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MODERN PATHOLOGY

Machine learning tools for whole-slide imaging in digital pathology

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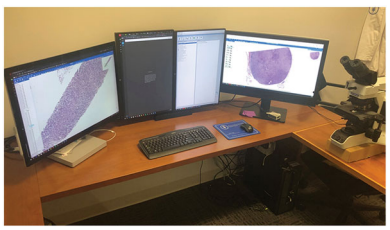

The addition of whole-slide imaging (WSI) resulting in big data acquisition with application of machine learning tools is a disruptive technology chain that makes digital assets of glass slides and transforms the work of pathologists. This is increasingly a practical diagnostic reality, and it requires a coordinated effort across an institution. The technology involves the use of digital scanners along with dynamic-robotic imaging devices and integrated microscopes. Idiosyncratic institutional culture and workflows must be considered. Success of digital pathology will depend on several converging influences, including the business case for digitizing pathology workflow, the availability of algorithmic tools to help pathologists do their jobs better and more efficiently, integration with the broader healthcare digital environment, and ultimate demonstration of the ultimate value proposition: significant improvements in patient care. Advancing across all these areas simultaneously is a challenging prospect, but it is necessary if we are to realize the transformative promise of this technology.

Clonal evolution of HPV-independent vulvovaginal SqCC

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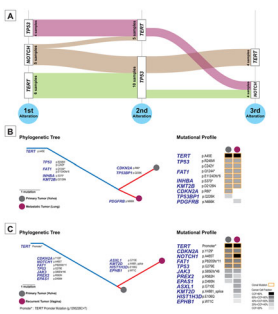
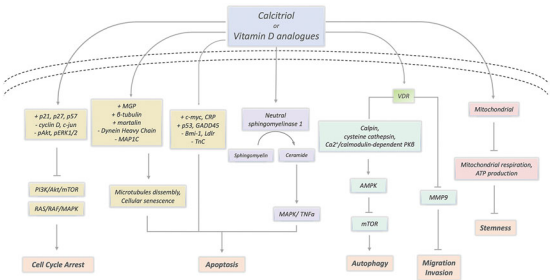


The relationship between human papillomavirus (HPV) and squamous cell carcinomas (SqCC) of the lower female genital tract is a critical area of study. Salama et al. studied clinical data of 28 samples from 26 patients, of whom 11 had HPV-associated SqCC and 15 had HPV-independent SqCC. Well-differentiated SqCC were always HPV-independent. TERT, TP53, *CDKN2A*, and *NOTCH1* gene alterations strongly point away from an HPV-driven process, whereas *PIK3CA* activating mutations without the other mutations strongly favors an HPV-driven tumor. *TP53* mutations were more likely to be a second step in the tumor evolution of some HPV-independent vulvovaginal SqCC. The group showed that *NOTCH1* loss of function is a driver in the carcinogenesis of HPV-independent vulvovaginal SqCC and can be associated with increased tumor cell budding. *TERT*, *NOTCH*, and *TP53* alterations may all be initiating events in HPV-independent squamous cell carcinomas, and all of these provide potential therapeutic targets.

LABORATORY INVESTIGATION

Anti-tumor effects of vitamin D in glioblastoma

https://doi.org/10.1038/s41374-021-00673-8



Glioblastoma is the most malignant and lethal subtype of glioma in adults, with high resistance to conventional chemotherapeutics. Vitamin D, with its endocrine function as a neurosteroid, in conjunction with chemotherapies has become a target of interest. In glioblastoma, vitamin D has been shown to promote cell cycle arrest and induce cell death to suppress tumor growth. Glioblastoma cells show reduced migratory and invasive phenotypes, and reduced stemness following vitamin D treatment. There is evidence of a protective role of vitamin D in cancer survival. Lo et al. found that treatment with vitamin D could cause hypercalcemia in vivo whereas vitamin D analogs did not. Clinical trials utilizing vitamin D and its analogs in combination with chemotherapeutics are ongoing in glioblastoma patients. There is no unified theory as to the mechanism, but there are enough data to support testing of vitamin D combined with standard therapeutics.

