Modern Pathology (2020) 33, 762–763

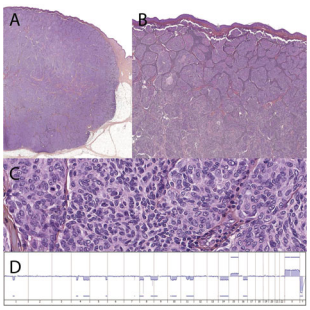
INSIDE THE USCAP JOURNALS

https://doi.org/10.1038/s41379-020-0541-0

MODERN PATHOLOGY

Features of melanocytic tumors with *MAP3K8* fusions

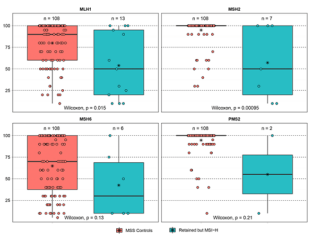
https://doi.org/10.1038/s4137-019-0384-8



In a study of *MAP3K8* gene fusions in 33 skin tumors, Houlier et al. demonstrated that the intact kinase domain was retained without the C-terminal inhibitory domain, this junction being where the fusion partners *SVIL* (46% of cases), *DIP2C*, or *UBL3* were attached. The tumors fell into the family of Spitz tumors and were found mostly in young adults. They involved the lower limbs in 55% of cases. In the atypical (13 of 33) and malignant (15 of 33) cases, there was also frequent inactivation of *CDKN2A* (21 of 26). When compared with a group of 57 Spitz lesions harboring other kinase fusions, *MAP3K8* expression levels were significantly elevated. The authors propose that pathologists be on alert for the presence of large multinucleated cells in the dermis along with ulceration as key features of lesions with *MAP3K8* fusions. In the subset of cases with follow-up, regional nodal involvement, but no distant metastasis, was seen. These data require further maturation.

IHC can miss a small subset of MSI-high cancers

https://doi.org/10.1038/s41379-019-0414-6

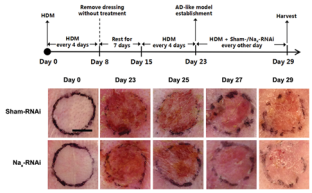


Immunohistochemistry (IHC) as a surrogate for microsatellite instability (MSI) status is common, but broad systematic analyses examining the sensitivity of the test are lacking in the literature. Hechtman et al. classified germline/somatic mutation types in *MLH1*, *MSH2*, *MSH6*, and *PMS2* as either truncating or missense, and then correlated that with MSI and IHC status. Of the examined cohort of 29,530 clinical cases sequenced with the MSK-IMPACT assay, 582 (2%) were MSI-high. Of the 443 MSI-high cases for which IHC results were also available, 36 had discordant IHC: 30 were mismatch repair-proficient and 6 retained expression of the defective mismatch repair protein and lost its dimerization partner (MLH1/PMS2 and MSH2/MSH6). Thus, roughly 6% of MSI-high cases (mostly colorectal and endometrial carcinomas) retained mismatch repair protein expression and would be missed by IHC-based testing, which could impact access to immunotherapy.

LABORATORY INVESTIGATION

Novel target for dermatitis therapeutics

https://doi.org/10.1038/s41374-020-0371-1

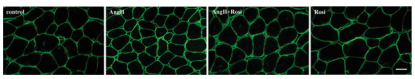


Zhao et al. examined the role of Na_x, a sodium channel known to regulate inflammatory gene expression in response to perturbation of skin barrier function in the context of dermatitis. Using RNA interference to knockdown expression of Na_x in a rabbit ear dermatitic skin model, they showed a reduction in hyperkeratosis and keratinocyte hyperproliferation (epidermal thickening and aberrant differentiation characteristic of dermatitis), along with decreased infiltration of inflammatory cells. Decreased expression of COX-2, IL-1β, IL-8, and S100A9 was involved in produced dermatitic features. The mouse knockdown model also showed that these are downstream genes from Na_x. Current dermatitis treatments include emollients, which restore the barrier function of skin, and topical calcineurin inhibitors and corticosteroids, which are broad and nonspecific

anti-inflammatory therapies and can have adverse effects. Inhibition of Na_x could be a novel therapeutic target for dermatitis.

