Laboratory Investigation (2017) 97, 230–231

INSIDE THE USCAP JOURNALS

doi:10.1038/labinvest.2017.7

MODERN PATHOLOGY

Rare papillary thyroid carcinoma variant nomenclature

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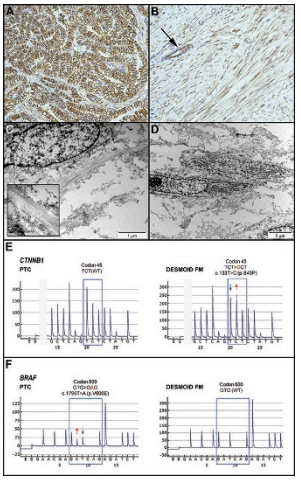

In the February issue of *Modern Pathology*, Rebecchini and colleagues described the exceedingly rare entity 'papillary thyroid carcinoma with nodular fasciitis-like stroma.' They demonstrated that the papillary thyroid carcinoma component harbored a characteristic *BRAF* V600E mutation that was present only in the epithelial component. Immunohistochemistry for β-catenin revealed strong membranous staining in the epithelial component whereas the stromal component revealed nuclear accumulation. Assessment of the *CTNNB1* gene that encodes β-catenin revealed an S45P mutation in the stromal component that was absent in the epithelial component. Thus, surprisingly, the two components have distinct mutational profiles. This was demonstrated in two independent cases. The stromal component is histologically more compatible with desmoid fibromatosis and has a *CTNNB1* exon 3 mutation characteristic of desmoid fibromatosis. Nodular fasciitis harbors an *MYH9–USP6* gene fusion rather than *CTNNB1* activating mutations. Therefore, the authors suggest the new term 'papillary thyroid carcinoma with desmoid-type fibromatosis.'

Molecular profile of vulvar lesions

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Watkins *et al* investigated the pathogenesis of the atypical verruciform proliferations sometimes associated with human papillomavirus–negative vulvar carcinoma. The former generally had *TP53* and *CDKN2A* mutations while the latter carried *PIK3CA* and *ARID2* mutations. Therefore, the two lesions appeared distinct from a molecular perspective. One patient developed an atypical verruciform proliferation with *PIK3CA* mutations followed by a

keratinizing carcinoma with both *PIK3CA* and *TP53* mutations. This finding confirms a pathogenic connection between these two tumors and demonstrates the molecular alterations involved in progression. While these two lesions appear to be unrelated in most instances, progression can also occur. Further investigation will probably further elucidate the exact transitions and development of these lesions from an atypical verruciform proliferation to keratinizing carcinoma, and the current findings suggest the appropriate genetic investigation needed to further explore this mechanism.

LABORATORY INVESTIGATION

Optimizing core size for tissue microarray

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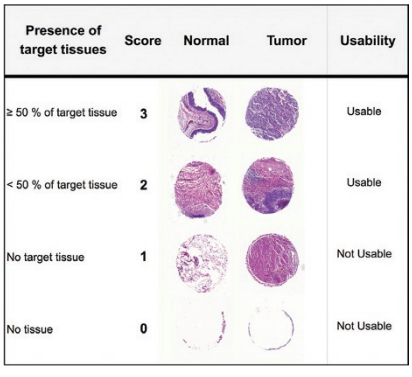

One of the great challenges of tissue sampling for microarray analysis is that the core selected must be both taken from the correct histological area of the tumor and representative of the tissue of origin. Intratumor heterogeneity, along with the inadvertent inclusion of cells from normal underlying tissue, can skew the microarray data. Using samples of bladder cancer tissue, Eskaros *et al* compared results obtained using

the traditional 0.6-mm core with those with a larger (1.0-mm) core and found that the latter had better technical and analytical accuracy as well as superior repeatability, especially when focused histological features or substantial heterogeneity were present. The balance between building an effective tissue microarray that encompasses sufficient patient tissue for comparison and not depleting a patient's sample could thus best be achieved with a slightly larger (1.0-mm core) in certain instances, but core sizes larger than this offered few advantages.

Immunofluorescence: quantitative potential

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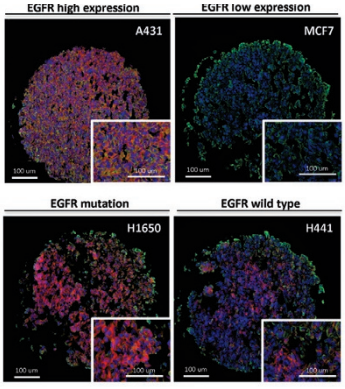

Immunohistochemistry (IHC) has long been used to assess protein levels in tissue. Compared with mass spectrometry, it is known to be subject to variability in sensitivity, specificity, and replicability and is thus usually deemed semiquantitative. Toki and colleagues assessed automated quantitative immunofluorescence with standardization as a method to compare the method with mass spectrometry. Using a continuous scale by quantifying immunofluorescence at the pixel level per unit area, the team found a substantial reduction in the subjectivity and operator error inherent in IHC scoring. Multiple cell lines and antibodies were tested to standardize the scoring system, using EGFR protein as a test case. As yet—with only cell lines, not heterogeneous primary tissue, tested—there are necessary limitations of the findings. However, the group maintains that their results open doors for IHC to become a truly quantitative assay in diagnostic testing.

