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MODERN PATHOLOGY

Validation of the Vanderbilt staging system

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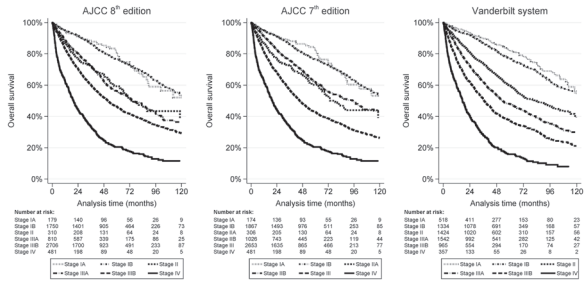
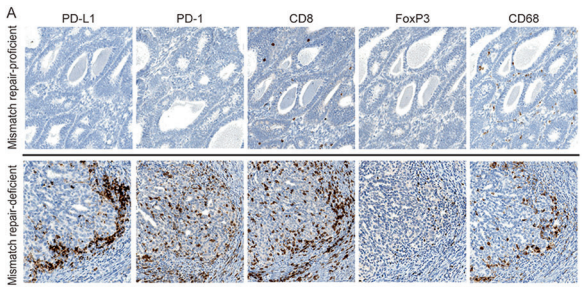


Huggett and Cates sought to compare the Vanderbilt staging system for retroperitoneal sarcoma with both the seventh and eighth editions of the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual*. In an independent cohort of 6857 patients from the National Cancer Database, they assessed degree of discrimination for stage groupings. Using several statistical criteria, they found that the eighth (current) edition of the manual, which recommends separating staging algorithms for soft-tissue sarcoma by anatomic site, was inferior to their proposed Vanderbilt system in categorizing risk of death. The latter system—which incorporates measures of regional tumor extension or multifocality in addition to information regarding histologic subtype—showed greater discrimination between adjacent tumor stage groupings, higher predictive accuracy for 5-year survival, and more accurate prediction of clinical outcomes, resulting in a better-fitting regression model. Aspects of the Vanderbilt system seem worthy of further exploration in the quest for better staging systems in this rare disease family.

Combination immunotherapy in mismatch repair–deficient endometrial cancer

doi:10.1038/s41379-018-0172-x

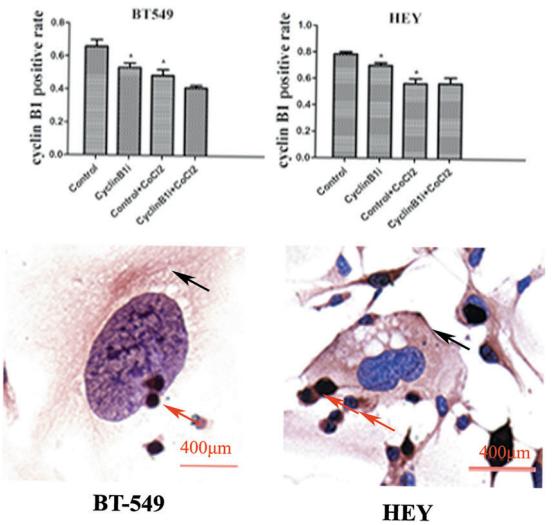


Seventy-six endometrial cancer hysterectomy specimens were evaluated for tumor-infiltrating immune cells by immunohistochemistry, to assess the immune suppressive mechanisms involved and elucidate the potential benefit of immunotherapy for patients with this disease. Compared with mismatch repair–proficient endometrial cancers the mismatch repair-deficient cancers showed higher levels of infiltrating $CD8^+$ T lymphocytes, FoxP3 regulatory T cells, PD-1-positive immune cells, and PD-L1-positive immune cells, with no difference in $CD68^+$ tumor-associated macrophage infiltration. Asaka et al. concluded that the increased number of $FoxP3^+$ regulatory T cells could be the basis for trials of combination therapy targeting both regulatory T cells (CTLA-4 and CCR-4 monoclonal antibodies) and immune checkpoints (anti-PD-1/PD-L1) to improve clinical efficacy in these patients, given how effective this therapy has proved in other cancer types.

LABORATORY INVESTIGATION

Nuclear translocation failure of cyclin B1 in cell cycle arrest

doi:10.1038/s41374-018-0157-x



Animal xenograft models of BT-549 and HEY cells $CoCl_2$ show increased proportion of polypoid giant tumor cells following $CoCl_2$ induction, higher nucleus:cytoplasm ratio, and increased spindle cell morphology. Using immunohistochemistry, the group demonstrated higher numbers of cyclin $B1^+$ cells, and a nuclear location of the cyclin B1 in these polypoid giant cancer cell derived xenografts compared with control. Following $CoCl_2$ treatment, cyclin B1 was present in the cytoplasm of polypoid giant cancer cells, and the group proposes that translocation failure of cyclin B1, CDC25B and CDC25C from the cytoplasm to the nucleus could be related to G2/M arrest in these cells. In samples of formalin fixed paraffin embedded human breast cancer tissues ($n = 188$) and human ovarian

cancer samples ($n = 67$), the data were corroborated, with positive staining for cyclin B1 in the cytoplasm of polypoid giant cancer cells and in the nuclei of diploid cancer cells. New therapeutic strategies could be conceived via a better understanding of this nuclear translocation failure.

