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survival, injury, and incidence of premature males compared with premature females at the same gestational age, there may be a signaling role for HIF-1 α in this difference.

Thyroid regeneration following thyroidectomy

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Lee and colleagues found that, after partial thyroidectomy, the remaining gland was unable to produce T4 at a level comparable to that in control mice, even 7 days following the removal. This is thought to be reaction to negative feedback loops as thyroid-stimulating hormone attempts to induce differentiation in newly developing thyroid follicular cells. The group observed that primitive ciliated cells with large vesicular nuclei and coarsely vacuolated cytoplasm were involved in folliculogenesis in the newly developing thyroid tissue following a thyroidectomy, with many follicles showing a primitive morphology and consisting of multiciliated follicular cells. These primitive follicles exhibit nuclear FOXa2 whereas most mature follicular cells are negative for this marker; they are also low expressers of PAX8, a crucial transcription factor for organogenesis and negative for thyroid transcription factor-1. Regeneration of the thyroid following thyroidectomy is hindered by the removal of more than 50% of the central zone of the lateral thyroid lobe, now thought to be the element responsible for regeneration in adulthood.

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NCF1 and autoimmunity

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease. Zhao *et al* identified a germline missense variant (g.74779296G>A; p.Arg90His) in *NCF1*, encoding the p47^{phox} subunit of the phagocyte NADPH oxidase. Others have suggested that this variant is

associated with reduced reactive oxygen species generation. The *NCF1* region is inadequately covered by variants in the phase 1 data from the 1000 Genomes Project because *NCF1* has 98% sequence identity with nonfunctional pseudogenes *NCF1B* and *NCF1C*. Decreased and increased copy numbers of this substitution exhibit differing predispositions to SLE, Sjögren's syndrome, and rheumatoid arthritis in different racial populations. This suggests that other modifying genes may be involved the production of the disease phenotype. The findings elucidate the pathogenic role of reduced reactive oxygen species production in autoimmune diseases and indicate the presence of missing heritability in complex genomic regions.

Nature Genetics 2017;49:433–437; doi:10.1038/ng.3782

DNA methylation in Ewing's sarcoma

Sheffield *et al* sought to explore the distinction between the diverse clinical presentation and minor genetic alterations observed in Ewing's sarcoma by focusing on epigenetic heterogeneity in these genomically relatively simple and homogeneous cancers. Despite this genomic simplicity, genome-scale DNA methylation assessment for a large cohort of Ewing sarcomas revealed a relatively broad epigenetic spectrum within this disease, probably related to the strength of signaling through the EWSR1-FLI1 fusion protein. The strength of this signal influenced whether the tumor profile was more stem cell-like or mesenchymal-like. Epigenetic reprogramming of enhancer regions appears to be a characteristic feature of Ewing's sarcoma and unique to this cancer type. Its broad epigenetic heterogeneity may help explain heterogeneous responses to therapy and variable clinical courses. The methylation downstream of EWSR1-FLI1 might mediate the major effects of this fusion oncogene.

Nature Medicine, published online 30 January 2017; doi:10.1038/nm.4273

Telomere length and somatic alterations in cancer

Telomere maintenance is critical to the survival of cancer cells. Barthel *et al* used the Cancer Genome Atlas data set (6,835 cases plus normal samples encompassing 31 cancer types) to investigate telomere length and pathways that the cells can use for telomere maintenance. They found that nearly three-quarters of cancers expressed telomerase reverse transcriptase (*TERT*), a factor used to maintain telomeres. *TERT* promoter point mutations, rearrangements, DNA amplifications, and transcript fusions were all predictive of telomerase activity. A broad range of telomere lengths was noted, with low-grade gliomas and sarcomas having significantly longer telomeres than other cancer types. Different cancers tended to rely on the various mechanisms to different degrees. Of those lacking *TERT* expression, 5% showed alteration of *ATRX* or *DAXX* with elongated telomeres. For the final 22% lacking *TERT* expression, *TP53* and *RB1* mutations correlated with telomere length. This study shows the remarkable diversity of pathways used by cancers to maintain telomeres.

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Emma Judson contributed to these reviews.