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MODERN PATHOLOGY

Treatment choice following breast biopsy

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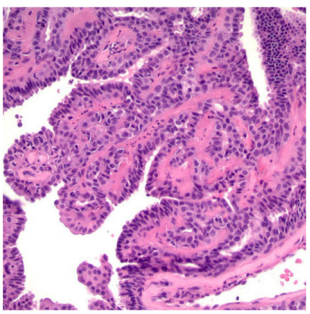

Harbhajanka et al. examined current data related to the necessity of immediate surgical excision of high-risk and selected benign breast cancer lesions diagnosed by the standard percutaneous core needle biopsy (CNB). Concern about underestimating malignancy with CNB and the potential to upgrade a lesion to malignancy at surgical excision influence treatment options. Two cited studies indicated that an upgrade rate from nonmalignant to malignant of ≤3% could be a reasonable threshold for offering surveillance versus surgery. In the cases of radial scars and papillomas without atypia, there may be a case for surgery in order to explore for additional lesions. However, the data did not support a change in the clinical management of 96% of these patients since a vast majority showed multiple lesions. There are also financial and psychological costs of surgical excision versus continued radiologic surveillance. Patients can experience anxiety associated with surveillance and must therefore take an active role in their care plan and follow-up while avoiding the effects of an invasive surgery.

The immune milieu of mucinous colonic adenocarcinoma

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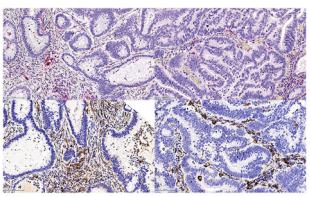

Mucinous adenocarcinoma (MAD) is the most common subtype of colonic adenocarcinoma (CA). There are limited data on how MAD impacts lymphocyte subsets and other immune microenvironmental elements. In a set of 903 CAs, Neyaz et al. identified 225 with mucinous differentiation, defined by ≥10% mucin, as assessed by two pathologists. There was no correlation with disease-specific survival (DSS), and there were no differences in histological or molecular features between MAD and CA with mucinous differentiation. Patients with MAD exhibited a correlation between tumor grade and DSS but not mismatch repair (MMR) status. MAD and conventional CA showed no difference in the numbers of CD8 or CD163 positive immune cells; however, deficient MMR MADs showed fewer CD8, CD163, and PD-L1 positive immune cells compared with proficient MMR MADs. Identification of these features in the immune milieu of the individual samples, despite the limited clinical significance, could influence therapeutic selection for these patients.

LABORATORY INVESTIGATION

Gut microbiota and breast tumor treatment response

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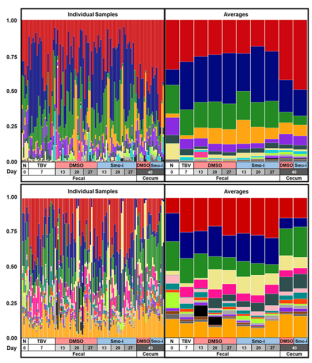

Hinshaw et al. explored the role of the gut microbiome in breast cancer progression and treatment. Orally available therapeutics, such as vismodegib (a Hedgehog inhibitor), can act on cancer cells as well as the gut microbiota. The group utilized a 4T1 mammary carcinoma mouse model and 16 S rRNA sequencing to map alterations in immunomodulating gut microbes during mammary tumor development. The abundance of specific bacteria increased and decreased in predictable and longitudinal patterns during tumor progression. Vismodegib treatment resulted in modifications in the overall diversity of the gut microbiome. The authors noted modulation of the abundance of bacteria involved in systemic immunomodulation and proliferation of $CD8^+$ T cells without gastrointestinal side effects such as drug-induced

colitis. Further assessment of the gut microbiome is needed to improve responsiveness to immunotherapy and optimization of protocols for patient therapeutics.

L1CAM and laminin as prognostic indicators in uveal melanoma

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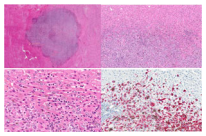

Barnhill et al. examined histopathologic growth patterns of melanoma liver metastases as well as replacement (rHGP) and desmoplastic (dHGP) histopathologic growth patterns in a uveal melanoma cohort. Metastases with pure or >50% rHGP were characterized by nondestructive infiltration of surrounding liver hepatic plates, progressive replacement of hepatocytes with melanoma cells, and individual aggregates of melanoma cells aligned along sinusoidal vascular channels. An advancing front L1CAM and a "laminin vascular network" were observed in a majority of rHGP cases but not in dHGP. L1CAM was present as a progressive extension of angiotropic melanoma cells; laminin labeled the basement membrane zone between sinusoidal vascular channels and angiotropic melanoma cells. Any percentage of rHGP had a significantly adverse effect on metastasis-specific overall survival and was associated with a decrease in metastasis-free survival relative to dHGP. These growth patterns and the roles of L1CAM and laminin correlate with outcomes in uveal melanoma patients and have therapeutic implications.

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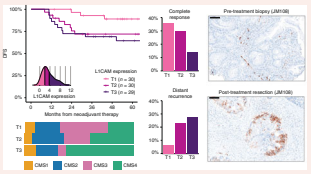
Genomic profiling of rectal cancer for improved therapeutic triage

Recent data indicate that some patients with locally advanced rectal cancer can avoid the traditional surgery following treatment with neoadjuvant chemoradiation. In an analysis of the genomic and transcriptomic profiles of 738 untreated rectal cancers, Chatila et al. found that *APC* mutations were less frequent in the lower than in the middle and upper rectum. *KRAS* mutations were associated with faster relapse in patients treated with neoadjuvant chemoradiation followed by consolidative chemotherapy. The group isolated specific response profiles into individual groups and identified a set of immune hot tumors (IG3) that exhibited extensive immune infiltration. Markers that came through as indicators of poor response to neoadjuvant therapy were overexpression of *IGF2* and *L1CAM*. Genes encoding targets of immune checkpoint blockade, such as PDCD1 (PD-1), CD274 (PD-L1), CTLA4, HAVCR2 (TIM3), and LAG3, were overexpressed in two tumor groups, suggesting benefits of immune checkpoint inhibitors. This profiling system could improve both prognostication and therapeutic selection for these patients.



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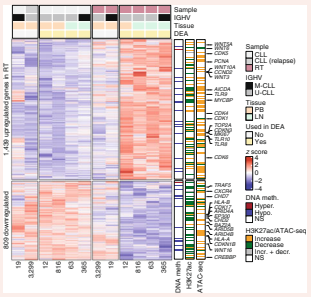
Richter transformation seeded early in CLL

Nadeu et al. studied progression of chronic lymphocytic leukemia (CLL) through the Richter transformation (RT) to large B cell lymphoma. They used 54 longitudinal CLL samples from 19 cases covering up to 19 years of disease course. By performing whole-genome, epigenome, and transcriptome sequencing analysis, as well as functional experiments, the group identified minute subclones. These carried genomic, immunogenetic, and transcriptomic features of RT cells already at CLL diagnosis, which were clinically dormant for up to 19 years before transformation. New driver alterations were identified, including a new mutational signature (SBS-RT) that the group recognized as an oxidative phosphorylation $(OXPHOS)^{high}$–B cell $receptor^{low}$-signaling transcriptional axis in RT. They showed that OXPHOS inhibition reduced the proliferation of RT cells in vitro, suggesting a therapeutic strategy. Given the RT-specific therapeutic targets identified, the data indicate that early intervention to eradicate dormant RT subclones could benefit patients.



Nature Medicine 2022;28:1662–1671; https://doi.org/10.1038/s41591-022-01927-8

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