Exploring phenotypes of GICs to search for therapeutic vulnerabilities

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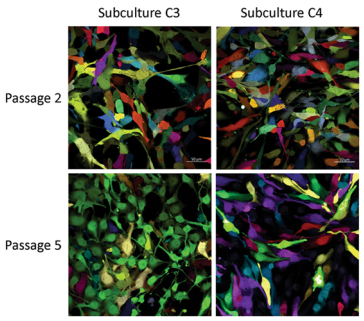

Understanding cancer stem cell heterogeneity and plasticity is of increasing importance for developing and refining personalized cancer therapies. Innes et al. developed a fluorescent barcoding approach to generate, and long-term track mixed clonal populations derived from human glioma stem cells. In combination with the glioma stem cell markers CD133, CD15, CD44 and A2B5, and a computational approach, clonal tracking demonstrates that bulk population stem cell marker plasticity is underpinned by outgrowth of dominant clones in both adherent culture and glioma organoids. In addition to the persistence of dominant clones, there is also a remarkable plasticity of stemness marker expression. This experimental approach is highly scalable and can be used to rapidly establish and characterize hundreds of clones from newly derived glioblastoma cell lines. It offers a powerful and affordable method to identify specific therapeutic vulnerabilities in heterogenous tumor cell populations. nature.com/pathology

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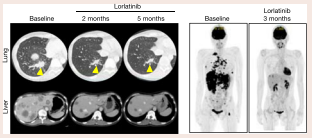
CLIP1-LTK driver of NSCLC responds to lorlatinib

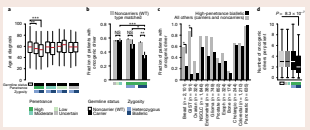
The development of targeted therapeutics for non-small cell lung cancer (NSCLC) has significantly improved patient outcomes; however, oncogenic drivers are not found in 25–40% of lung adenocarcinoma cases, the most common subtype of NSCLC. Using whole-transcriptome sequencing in a multi-institutional genome sequencing platform, Izumi et al. identified a novel fusion transcript of *CLIP1* and *LTK*. The *CLIP1–LTK* fusion was present in 0.4% of NSCLCs and was mutually exclusive with other known oncogenic drivers. The kinase activity of the CLIP1–LTK fusion protein is constitutively activated with transformational properties, and cells expressing the fusion treated with lorlatinib, an ALK inhibitor, inhibited activity and suppressed proliferation and induced apoptosis. One patient with NSCLC harboring the fusion showed a good clinical response to off-label lorlatinib treatment. With limited numbers of patients in the study, there is additional work to do to validate, but there is reason to initiate clinical screening and validation of this result.



Nature 2021;600:319–323; https://doi.org/10.1038/s41586-021-04135-5

Cell lineage matters for germline mutations in cancer

Srinivasan investigated the relationship between the environmental, heritable, and somatic factors that interact during tumorigenesis in human cancers. Utilizing 17,152 prospectively sequenced patients with 55 distinct cancer types, the group identified pathogenic germline variants in cancer-predisposition genes. Two routes of tumorigenesis were revealed. In carriers of pathogenic germline variants in high-penetrance genes, lineage-dependent patterns of biallelic inactivation led to tumors exhibiting mechanism-specific somatic phenotypes and fewer additional somatic oncogenic drivers. However, 27% of cancers in these patients lacked the hallmarks of tumorigenesis associated with the germline allele. The dependence on the pathogenic germline allele was often dictated by both penetrance and lineage, and as such does not diminish the importance of cancer screening but does emphasize that not all cancers have a biology directly related to the alteration in their germline allele. The germline and somatic characterization becomes more crucial to assessing the role in the biology of the patients' disease and influencing therapeutic management.



Nature Genetics 2021;53:1577–1585; https://doi.org/10.1038/s41588-021-00949-1

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For a Chinese version of Inside the USCAP Journals, see the supplementary material.

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