Laboratory Investigation (2019) 99, 282–283

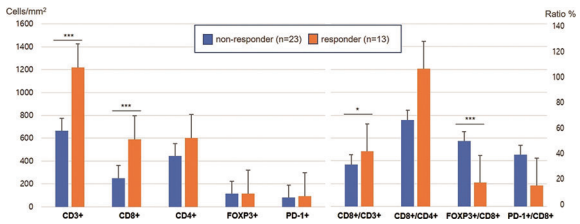
INSIDE THE USCAP JOURNALS

doi:10.1038/s41374-019-0200-6

MODERN PATHOLOGY

Infiltrating T cells as predictive biomarkers of PD-1 blockade response

doi:10.1038/s41379-018-0142-3

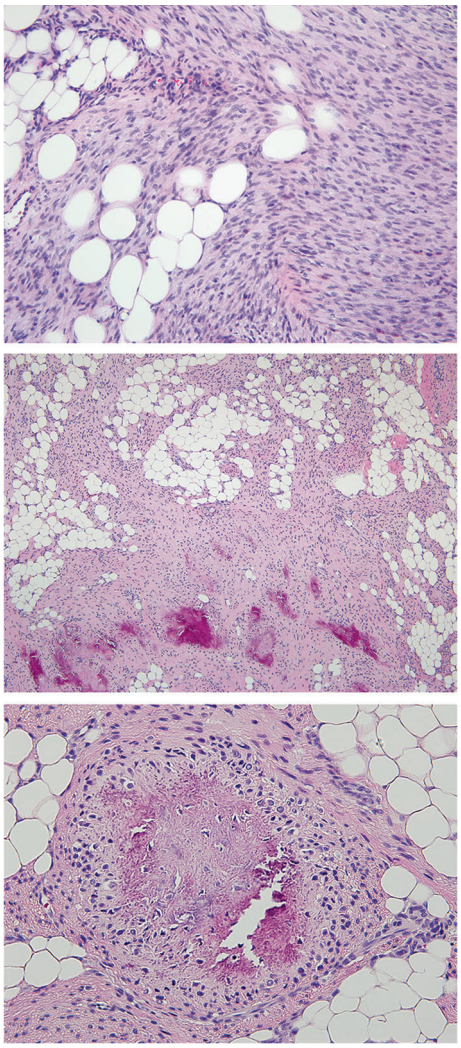


Using specimens from 36 patients with advanced, treatment-refractory non–small cell lung cancer, Kim et al. sought to investigate levels of both programmed cell death ligand-1 (PD-L1) and tumor-infiltrating lymphocytes and their relationship to treatment response. $CD3^+$ and $CD8^+$ T cells were more numerous in PD-L1-positive samples than in PD-L1-negative samples, and the higher numbers were seen in the patients who received clinical benefit from PD-1 blockade. Operator characteristic curves showed that $CD3^+$ T-cell infiltration and a low $FOXP3^+/CD8^+$ T-cell ratio were independent predictors of clinical benefit from PD-1 blockade. The authors propose that a $CD3^+$ T-cell count >120 per high-power field and a $CD8^+$ T-cell/$FOXP3^+$ T-cell ratio >4:1 are sufficient to indicate a promising biomarker for predicting response to PD-1 blockade and potentially for guiding therapeutic decisions.

Seeking a genetic signature of lipofibromatosis

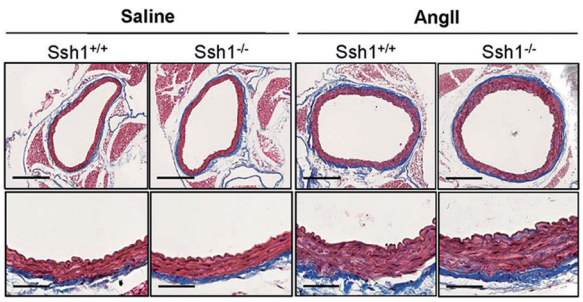
doi:10.1038/s41379-018-0150-3

Classic features of lipofibromatosis, a rare pediatric soft-tissue tumor, include mature adipose tissue, short fascicles of bland fibroblastic cells, and lipoblast-like cells. Al-Ibraheemi et al. analyzed a cohort of 20 patients, all of whom exhibited these features. Using fluorescence in situ hybridization and RNA sequencing, they observed incidents of *FN1-EGF* fusion, previously identified by the group, in four of the cases while the others showed different gene-fusion events. Since *FN1-EGF* was the only recurring gene fusion, the authors suggest that cases of calcifying aponeurotic fibroma may have been misidentified as lipofibromatosis. The other gene fusions identified, however, involved either receptor tyrosine kinases or ligands, and the authors note that further investigation is needed to determine whether this finding is confirmation of a shared downregulation of the PI3K-AKT-mTOR pathway in lipofibromatosis. If confirmed, it would open up this pathway as a target for therapeutic intervention in such cases.



