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INSIDE THE USCAP JOURNALS

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MODERN PATHOLOGY

Sequencing in triple-negative breast cancer

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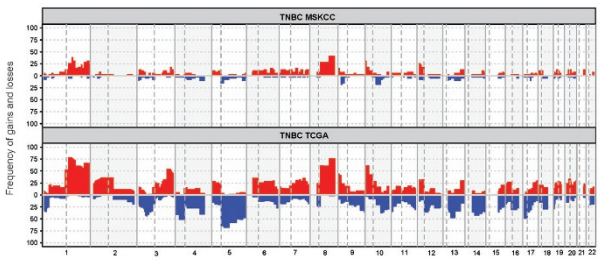

Weisman *et al* performed targeted high-depth massively parallel sequencing in 39 triple-negative breast cancers and paired this with detailed morphologic analysis looking for correlation in this heterogeneous group of cancers. They identified *TP53* as the most frequently mutated gene in their cohort, at 74%, with *KMT2D* (*MLL2*) at 15% and *PIK3CA* at 10%. Comparisons were drawn between their data and those from The Cancer Genome Atlas (TCGA) breast cancer study, in which the overall pattern of copy-number alterations was similar. Where the data add information is in the distinction between these copy-number changes and the morphological subtypes of cancer in which they were found. Activating *PIK3CA* mutations were enriched specifically in apocrine triple-negative breast cancer (75%). Correlations between mutations and histologic changes provided a more specific analysis, and the group found that by selecting actionable targets they were able to provide data that would influence systemic therapy.

TERT promoter mutations in bladder cancer

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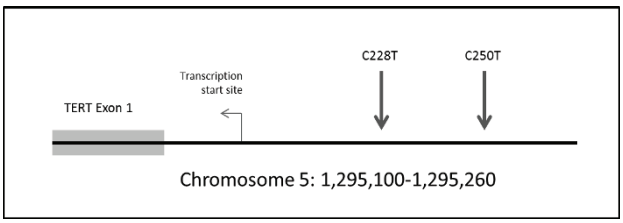

Cowan *et al* searched institutional pathology archives to identify 15 bladder cystectomy specimens of squamous cell carcinoma (2000–2014). Their goal was to perform a retrospective analysis of the samples to identify *TERT* promoter mutations with the aim of developing a urine-based molecular screen for bladder cancer. *TERT* promoter mutations were initially described in melanoma and have subsequently been encountered in several tumor types, including the great majority of conventional bladder urothelial carcinomas. This study is distinctive in that it focused on the rare bladder squamous cell carcinomas lacking urothelial differentiation. Twelve of 15 patients (80%) harbored *TERT* promoter mutations similar to those seen in conventional urothelial carcinomas. The authors' data place conventional urothelial cancer and urinary bladder squamous cell carcinomas into a common group with regard to *TERT* promoter mutations and suggest that a molecular urine-based screening assay might be applicable to both.

LABORATORY INVESTIGATION

Stem cells alleviate lung injury

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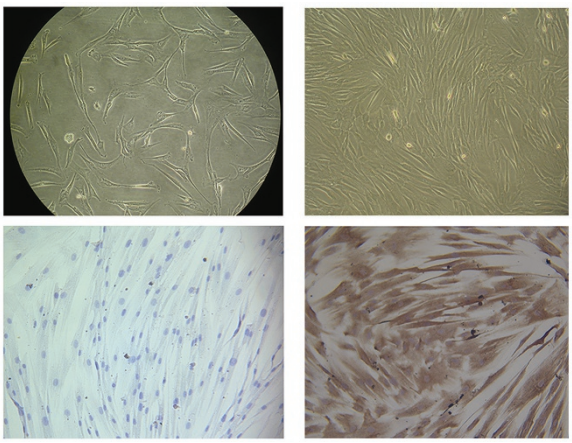

Qiang *et al* developed a model of ischemia/reperfusion injury following cardiopulmonary bypass (CPB). Dogs underwent either mock surgery (sham), cardiopulmonary bypass (model), or cardiopulmonary bypass with a femoral injection of human amniotic stem cells (modification). Several assays were employed to assess features such as location of the injected stem cells, venous-blood tumor necrosis factor-α, interleukin-8 (IL-8), matrix metalloproteinase-9, and IL-10 concentrations as well as pathological changes in the lungs. Significant changes were observed in alveolar septum width and infiltration of neutrophil granular cells in the lung interstitial tissue, among others. These were worst in the model group compared

with the sham group, and were improved in the stem cell group. The authors conclude that venous transplantation of stem cells can significantly alleviate lung injury induced by ischemia/reperfusion in dogs; the therapeutic effect is associated with downregulation of proinflammatory factors. Future work is warranted to assess the mechanisms underlying induced lung injury.

