Nature Reviews Cancer | Published online 23 Aug 2016

IN BRIEF

METASTASIS

RIP endothelial cells

In order to metastasize, circulating tumour cells must exit the bloodstream by passing through the endothelial barrier. This process of extravasation is poorly understood. Strilic *et al.* now provide evidence that tumour cells can induce necroptosis of endothelial cells to drive transendothelial migration and metastasis. This is achieved through a mechanism involving the interaction of the amyloid precursor protein (APP) on tumour cells with its receptor, death receptor 6 (DR6) on endothelial cells. Consistent with involvement of a necroptotic signalling pathway, treatment of experimental mouse models of lung metastasis with necrostatin 1, an inhibitor of receptor-interacting serine/threonine protein kinase 1 (RIPK1), decreased endothelial cell death. Exactly how this endothelial cell killing enables tumour cells to colonize a new tumour site should be an exciting area of future research.

ORIGINAL ARTICLE Strilic, B. *et al.* Tumour-cell-induced endothelial cell necroptosis via death receptor 6 promotes metastasis. *Nature* http://dx.doi.org/10.1038/nature19076 (2016)

LEUKAEMIA

Common driver gets new oncogenic mechanism

Mutations in the genes isocitrate dehydrogenase 1 (*IDH1*) and tet methylcytosine dioxygenase 2 (*TET2*) are common drivers in myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), which has led to the assumption that mutant IDH1 might drive alterations in DNA methylation through inhibition of TET2. However, the clinical variations between *IDH1*- and *TET2*-mutant malignancies suggested that these genes could have different oncogenic mechanisms. Inoue *et al.* have used a mouse model to reveal a novel TET2-independent mechanism for mutant IDH1 in the DNA damage response of haematopoietic stem cells (HSCs). Mutant IDH1 downregulates ataxia telangiectasia mutated (ATM) through changes in histone methylation, which in turn leads to impaired DNA repair and reduced HSC self-renewal. This study proposes that targeting the DNA damage response may be a beneficial therapy for *IDH1*-mutant haematological diseases.

ORIGINAL ARTICLE Inoue, S. *et al.* Mutant IDH1 downregulates ATM and alters DNA repair and sensitivity to DNA damage independent of TET2. *Cancer Cell* **30**, 337–348 (2016)

ONCOGENES

piRNA flies in

It is recognized that in a number of different soma-derived human cancers, expression of genes typically restricted to germ cells can become reactivated, and amongst these are components of the PIWI-interacting RNA (piRNA) pathway. This phenomenon of germline gene re-expression has also been shown to occur in brain tumours in flies. Fagegaltier *et al.* used the model organism *Drosophila melanogaster* to demonstrate that overexpression of oncogenic RAS in combination with loss of the Hippo tumour suppressor pathway is sufficient to reactivate primary piRNA pathway genes in somatic cells. Inactivation of the piRNA pathway in these transformed somatic cells resulted in loss of transposon repression and a decrease in cell proliferation, two processes associated with oncogenesis. Subsequent work will need to address whether this observation translates to human tumours with RAS activation.

ORIGINAL ARTICLE Fagegaltier, D. *et al.* Oncogenic transformation of *Drosophila* somatic cells induces a functional piRNA pathway. *Genes Dev* **30**, 1623–1635 (2016)

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