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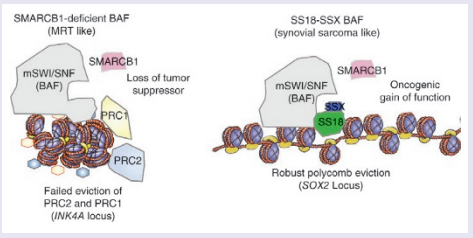
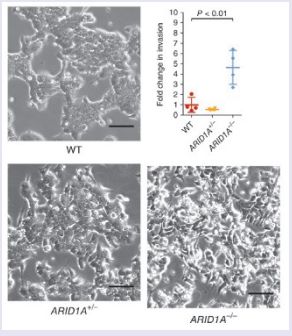
Assaying the BAF–Polycomb battle



Kadoch and team note that, while mutations in the genes encoding BAF subunits contribute to fully 20% of human malignancies, the underlying mechanisms remain unclear due to a lack of assays to assess BAF (SWI/SNF) function in living cells. The group developed a recruitment assay system and showed that BAF opposes Polycomb repressive complexes (PRC) by rapid, ATP-dependent eviction. This leads to formation of accessible chromatin, even in the absence of RNA polymerase II occupancy, transcription, and replication. Ultimately, accessible chromatin is permissive for gene activation. Reverse leads to facultative or inaccessible/inactive heterochromatin reassembly with gene silencing. The study indicated that widespread opposition between BAF complexes and Polycomb removal is constant, dynamic, and plastic, with strong implications for cancer. Examples include epithelioid sarcoma or malignant rhabdoid tumor, in which SMARCB1 loss leads to PRC1 and 2 chromatin inactivation whereas the synovial sarcoma fusion protein results in BAF gain of function and PRC1 and 2 kickout with oncogenic activation.

Nature Genetics, published online 12 December 2016; doi:10.1038/ng.3734

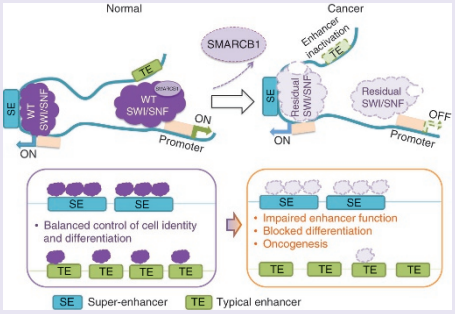
ARID1A regulation in cancer



Seeking to investigate how inactivation of SWI/SNF (BAF) family member *ARID1A* promotes tumorigenesis, Mathur and team observed that *Arid1a* functions as a tumor suppressor in the mouse colon and that invasive *ARID1A*-deficient adenocarcinomas resemble human colorectal cancer. This action is independent of APC/β-catenin signaling components, which are critical early gatekeepers in human colorectal carcinoma. ARID1A was shown to target SWI/SNF complexes to enhancers, functioning in coordination with transcription factors to facilitate gene activation. ARID1 loss was shown to change levels of histone modification at enhancers impairing enhancer configuration and activity, with marked consequences for gene expression. Improved colon cancer modeling with more detailed information about how the enhancer-mediated gene regulation functions as a principal tumor suppressor will almost certainly arise from this model.

Nature Genetics, published online 12 December 2016; doi:10.1038/ng.3744

SMARCB1/INI1 and cancer gene regulation



Wang *et al* used genomically stable pediatric rhabdoid tumors as a model in which broad alterations in epigenetically influenced gene expression are induced by loss of *SMARCB1/INI1*, a member of the SWI/SNF (BAF) chromatin remodeling complex. Human rhabdoid tumors exhibited distinct enhancer H3K27ac signatures, and the group assessed the significance of this in identifying differentiation programs. SMARCB1 was shown to be required for the integrity of SWI/SNF complexes for enhancing targeting. Its absence markedly impairs SWI/SNF binding to typical enhancers required for differentiation while retaining binding to certain super-enhancers required for survival. In mice, *Smarcb1* inactivation lead to extremely rapid-onset cancer, with only a limited number of cell types susceptible to transformation, whereas the vast majority of cells undergo arrest. The group asserts that these insights into mechanisms by which SWI/SNF subunit mutations cause cancer are essential to identifying potential therapeutic targets.

Nature Genetics, published online 12 December 2016; doi:10.1038/ng.3746
Emma Judson contributed to these reviews.