IN BRIEF

LEUKAEMIA

The part played by pathogens in pB-ALL

A study in *Cancer Discovery* has provided evidence to support the hypothesis that infection is a causal factor in the pathogenesis of B-precursor acute lymphoblastic leukaemia (pB-ALL). The authors show that pathogen exposure is required for pB-ALL development in susceptible *Pax5*$^{+/-}$ mice, and that pB-ALL in these mice closely resembles human pB-ALL. *Pax5* heterozygosity creates a preleukaemic clone that is transformed by activating *Jak3* mutations, which occur in response to the selection pressure imposed by infection and provide the second hit needed for pB-ALL development.

ORIGINAL RESEARCH PAPER Martín-Lorenzo, A., Hauer, J., Vincente-Dueñas, C. *et al.* Infection exposure is a causal factor in B-precursor acute lymphoblastic leukemia as a result of *Pax5* inherited susceptibility. *Cancer Discov.* http://dx.doi.org/10.1158/2159-8290.CD-15-0892 (2015)

ONCOGENES

A new start for *ALK* transcription

Wiesner *et al.* report a mechanism of oncogene activation that is independent of somatic genetic aberrations. The use of a *de novo* alternative transcription initiation (ATI) site generated an anaplastic lymphoma kinase (*ALK*) transcript (*ALK*^{ATI}) comprising only exons 20–29 of wild-type *ALK*. *ALK*^{ATI} was found in ~11% of melanomas and sporadically in other cancer types in a set of >5,000 samples but was not present in >1,600 samples from normal tissues. *ALK*^{ATI} expression promoted transformation and growth factor-independent proliferation in cell lines and induced tumour growth *in vivo*. Furthermore, cells and tumours expressing *ALK*^{ATI} were sensitive to ALK inhibitors.

ORIGINAL RESEARCH PAPER Wiesner, T. *et al.* Alternative transcription initiation leads to expression of a novel *ALK* isoform in cancer. *Nature* http://dx.doi.org/10.1038/nature15258 (2015)

MELANOMA

Dual effects of PD1 blockade

Antibodies targeting the immune checkpoint receptor programmed cell death protein 1 (PD1) are effective in treating melanoma. Although this clinical efficacy is presumed to result from activating antitumour immunity, Kleffel *et al.* have shown that blockade of PD1 signalling in melanoma cells might also have a role. PD1 inhibition blocked growth of PD1^{+} melanomas in immunocompromised or PD1-deficient recipient mice, and PD1 overexpression in melanoma cells promoted tumour growth. PD1 blockade inhibited mTOR effectors in melanoma cells, which might contribute to therapeutic efficacy.

ORIGINAL RESEARCH PAPER Kleffel, S. *et al.* Melanoma cell-intrinsic PD-1 receptor functions promote tumor growth. *Cell* **162**, 1242–1256 (2015)

TUMOUR EVOLUTION

Genetic and epigenetic co-dependency

Cancer genomic information can provide considerable detail on the evolutionary history of a tumour. However, as epigenetic alterations might contribute to tumour evolution, a more complete picture requires epigenomic analyses. DNA methylation dynamics in low-grade gliomas and matched recurrences indicated that epigenetic changes and somatic mutations evolved in parallel to deregulate the cell cycle. This phyloepigenetic analysis recapitulated phylogenetics and suggests co-dependency of epigenetic and genetic events.

ORIGINAL RESEARCH PAPER Mazor, T., Pankov, A. *et al.* DNA methylation and somatic mutations converge on the cell cycle and define similar evolutionary histories in brain tumors. *Cancer Cell* **28**, 307–317 (2015)