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Modern Pathology

TERT promoter mutations can have opposing effects on cancer

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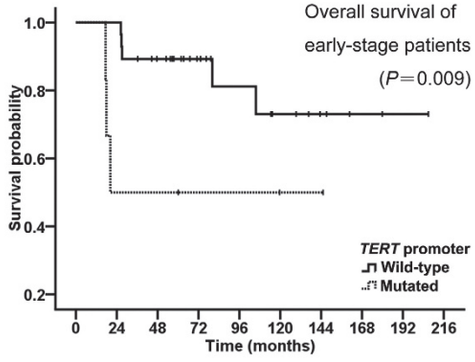

Since the initial discovery that recurrent point mutations in the *TERT* promoter lead to overexpression of the encoded protein in melanoma, the same finding has been documented with multiple neoplasms. Huang *et al* found that *TERT* promoter mutations were present in ovarian and endometrial clear cell carcinomas in 16 and 21% of their cohorts, respectively. The presence of these mutations correlated significantly with older patient age, intact ARID1A expression by immunohistochemistry, and low incidence of activating *PIK3CA* mutations. In ovarian clear cell carcinomas, *TERT* promoter mutations were independent predictors of both reduced disease-free and overall survival on multivariate analysis. Interestingly, in another article in this issue, Chan *et al* report an association between *TERT* promoter mutations and a more favorable overall survival in patients with lower-grade gliomas. Thus, the effects of *TERT* mutations on tumor biology appear to be context-dependent.

mRNA biomarkers for cervical cancer

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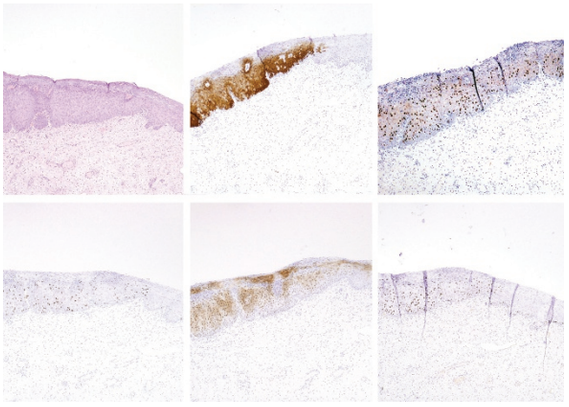
Human papilloma virus (HPV) genotyping is currently used to screen for patient populations with an increased incidence of cervical high-grade squamous intraepithelial lesions (HSILs). del Pino *et al* used six mRNA biomarkers in liquid cervical PAP-smear preparations to investigate whether this approach can also select a population at higher risk of developing HSILs. Reverse-phase polymerase chain reaction was initially used to measure mRNA expression for six genes (*CDKN2A/P16*, *BIRC5*, *MMP9*, *TOP2A*, *MCM5*, and



MKI67), with immunohistochemistry for the encoded proteins in biopsy material as well. Messenger RNA of adequate quality for testing was obtained in 92% of the specimens. A combination of *TOP2A* (higher sensitivity) and *CDKN2A/P16* (higher specificity) showed robust sensitivity (100%) and specificity (43%)—laudable for a screening test. Immunohistochemistry for p16 showed equivalent sensitivity and improved specificity (63%) in tissue biopsies. The test-performance characteristics in this cohort show significant improvement over those for cytology and high-risk HPV testing.

Laboratory Investigation

Two-dimensional pancreatic cancer model

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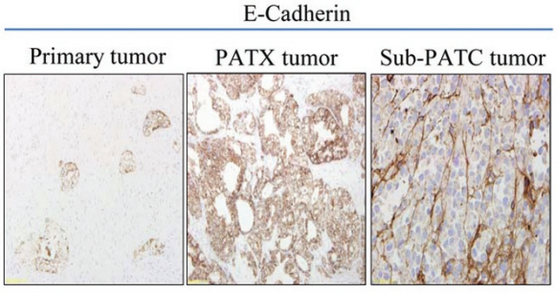

Long-term cell culture monolayers have limitations for human cancer studies. Kang and colleagues determined that human pancreatic ductal adenocarcinoma cells grown as mouse xenografts from surgical-resection specimens differed dramatically from the same tumor cells later isolated for monolayer culture. In particular, early passages of cells from the xenograft conditioning showed lower rates of doubling time and colony

formation, were more concentrated in the G0/G1 checkpoint phase, and were less sensitive to gemcitabine and 5-fluorouracil than later-passage cells. Induction of epithelial–mesenchymal transition was noted with increasing passage of cells *in vitro* and in the subcutaneous *in vivo* model. This study demonstrates critical changes occurring with increased time in monolayer culture. A continuous source of low-passage cells could better model what is seen *in vivo*. Passaged mouse xenografts present a ready supply of low-passage and presumably isogenic cell lines for study.