LABORATORY INVESTIGATION

The pathophysiological basis of vascular disease

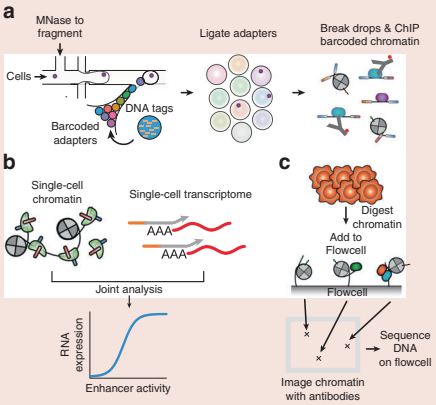


Cardiovascular disease remains the leading global cause of death. In 2017, an estimated 17.8 million deaths worldwide were attributed to cardiovascular disease, and that number continues to grow. This month, guest editors Alicia N. Lyle and W. Robert Taylor present a special issue of *Laboratory Investigation* that focuses on the pathophysiological basis of vascular disease. The issue contains a spectrum of papers that address some of the fundamental issues in cardiovascular biology. One theme common to many of these studies is the contribution of inflammation and repair to cardiovascular pathology. Indeed, many aspects of cardiovascular pathology reflect a maladaptive inflammatory process that is critical in the development and repair of the cardiovascular system. Evolution has selected for highly efficient developmental and repair mechanisms involving production of reactive oxygen species, calcification, recruitment of inflammatory cells, and other processes that lead to adverse outcomes in the disease state. A better understanding of these fundamental mechanisms will enhance our knowledge of the cardiovascular system throughout the life cycle.

nature.com/pathology

Technological advances in epigenomic analysis

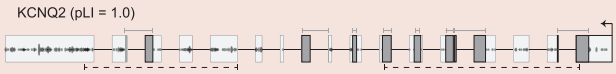
Shema et al. evaluated the technologies and assays that have been used to describe epigenomics at the single-cell and single-molecule level and use the findings to demonstrate the essential role this process plays in genetic diversity. Technologies capable of combining different levels of epigenomic regulation are available to provide an integrated approach, and improvements in imaging probes, resolution, and throughput will also advance capabilities for measuring regulatory interactions across single molecules within single cells. The authors, building on their previous work with single-molecule imaging of histone modifications followed by sequencing on a high-throughput platform, propose that a method would decode the interplay between transcription-factor binding and chromatin structure within a single DNA molecule. The consequences of this would be far-reaching in enhancing our understanding of how localization of regulatory elements leads to the expression of nearby genes.



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

Identifying new coding regions that drive disease phenotypes

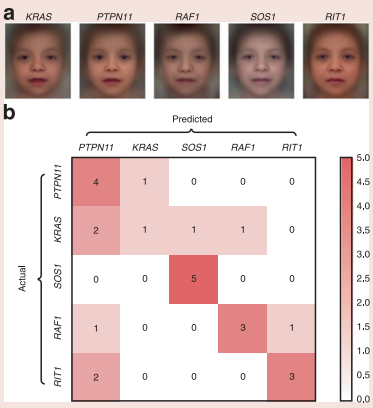
Havrilla et al. sought to identify localized, highly constrained coding regions (CCRs) in the human genome, hypothesizing that those under extreme purifying selection would be devoid of protein-changing variation in healthy individuals. They generated a CCR map and observed that these regions were enriched in disease-causing loci, with pathogenic variants for autosomal dominant disorders similarly enriched in the 95th CCR percentile or higher. The genes exhibiting multiple CCRs are known to be involved in developmental delay, seizure disorders, and congenital heart defects. The investigators propose that optimizing the use of CCRs in looking for de novo mutations in disease, along with targeted disruption of these regions, would generate opportunities to identify new coding regions that drive disease phenotypes, which could have implications for development of treatment for the associated diseases.



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

Computer model of facial recognition of syndromic disorders

Syndromic genetic disorders are often distinguishable by associated facial features. Gurovich et al. developed a deep-learning computer model with a high-level flow and network architecture to analyze features of patients' photographs. They applied a series of algorithms to quantify similarities to the features reported in hundreds of syndromes as well as to distinguish different genetic subtypes of the same syndrome. They showed that the model, called DeepGestalt, was capable of 91% top-10 accuracy in identifying the syndrome in 502 different images, having been trained on 17,000 images representing more than 200 syndromes. Standardization of the images in this manner has implications for both diagnosis and the subsequent prioritization of confirmatory genetic testing and also has broad implications for precision medicine in these patients.



Nature Medicine 2019;25:60–64; doi:10.1038/s41591-018-0279-0