Rapid diagnosis of IDH1-mutated gliomas by GC-MS

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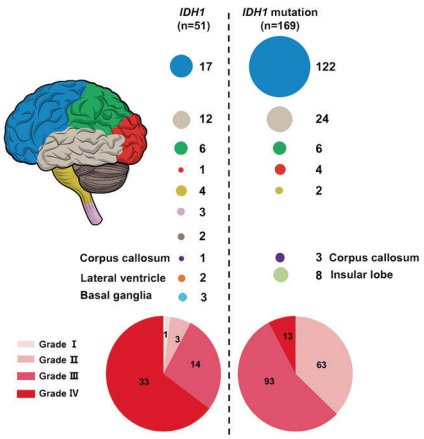

IDH1, 2 have been identified as being frequently mutated in glioma, with mutation of IDH1 defining a distinct subtype of glioma as well as being a predictive biomarker of therapeutic response. The conversion of α-ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG) is a process enhanced following IDH mutation and therefore analysis of 2-HG concentrations is a prognostic biomarker of glioma. The group compared PCR-sequencing, immunohistochemistry staining and gas-chromatography mass spectrometry and while the sensitivity and specificity was equivalent PCR and IHC could take 1–2 days. The levels of 2-HG appeared to be higher in young IDH1-mutated patients compared with elderly patients, and higher in GBM compared with LGG. Methods were optimized to detect 2-HG qualitatively and quantitatively to a specificity of 100% within 40 minutes without complex or time-consuming preparation. Xu et al. propose that this is a promising strategy for intraoperative diagnosis of IDH1-mutated gliomas in the future, as well as to identify intraoperative tumor boundaries.

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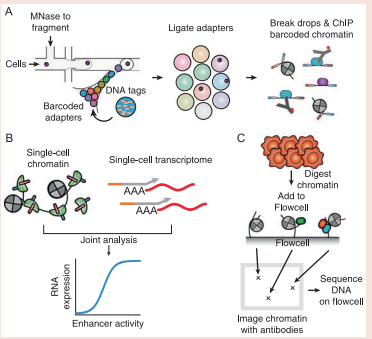
Delving into multilayered complexity of epigenomic regulation

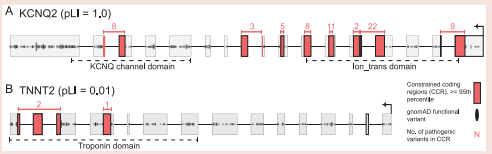
Shema et al. evaluated the technological advances that have allowed the study of epigenomic regulation at a single-cell and single-molecule level to understand the regulatory diversity at single-molecule resolution within single cells. The group compared five sequencing-based technologies and four imaging-based technologies and tabulated the results obtained with the different methods and the comparative utility of each. Noncoding region conservation—and noncoding regions in general—have been shown to be influential in evolutionary studies as well as the analysis of most human disease–associated variants, which lie outside coding regions. As things stand, even with single-cell technologies available, the multilayered complexity of epigenomic regulation makes the analysis of integrative regulatory models of cells a future aspiration. With new technologies being developed, computational models will be required to stitch layers together and generate more complete models of regulatory changes across cell types.



Nature Genetics 2019;51:19–25; doi:10.1038/s41588-018-0290-x

Disrupting CCRs as model for disease phenotype

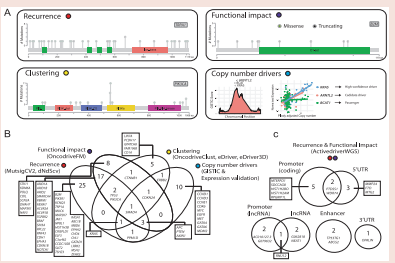
Constrained coding regions (CCRs) in the human genome are, by definition, devoid of protein-changing variants and should coincide with pathogenic mutations observed in patients with de novo dominant disorders. Havrilla et al. demonstrated that CCRs at or above 95% showed a 7.1-fold enrichment of pathogenic mutations. The least constrained CCRs showed a fourfold depletion in these mutations but are insufficient as a solitary metric for identifying these regions. The researchers acknowledge the limitation of this as a predictive tool in recessive disease but confirmed, via comparison with other metrics, that it is empowered to reveal constrained regions under autosomal dominant disease models. Another limitation is that some of the regions studied exhibit such significant constraint because extreme developmental disorder or embryonic lethality results from mutations. All the same, the authors propose that systematic analysis of the phenotypes exhibited when these CCRs are disrupted will reveal drivers for disease phenotypes.



Nature Genetics 2019;51:88–95; doi:10.1038/s41588-018-0294-6

Genetic drivers of poor-prognosis esophageal adenocarcinoma

The search for meaningful genetic drivers of cancers is a common goal and can lead to targeted therapeutics and optimized prognostication. Seeking drivers of esophageal adenocarcinoma, Frankell et al. assessed a cohort of 551 genomically characterized esophageal adenocarcinomas and identified 77 driver genes and 21 noncoding driver elements. The group found that *SMAD4* and *GATA4* were poor prognostic markers. Mutations suggesting sensitivity to CDK4/CK6 inhibition were common, accounting for about half of cases. Using esophageal adenocarcinoma cell lines and organoids, the researchers demonstrated effects with the CDK4 and CDK6 inhibitors palbociclib, ribociclib, and abemaciclib. The results were comparable to that seen with T47D, an estrogen receptor–positive breast cancer; CDK4/CDK6 inhibitors are Food and Drug Administration–approved therapeutics for breast cancer. The authors conclude that comprehensive studies such as this one should be instrumental in the design of evidence-based clinical trials.



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