Remodeling the cornea with epithelial cells

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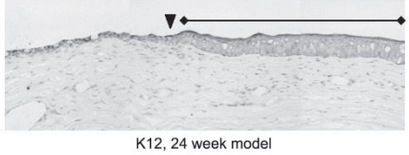

K12, 24 week model

Corneal epithelial stem cells in the limbus supply the corneal epithelial cells of the eye. Kameishi *et al* studied a rabbit cornea-regeneration model in which the eye was stripped of keratin-12 expressing corneal and limbal epithelia. Keratin-13-expressing conjunctival epithelium then migrated to and completely colonized the corneal surface. This was accompanied by neovascularization and corneal opacification. Interestingly, at 24 and 48 weeks after surgical stripping, keratin-12-positive cells reappeared as growing islands on the surface of the eye. These cells appear to have transdifferentiated from the keratin-13 cell population, perhaps in association with an epithelial–mesenchymal transition—and presumably back to a different epithelial cell. This model should provide insight into corneal stem cell deficiency and a better understanding of the epithelial stem cell niche and the degree of its differentiation plasticity.

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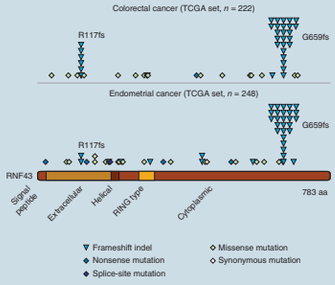
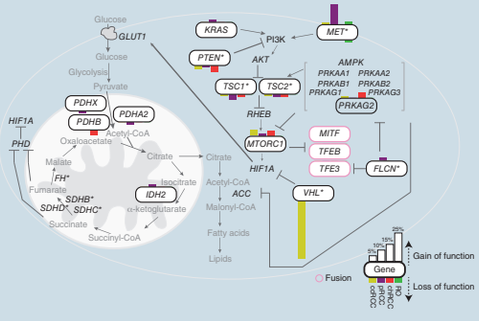
RNF43 mutations in cancer



In a study recently reported in *Nature Genetics*, Giannakis and colleagues demonstrated somatic mutation of *RNF43* in almost one in five colorectal and endometrial carcinomas. *RNF43* is an E3 ubiquitin ligase that negatively regulates the Wnt pathway. Thus, loss-of-function mutations in this gene result in increased activity of the Wnt pathway, similar to what is seen with common *APC* loss-of-function mutations in colonic carcinoma. Not surprisingly, then, *RNF43* and *APC* loss-of-function mutations are mutually exclusive. *RNF43* mutation was also more frequent in microsatellite-instable carcinomas owing to the presence of sizable homopolymeric G-C-tract microsatellites within exons. These tracts are also common mutational sites of single-base deletions and frameshifts in microsatellite-stable tumors. The frequency of these mutations and the mutually exclusive relationship with *APC* mutations argue that selection for these mutations occurs in carcinogenesis.

Nature Genetics 2014;46:1264–1266; doi:10.1038/ng.3127

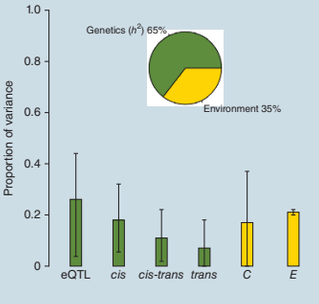
Genomic diversity in non–clear cell renal cell carcinoma



Non–clear cell renal cell carcinoma subtypes include oncocytoma, papillary, chromophobe, and translocation. Clear cell renal cell carcinomas represent about three-quarters of renal carcinomas, and each subtype is relatively uncommon. Durinck *et al* found that, overall, the profiles of significantly mutated genes varied between the various subtypes. Compared to the clear cell, the number and diversity of protein-altering mutations was somewhat higher in papillary carcinoma and significantly lower in both chromophobe and oncocytoma. Gene-expression analysis defined a five-gene panel that enabled robust distinction of the chromophobe, oncocytoma and papillary subtypes. Aberrations at multiple levels of the MET/AKT/mTOR signaling cascade were common among subtypes, as were certain mitochondrial metabolic perturbations. The genomic variation between subtypes reveals different pathogenesis and treatment approaches. Molecular testing within subtypes is also important, such as documentation of the significant portion of papillary tumors showing *MET* mutations.

Nature Genetics 2105;47:13–21; doi:10.1038/ng.3146

A genomic twist on the nature-vs.-nurture debate



Quantitating gene expression by RNA-sequencing techniques allows for allele-specific expression studies. Differences in allele expression are presumed to be due primarily to genetic variation of the *cis* regulatory elements because each element would be exposed to the same environmental influences. The remaining variation is due to environmental and/or experimental variables. Buil and colleagues assessed gene-expression in matching normal tissue from twins. Some of the variation in allele-specific expression could not be explained by *cis* genetic variation. This amount varied in different tissue types. In the authors' proposed model, differences in allele-specific expression are caused by sequence divergence of *cis* regulatory sequences, but the magnitude of these effects is strongly influenced by *trans* genetic and environmental factors. Thus, the answer to the age-old nature-vs.-nurture question remains: both—even at the genomic level.

Nature Genetics 2015;47:88–91; doi:10.1038/ng.3162