Novel therapeutic approach for skeletal muscle-wasting

https://doi.org/10.1038/s41374-019-0355-1

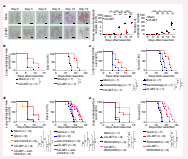


The mechanism by which angiotensin II (Ang II) induces skeletal muscle wasting in patients with chronic kidney disease or heart failure is unknown. Liu et al. used a mouse model to identify this mechanism and determine its potential as a therapeutic target. They demonstrated that Ang II increased expression of Ang II–induced NLR family pyrin domain containing 3 (NLRP3) inflammasome activation in cultured C2C12 myotubes in a dose-dependent fashion. A mitochondrial-targeted antioxidant not only decreased mitochondrial reactive oxygen species and mitochondrial dysfunction (MtD) but also significantly inhibited NLRP3 inflammasome activation and improved or prevented skeletal muscle atrophy. In addition, a PPAR-γ agonist protected against Ang II–induced muscle wasting by preventing MtD, oxidative stress, and NLRP3 inflammasome activation. Thus, there is a potential role of MtD/NLRP3 inflammasome pathway in the pathogenesis of this skeletal muscle wasting and the PPAR-γ/MtD/NLRP3 pathway may provide a therapeutic approach.

Nature.com/pathology

Adjuvant epigenetic therapy to prevent metastatic recurrence

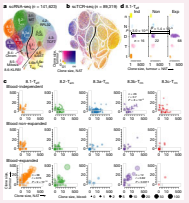
There are currently no effective interventions that prevent the formation of the premetastatic microenvironment, a known factor in distant recurrence of cancer after surgery. Lu et al. found that myeloid-derived suppressor cells (MDSCs) contribute to the development of both premetastatic niches and settlement of residual tumor cells. A mouse model was used to test the hypothesis that the low-dose adjuvant epigenetic therapeutics 5-azacytadine (a DNA methyltansferase inhibitor) and entinostat (a histone deacetylase inhibitor) could disrupt this premetastatic niche. This treatment inhibited the trafficking of MDSCs through downregulation of CCR2 and CXCR2 and by promoting MDSC differentiation. Decreased accumulation of MDSCs in the premetastatic lung ultimately led to increases in both disease-free survival and overall survival when compared with conventional chemotherapy. The group proposes translating these findings to a phase 1 clinical trial in early-stage cancer using adjuvant low-dose combinations of epigenetic modifiers to reduce metastasis.



Nature 2020;579:284–290; https://doi.org/10.1038/s41586-020-2054-x

T-cell expansion in peripheral blood predicts clinical response

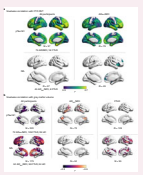
Wu et al. identified specific populations of T cells and T-cell receptors in tumors, normal adjacent tissue, and peripheral blood and performed deep single-cell sequencing of RNA and T-cell receptors in patients with various types of cancer to elucidate the mechanism of action of PD-1/PD-L1 blockage. They found clonotypic expansion of effector-like T cells not only within the tumors but also in normal adjacent tissue, and showed that patients with this signature tended to respond better to anti-PDL1 therapy. The group also demonstrated that, especially in responsive patients, T-cell populations were replenished from sites outside the tumor and confirmed continued activity of cancer immunity cycles in these patients. Their data support the use of peripheral blood as a noninvasive method for identifying specific T-cell populations and thus patients likely to benefit from immunotherapy.



Nature 2020;579:274–278; https://doi.org/10.1038/s41586-020-2056-8

pTau181 as a biomarker for Alzheimer's disease

Currently approved tests for Alzheimer's disease (AD) are cerebrospinal fluid and amyloid β positron emission tomography (PET) scans. Thijssen et al. sought to identify a much less invasive and less expensive diagnostic biomarker for AD and proposed plasma tau phosphorylated at residue 181 (pTau181). They distinguished clinically diagnosed or autopsy-confirmed AD from frontotemporal lobar degeneration by demonstrating that expression of pTau181 was 3.5-fold higher in AD samples than in controls. Levels of plasma pTau181 were also associated with rate of decline on clinical measures of disease severity over a 2-year follow-up period, whereas levels of NfL (a nonspecific biomarker of neurodegeneration) were not. Given the strong relationship between plasma pTau181 and FTP-PET uptake, plasma pTau181 could be useful as a screening tool to measure treatment effects of new AD therapies.



Nature Medicine 2020;26,387–397; https://doi.org/10.1038/s41591-020-0762-2

Emma Judson contributed to these reviews.