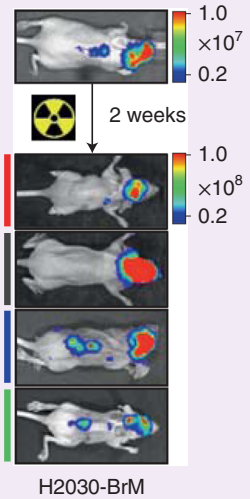
Whole-brain radiotherapy (WBRT) is standard treatment for many patients with brain metastases, but its limited efficacy in preventing disease progression and associated toxicity warrant alternative therapeutic options. With in vivo modeling of brain metastases resistant to WBRT, Monteiro et al. identified the S100A9–RAGE–NF-κB–JunB pathway, activation of which was a potential mediator of resistance. The authors demonstrated that either genetic or pharmacological targeting of this pathway could revert WBRT resistance and increase therapeutic benefit—and do so at lower doses of radiation in vivo. In human samples, they demonstrated that S100A9 levels correlated with clinical responses to WBRT and that levels in the bloodstream could therefore act as a biomarker for patient benefit. The team propose a clinical trial to further evaluate their strategy to best balance therapeutic benefit with toxicity and the likelihood of recurrence.



Nature Medicine 2022;28:752–765; https://doi.org/10.1038/s41591-022-01749-8

Swarm learning in AI modeling of cancer histopathology

Development of robust artificial intelligence (AI) systems—in this paper, for the prediction of molecular alterations from histopathology slides—requires large datasets. There are significant practical, ethical, and legal barriers to collecting sufficient data. Saldanha et al. propose swarm learning (SL) as a way to bypass the need for large datasets to be shared by having multiple teams jointly train AI models, employing blockchain-based communication. SL was used across multicentric datasets of gigapixel histopathology images from over 5000 patients, and the AI model was able to predict *BRAF* mutational status and microsatellite instability directly. The independent groups from Northern Ireland, Germany, and the United States validated the prediction performance of two independent data sets from the United Kingdom. They demonstrated that their SL-trained AI models were an improvement over locally trained models and performed on a level with models trained on merged datasets. While acknowledging the substantial practical effort that will be required to develop SL servers in multicentric institutions, eliminating the need for data transfer in training AI models for histopathological analysis will allow the use of larger sets without the limitations of independently trained models.



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