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MODERN PATHOLOGY

Genomic landscape of follicular dendritic cell sarcoma

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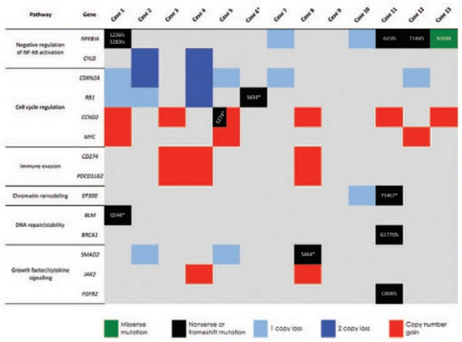

Griffin and colleagues evaluated 13 cases of follicular dendritic cell sarcoma using a targeted sequencing assay to identify alterations in 309 cancer-related genes. In their paper in this issue, they highlight genes involved in the regulation of NF-κB activation (*NFKBIA* and *CYLD*), cell cycle progression (*CDKN2A* and *RB1*), and immune evasion (*CD274* and *PDCD1LG2*). Thirty-eight percent of the patients in the study showed recurrent likely pathogenic variants in tumor-suppressor genes critical for negative regulation of nuclear factor–κB activation. The authors also found functional alterations and copy-number gain of cell cycle progression genes. Their hypothesis was that the accumulated mutations in these key pathways might correlate with a more aggressive disease course, given that one of their cases with the highest disease burden had four of the listed pathogenic variants. They acknowledge that a more extensive study would be needed to support conclusions yet to be made between the molecular changes and clinical behavior.

Potential new biomarker for assessing disease progression in renal cell carcinoma

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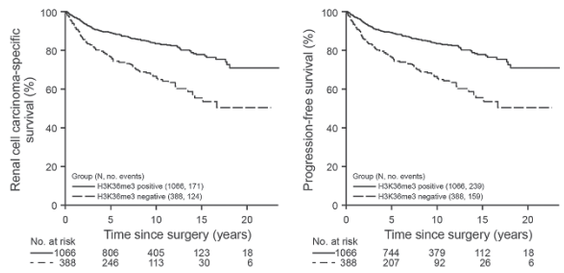
Ho *et al* found that histone H3 lysine 36 trimethylation (H3K36me3) is progressively deregulated in metastases of clear cell renal cell carcinoma and identified an association between loss of H3K36 methylation and disease-free survival. In a cohort of 145 patients from the Mayo Clinic, those with H3K36me3-negative tumors were twice as likely to experience renal cell carcinoma–specific death as patients with H3K36me3-positive tumors. The authors' investigation



into whether there was a relationship between copy-number loss and mutation in *SETD2* (a gene coding a nonredundant methyltransferase responsible for H3K36 methylation) showed no correlation in either disease progression or disease-free survival. However, they did observe that loss of H3K36me3, a posttranslational histone modification, is associated with poorer outcomes. Loss of H3K36me3 expression could be a biomarker of clinical utility to urologists.

LABORATORY INVESTIGATION

Transcription factor regulation as a mechanism for mesenchymal tissue formation

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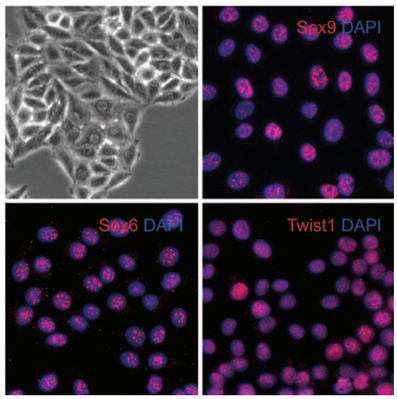

Matsumoto and colleagues aimed to show a new transcription factor microenvironment for the inductive chondrogenesis in salivary gland cells. Using reverse-transcriptase and quantitative real-time–polymerase chain reaction as well as knockdown and overexpression models, they were able to show that the Sox transcription factor trio Sox5, Sox6, and Sox9 were all expressed, along with Twist1 (expressed only in the salivary gland cells). They showed that when Twist1 was knocked down, there was

resulting upregulation of aggrecan and type II collagen gene expression (indicative of cartilage formation); the reverse was true when Twist1 was overexpressed. The authors' conclusion was therefore that it was Twist1 depletion concurrent with neoplastic transformation that allowed the cells to differentiate toward the chondrocyte lineage that is so characteristic in pleomorphic adenoma.

