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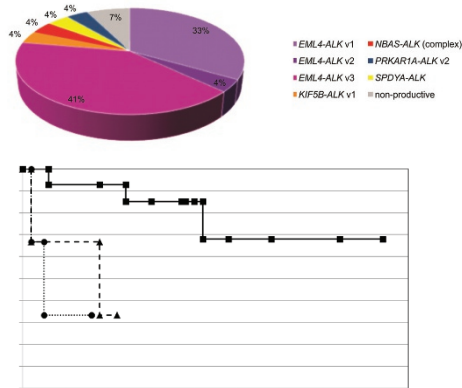
MODERN PATHOLOGY

### Genomic heterogeneity of ALK fusions
doi:10.1038/modpathol.2017.181

Rosenbaum et al. investigated the heterogeneity of *ALK* fusion breakpoints in the 2–7% of lung adenocarcinoma patients in whom this is identified. They then generated a hypothesis as to why only 60% of these patients respond to anti-ALK therapeutics. Using next-generation sequencing of DNA and RNA, rather than the often diagnostically employed in situ hybridization, they characterized genomic breakpoints in 33 ALK-positive lung adenocarcinomas to examine partners in the *ALK* rearrangement. As expected, the canonical *EML4-ALK* inversion on chromosome 2 was the most prevalent. The group went back to the survival data for those patients and found that those with this rearrangement survived an average of 20.6 months on anti-ALK therapy, whereas those without canonical *EML4-ALK* rearrangement survived an average of 5.4 months. The authors propose that, with the widespread availability and falling costs of next-generation sequencing, these tests should be brought into clinical decision making in order to improve therapeutic decision making.

Genomic index in uterine smooth muscle tumors
**doi:10.1038/modpathol.2017.185**
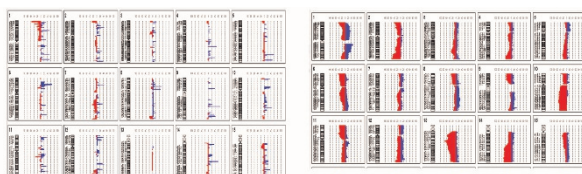
Diagnostic standards for uterine smooth muscle tumors, based on the Stanford criteria (cytologic atypia, mitoses, necrosis), is straightforward in most cases. However, morphology has a degree of subjectivity and the features occur on a spectrum.

In addition, external factors such as prior therapeutics and sample preparation can interfere, leaving such cases defined as smooth muscle tumors of uncertain malignant potential (STUMP) with uncertain clinical consequences. Using exome and transcriptome (DNA and RNA) data, Croce et al. developed a genomic complexity index. A genomic index <10 included all leiomyomas, 2 STUMPs, and no leiomyosarcomas; a genomic index ≥10 included all leiomyosarcomas and 12 STUMPs. The mean genomic index in the leiomyosarcomas was 55. Because of their high genomic index and clinical aggressiveness, the 12 STUMPS were reclassified as leiomyosarcomas. The group proposes that genomic profiling could help clarify the STUMP category.

LABORATORY INVESTIGATION

Reconsidering iNOS therapy for sepsis
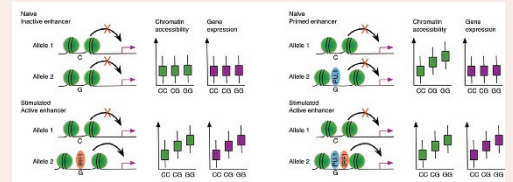**doi:10.1038/s41374-018-0021-z**
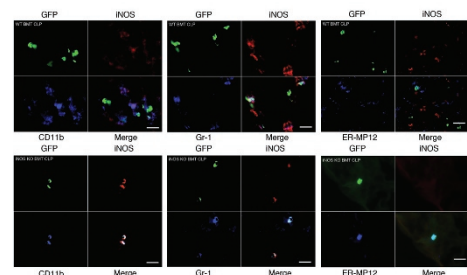
Takatani et al. generated a model system to examine the effects of hypothermia on sepsis in the presence of iNOS (inducible nitric oxide synthase) therapy. Wild-type (WT) mice showed temperature drops in a biphasic manner at the early and late stages of sepsis, with no survival past 48 hours. However, iNOS-knockout (KO) mice did not demonstrate the second temperature drop and showed improved mortality. iNOS-derived NO during the late phase of sepsis caused vasodilation-induced hypothermia and the lethal hypodynamic state that was observed in the WT mice, with iNOS messenger RNA expression high in the lungs of WT mice with sepsis. After bone marrow cells from green fluorescent protein transgenic mice were transplanted into WT and iNOS-KO mice, the investigators observed increased cell migration along with changes in the quantity and type of bone marrow–derived cells in the lung (fewer in the lungs of iNOS-KO mice than in WT). Thus, iNOS therapy might warrant reconsideration in the context of sepsis.

