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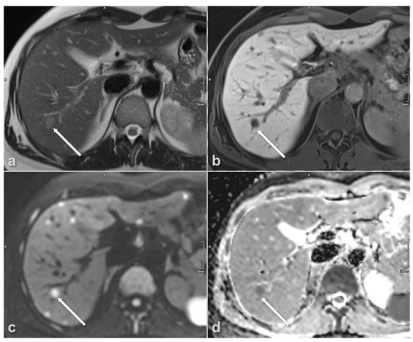
## MODERN PATHOLOGY

### Colorectal *NUTM1* sarcoma

https://doi.org/10.1038/s41379-021-00792-z



*NUTM1* gene rearrangements were originally identified in nuclear carcinoma of the testis, which is rare. Van Treeck et al. investigated five *NUTM1*-rearranged tumors occurring in the colons of five patients (four female and one male). The group assessed histological locations and tissue involvement, documented the cellular features, and looked for mitotic activity and necrosis. Next-generation sequencing identified *MXD4-NUTM1* rearrangements in all five cases. Of the four patients who presented with metastasis, one died of disease at 30 months and the other three were still alive; the one patient with no metastatic disease was disease-free 5 months after diagnosis. The group presents data that distinguish *NUTM1*-rearranged colorectal sarcomas from other *NUTM1*-rearranged neoplasias and states that recognition of the *MXD4-NUTM1* rearrangement may have therapeutic impacts because best treatment is currently unavailable.

### *TRIM63* as a diagnostic marker of MiTF-RCC

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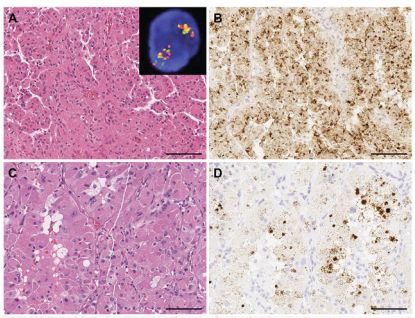

Microphthalmia-associated transcription factor (MiT) family aberration–associated renal cell carcinoma (MiTF-RCC) is a subtype of renal cell carcinoma harboring recurrent chromosomal rearrangements involving *TFE3* or *TFEB* genes. Diagnosis is challenging because MiTF-RCC shares many features with clear-cell RCC and papillary RCC. The study by Wang et al. was designed to characterize MiTF-RCC on a molecular level. Using RNAseq data, they identified *TRIM63* as a signature biomarker. *TRIM63* expression was high in known MiTF-RCC samples compared with other renal tumors, where it was either absent or expressed at low levels. Further evaluation may enhance this association when the functional role of *TRIM63* in MiTF-RCC is explored. *TRIM63* is a strong diagnostic marker that distinguishes MiTF-RCC from other renal cancers with overlapping morphology, and utilization of this marker in the clinic may improve therapeutic decision-making by reducing tumor misclassification.

## LABORATORY INVESTIGATION

### Investigating inflammatory markers following kidney transplant

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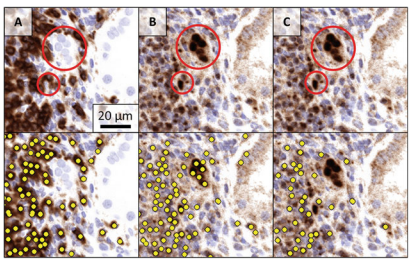
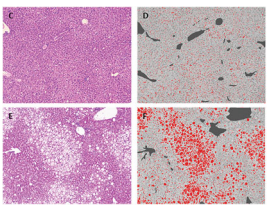



Following kidney transplant, development of interstitial fibrosis and tubular atrophy (IFTA) is often preceded by delayed graft function (DGF). Hermsen et al. explored possible predictive markers for IFTA development by assessing inflammatory infiltrates in kidney biopsies of DGF patients 6 weeks post-transplant using combined multiplex tyramide signal amplification (mTSA) and convolutional neural networks (CNNs). Three renal pathologists stratified the patients for IFTA development (<10% versus ≥10%) from 6 weeks to 6 months post-transplantation. The CNNs were then used to detect inflammatory cells, after which the authors assessed peritubular capillary extent, cell density, cell ratios, and cell distance in the two patient groups. $CD163^+$ cell density was higher in patients with ≥10% IFTA development 6 months post-transplantation, and there was also a high

correlation between CD163$^{+}$ and CD4$^{+}$GATA3$^{+}$ cell density. Although the authors did not identify a new predictive biomarker for IFTA development in DGF patients, they did successfully develop methods for the accurate, reproducible, and scalable assessment of inflammatory infiltrate in sparse tissue such as transplant biopsies.