The keratinocyte microenvironment and the role of TR3

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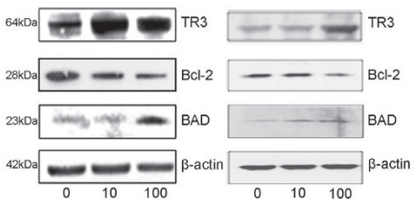

The function of TR3 has been shown to be different in different cell types, and its function in skin cells has yet to be investigated. Xie *et al* therefore sought to show that TR3 expression is important in androgen-induced follicular keratinocyte growth inhibition. They found that TR3 is expressed in distinct regions of the suprabasal layer of keratinocytes of the epidermis and suggest that it mediates androgen-induced keratinocyte growth inhibition, given that knocking down TR3 expression blocks the inhibitory effect of dihydrotestosterone on keratinocyte proliferation. Their results suggest that this is related to direct interaction between TR3 and BCL-2 family proteins within the keratinocytes, indicating a contribution by TR3 in regulating follicular keratinocyte proliferation and apoptosis by playing at least a partial role in the inhibitory effects of androgens on keratinocytes. The authors note the need for further investigation of the interaction between TR3 and the androgen signaling pathway.

Emma Judson is thanked for her contributions to all the summaries above.

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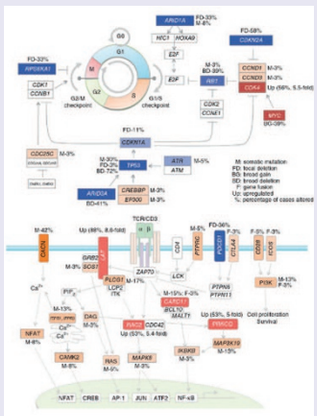
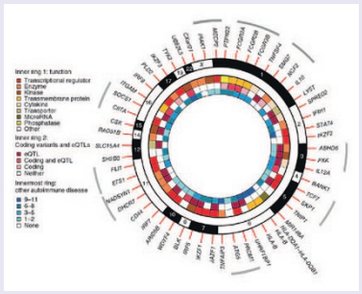
Genomic landscape of Sézary syndrome



As reported in *Nature Genetics*, Wang *et al* performed an extended genomic study in patients with Sézary syndrome that implicated dysregulation of cell cycle checkpoints as well as T-cell signaling errors in disease progression. Genomic profiling of 37 patients yielded a summary of genes that were most frequently mutated in the combined cohort. Survival studies indicated that African ancestry was correlated with poorer prognosis and that overexpression of *IL32* rather than the presence of the ultraviolet B signature mutation were associated with poorer prognosis. Activation of *CCR4* mutations is common in those with Sézary syndrome, highlighting the importance of *CCR4* in pathogenesis and targeted therapy of multiple diseases. A concurrent study by da Silva Almeida *et al* indicated that *CARD11* coiled-coil mutation and subsequent constitutive activation of nuclear factor–κB results in B- and T-cell activation. Taking together the findings of these two articles *CCR4* alteration, *IL32* overexpression, and *CARD11* mutations could be potential therapeutic targets for Sézary syndrome.

Nature Genetics 2015;47:1426–1434; doi:10.1038/ng.3444; *Nature Genetics* 2015;47:1465–1470; doi:10.1038/ng.3442

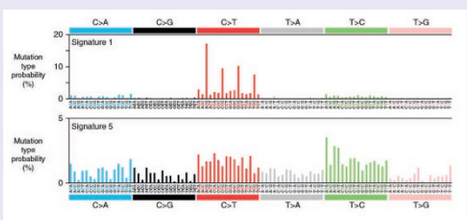
Overexpression of transcription factors implicated in SLE



The study of systemic lupus erythematosus (SLE) has been expanded exponentially by the increase in confidence in the genetic components of its pathogenesis. A study by Bentham *et al*, published in *Nature Genetics*, increased the previous typical sample size for genome-wide association studies to several thousand patients from different populations. Genome mapping identified 43 susceptibility loci, including 10 new associations. Significantly, an overexpression of transcription factors ($n = 16$) was observed within SLE-susceptibility genes. *TCF7* (encoding a T-cell transcription factor) and *IKZF2* (Helios; the third member of the Ikaros transcription factor family, after *IKZF1* and *IKZF3*, to be implicated in SLE) are two that lend themselves to further investigation. The authors say that these data support further investigation of *trans* expression quantitative trait loci and regulatory expression networks in multiple immune cells as being targets for the study of SLE pathogenesis as well as potential therapeutic targets.

Nature Genetics 2015;47:1457–1464; doi:10.1038/ng.3434

Cancer mutation signatures



Cell mutations are collected throughout life. Alexandrov *et al*, as reported in *Nature Genetics*, used *in silico* analysis to investigate the concept of classifying mutation signatures throughout three phases of life: embryonic and fetal development, postnatal development in normally differentiating cells, and postneoplastic transformation. Among more than 10,000 cancer samples, the authors identified 33 distinct patterns of mutation, of which 29 were validated. They found distinct correlations in different cancer types between signatures 1 and 5, with variability in the number of mutations per megabase, even with the same cancer type and age of diagnosis. There was a difference between the signature 5 mutation rate in clear cell and papillary cancers compared with chromophobe kidney tumors. This raises the possibility that continuous exposure to a ubiquitous metabolic mutation may account for the difference in signature 5 applicability, suggesting possibilities for future research.

Nature Genetics 2015;47:1402–1407;