Parallel evolution of metazoa and neoplasm suppression

doi:10.1038/s41374-018-0024-9

Genes and proteins involved in one or more steps in the metastatic cascade without having an appreciable effect on tumor growth are known as metastasis suppressors. Ćetković et al. saw a pattern in the literature that showed that metastasis-suppressor genes emerged at three distinct periods in the evolution of Metazoa (animals): before the origin of metazoans, with the emergence of the first animals, and with the origin of vertebrates. Members of the third group (*KISS1*, *LIFR*, *AKAP12*, *CD44*, *CDHs*, and *GAS1*), appearing after two rounds of whole-genome duplication, have few homologs in their genomes. The group posits that although there were metastasis suppressors in the early groups, neoplasms were rare in that setting. This indicates that these genes were transitioned to metastasis suppression because of the rise in complexity and multicellularity of organisms with the parallel consequence of increased neoplasia.

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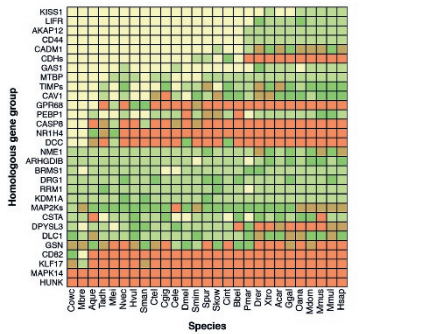## Chromatin accessibility in immune response

Alasoo et al. investigated epigenetic models to provide context for modulating gene expression in a subset of possible cellular states by looking at quantitative trait loci (QTLs) for chromatin accessibility and gene expression in human macrophages. The group used

human induced pluripotent stem cell–derived cells to study genetic effects in immune response and found that roughly 60% of stimulus-specific expression of QTLs had a detectable effect on chromatin, perturbing enhancer priming by altering the chromatin accessibility in naive cells. The investigators propose that these variants can influence binding of cell-type-specific transcription factors along with stimulus-specific transcription factors. They see this as a challenge to the detection of the downstream effects on gene expression that might result from chromatin accessibility. Their system allows methodical exploration of gene–environment interactions across cell states, and since they are readily engineered the exact cell types and conditions being studied can be generated.

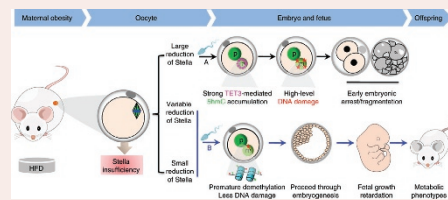*Nature Genetics* 2018;50:424–431; doi:10.1038/s41588-018-0046-7

## Maternal obesity and embryonic development

Han et al. explored the mechanisms by which maternal obesity can impair embryo development and offspring health. Using a mouse model, the group observed that mice on a high-fat diet (HFD) expressed significantly less (60–70%) Stella (DPPA3 or PGC7) protein in oocytes. They then established that pronuclear epigenetic asymmetry in the zygotes of obese mice was disrupted, inducing accumulation of maternal 5-hydroxymethylctosine modifications and DNA lesions. Maternal TET3-dependent 5hmC and γ-H2AX accumulation in HFD zygotes was shown to contribute to high levels of DNA damage and early embryonic developmental defects. Overexpression of Stella in the oocytes could restore the epigenetic remodeling and partially ameliorate maternal-obesity-associated developmental defects. These results indicate promise for future research into preventing transmission of these deficits, along with exploring Stella as a target for therapeutic intervention.

Nature Genetics 2018;50:432–442; doi:10.1038/s41588-018-0055-6

Regulation of coding genome through noncoding elements

With the human genome mapped, the noncoding genome has emerged as a new challenge in human genetics in terms of understanding genetic variation. Using 11, 257 whole-genome sequences, along with 16,384 heptamers, di Iulio et al. built a map of sequence constraints for the human species. Hi-C experimental data was used, allowing description of a strong pattern of coordination for chromatin 3D conformation over 2 Mb. This is where the most constrained regulatory elements associated with the most essential genes, and it was up to 52-fold enriched compared with unconstrained regions. Breaking down the constraint

elements, the group illustrated the distribution of these various elements across the whole genome. They assessed coordination of cis elements by attributing the haploinsufficiency probability (pLI) score of the closest gene to associate essentiality and context-dependent conservation of regulatory elements. Further exploration and identification of these constraint regions could allow development of regulatory tools/therapeutics for medically important genes.
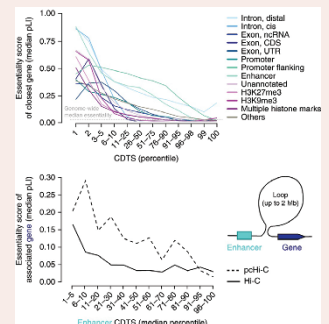
Nature Genetics 2018;50:333–337; doi:10.1038/s41588-018-0062-7

Emma Judson contributed to these reviews.