Distinct subtypes of Creutzfeldt-Jakob disease

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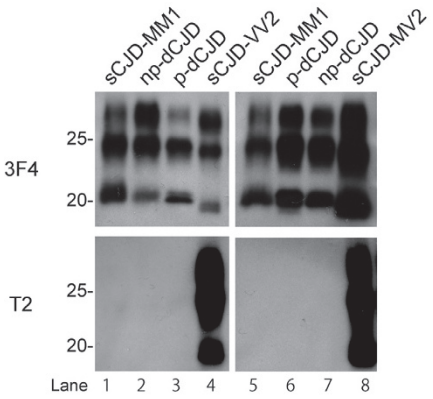

Takeuchi *et al* performed a study in plaque-type Creutzfeldt-Jakob disease (CJD) vs. non-plaque-type CJD. Prior studies on transmission have shown that the plaque-forming phenotype of plaque-type CJD is linked to the V2 prion strain also associated with sporadic CJD subtypes VV2 or MV2. Using protein-misfolding cyclic amplification, the group demonstrated that the prions in plaque-type CJD show amplification features that distinguish them from those in non-plaque-type CJD. Specifically, plaque-type CJD prions showed a preference for 129 V substrate and generated different amplified products. They propose that, with sufficient protection of patients at risk for CJD transmission, the tool might serve as a rapid diagnostic method for identifying acquired CJD associated with the V2 strain and for surveillance of acquired CJD cases as well as provide a means for analysis of patients' phenotypic features.

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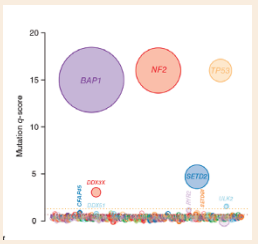
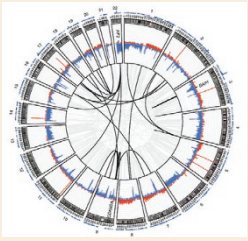
Genetics of malignant pleural mesothelioma





Bueno *et al* performed a large-scale sequencing study searching for genetic variation in patients with malignant pleural mesothelioma (MPM), for whom the outcome is currently dismal. They used RNA-seq data to identify significantly mutated genes (e.g., *BAP1* and *NF2*) and recurrent mutations (*SF3B1* and *TRAF7*). They also identified gene fusions leading to inactivation (*NF2*, *BAP1*) and splice alterations as a recurrent mechanism of inactivation (*BAP1*, *NF2*). Their goal was to use unsupervised consensus clustering of RNA-seq-derived expression data to identify different profiles of epithelioid, biphasic, or sarcomatoid populations, because these are groups that are routinely diagnosed for patient care. The exome analysis identified 10 significantly mutated malignant mesothelioma genes, with *TRAF7* and *NF2* mutated in enough cases to suggest that they engage in a common signaling cascade. The authors propose that incorporating genomic analysis in the care of patients with malignant mesothelioma will support the development of more comprehensive therapy.

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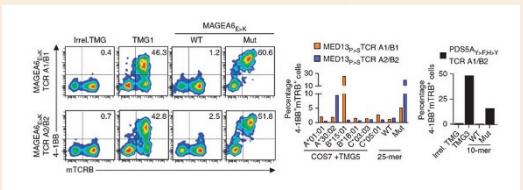
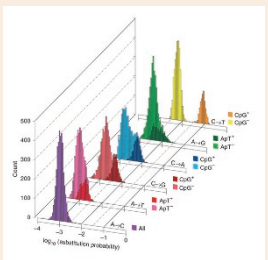
Noninvasive biomarker survey of melanoma



Gros *et al* followed up on their previous study showing that programmed cell death 1 (PD-1) receptor expression could help in identifying tumor-reactive $CD8^+$ lymphocytes within tumors on a patient-specific level. The present work sought to investigate whether PD-1 might be used as a biomarker to detect T cells that target neoantigens in peripheral blood lymphocytes. Using peripheral blood from melanoma patients, the investigators screened for and identified neoantigen-specific lymphocytes; $CD8^+PD\text{-}1^+$ versus $CD8^+PD\text{-}1^-$. In three of the four patients evaluated, the circulating $CD8^+PD\text{-}1^+$ and $CD8^+PD\text{-}1^{hi}$ cells showed recognition of one to three unique, patient-specific melanoma antigens. The data support the proposal that identification of antitumor T cells in peripheral blood might lead to a noninvasive surrogate strategy for evaluating tumor-infiltrating lymphocytes. They further suggest potential for developing personalized therapy for melanoma patients by isolating $CD8^+PD\text{-}1^+$ T cells from individual patients.

Nature Medicine, published online 22 February 2016; doi:10.1038/nm.4051

Expanded sequencing context for polymorphisms



Aggarwala and Voight sought to determine how much sequence context is needed to explain patterns of nucleotide substitution in genomes. They expanded the commonly used context of one nucleotide on each side of a prospective polymorphic site, claiming that this practice does not fully capture where, what type, or how frequently nucleotides might be expected to change. Assessing their model, they found that a 7-mer context predicted noncoding substitution rates, explaining a median of 81% of variability in probabilities across all substitution classes and fitting well with probabilities of C-to-T substitutions at CpG sites. Their 7-mer context model enabled them to identify new mutation-promoting motifs across several classes that appeared to segregate as mixtures of two distributions, potentially due to methylation events elevating these rates in context. They propose that comparative genomics applications to identify nonneutrally evolving regions would benefit from accurate models of nucleotide substitution.

Nature Genetics 2016; 48:349–355; doi:10.1038/ng.3511