## Color spectrophotometry in the assessment of steatosis

https://doi.org/10.1038/s41374-021-00600-x



In the setting of liver procurement, steatosis is the most important prognostic feature, while the currently utilized diagnostic tools are gross evaluation and frozen-section examination. Kanamori et al. assessed the accuracy of surface-color spectrophotometry in the quantitative assessment of steatosis in a murine model of fatty liver. A hand-held spectrophotometer was used to scan the livers of mice after 20 weeks on either a normal diet (the control group) or a high-fat diet (for one group with mild steatosis, the other with moderate-to-severe steatosis). Spectral reflectance data and color space values strongly correlated with histopathologic steatosis evaluation. The best predictor was the percentage reflectance at 700 nm, and there were also several parameters that could distinguish large-droplet steatosis. Should the technique prove as accurate in human livers, the group proposes adding surface-color spectrophotometry as a point-of-care tool for quantification of steatosis, which would be especially valuable in assessing livers during procurement of organs from deceased donors.

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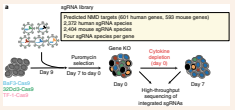
### Dysregulation via aberrant splicing

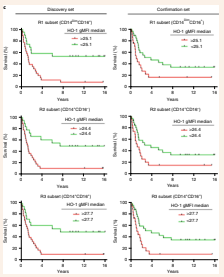
The minor spliceosome component ZRSR2 is subject to recurrent leukemia-associated mutations, yet functional connections among minor introns, hematopoiesis, and various cancers are unclear. Through CRISPR screens of hematopoietic cells, Inoue et al. determined that *LZTR1*, a regulator of RAS-related GTPases, is a minor intron-retaining gene that can confer cytokine independence. Interestingly, previous studies revealed that *LZTR1* was subject to loss of function in Noonan syndrome and in a diverse group of solid tumors, due to intronic mutations that disrupt splicing. The authors also show that minor intron recognition regulates hematopoiesis and that noncoding mutations within minor introns are potential cancer drivers. Since *LZTR1* is dysregulated via perpetuated minor intron splicing, other potential cancer-associated intron-containing genes may be dysregulated via similar aberrant splicing.



*Nature Genetics* 2021;53:707–718; https://doi.org/10.1038/s41588-021-00828-9

### Prognostic value of HO-1 as a tumor marker

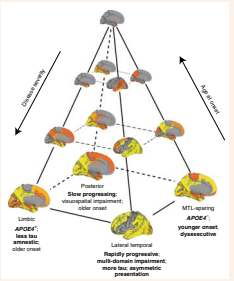
The pathological significance of tumor-associated macrophage (TAM) heterogeneity in the context of anticancer therapeutics is a growing area of research. Consonni et al. found that a distinct subset of TAMs with a high rate of heme catabolism by heme oxygenase-1 (HO-1) favored the pro-metastatic elements of immunosuppression, angiogenesis, and epithelial-to-mesenchymal transition in the tumor microenvironment. Originating in the bone marrow, this population of cells accumulated and preferentially localized at the invasive margin. Inhibition of this recruitment or myeloid-specific deletion of HO-1 decreased metastatic potential and improved anticancer immunotherapy responses. The group thus proposes further exploration of the prognostic value of HO-1 levels in circulating blood, as well as its use as a target for therapeutics to modulate TAM populations.



*Nature Immunology* 2021;22:595–606; https://doi.org/10.1038/s41590-021-00921-5

### Tau variation pathology in Alzheimer's disease

Vogel et al. explored the spread of tau pathology in 1612 patients with Alzheimer's disease (AD). Using tau-positron emission tomography scans, the group identified four distinct spatiotemporal trajectories of tau pathology. Two patterns had already been established in the literature: limbic-predominant and medial temporal lobe-sparing patterns. However, posterior and lateral temporal patterns, resembling atypical clinical variants of AD, were discovered in this study. The investigators explored the patterns in conjunction with distinct demographic and cognitive profiles and outcomes to determine whether the different subtypes may specifically correlate with these features. The data show that tau pathology variation is common and systemic, and the authors urge evaluation of tau pathological staging in AD patients. Such staging could impact clinical trials and has the potential to inform individualized clinical care and treatment of AD patients.



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Reviews written by Emma Judson.

For a Chinese version of Inside the USCAP Journals, see the supplementary material. Translated by Xinyang Xu, MD, PGY1 Pathology, Robert Wood Johnson Medical School and He Wang, MD, PhD, Associate Professor of Pathology, Yale University School of Medicine

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1038/s41379-021-00867-x.