LEUKAEMIA AND LYMPHOMA

The expansive reach of TET2

> TET2 … has pleiotropic effects on haematopoietic lineage commitment and the development of haematological malignancies

The gene encoding the methylcytosine dioxygenase TET2 is often targeted by monoallelic or biallelic loss-of-function mutations and genomic alterations in myeloid malignancies. To investigate the role of TET2 directly, two papers report mouse models of *Tet2* deficiency.

Moran-Crusio, Reavie, Shih and colleagues targeted exon 3 of *Tet2* to generate a conditional knockout in the haematopoietic compartment (vav-cre;$Tet2^{f/f}$). They found that *Tet2*-deficient $LIN^-SCA1^+KIT^+$ (LSK) progenitor cells were more able to undergo serial replating in colony-forming assays. The colonies that formed were poorly differentiated, had increased KIT expression levels and expressed a common myeloid progenitor (CMP) gene signature, indicating that loss of *Tet2* impairs myeloid lineage commitment. Consistently, *in vivo* competition assays suggested that *Tet2* loss increased the self-renewal of adult haematopoietic stem cells. Moreover, *Tet2*-deficient mice had increased populations of LSK and myeloid cells in the bone marrow, enlargement of the spleen and extramedullary haematopoiesis. Approximately 70% of *Tet2*-deficient mice developed phenotypes consistent with chronic myelomonocytic leukaemia (CMML). Interestingly, about 40% of patients with CMML have heterozygous *TET2* mutations. To investigate the effect of heterozygous loss of *Tet2*, the authors repeated their analyses using vav-cre;$Tet2^{WT/f}$ mice and found similar effects on haematopoiesis, indicating that *Tet2* haploinsufficiency contributes to myeloid transformation.

Quivoron, Couronné, Della Valle and colleagues generated two *Tet2*-deficient mouse models (a conditional haematopoietic-specific knockout targeting exon 11 (*Mx1*-cre; $Tet2^{Lox/Lox}$mice) and a gene trap targeting intron 9 ($Tet2^{lacZ/lacZ}$ mice)). Both homozygous and heterozygous loss of *Tet2* in these mice resulted in expansion of the LSK cell, short- and long-term stem cell, myeloid cell and erythroid cell populations, which was associated with increased colony-forming potential. Also, homozygous and heterozygous *Tet2* deficiency in the gene trap model caused the development with age of phenotypes consistent with CMML. LSK cells from either *Tet2*-deficient model reconstituted all haematopoietic lineages (including lymphoid lineages) *in vivo*, which indicates that *Tet2* loss has a cell autonomous affect. Interestingly, these authors also found that $CD4^-CD8^-$ T cell progenitors were increased in the thymus and B cell lineages were decreased in the bone marrow, indicating that *Tet2* loss also affects lymphoid lineage development. Indeed, the authors found *TET2* mutations in human samples of B cell lymphoma (2%), T cell lymphoma (11.9%) and angioimmunoblastic T cell lymphoma (~33%). The mutations were mainly heterozygous insertions and deletions that generated frameshifts and nonsense mutations. They also found genomic alterations targeting *TET2* in T cell lymphoma samples, although, like myeloid malignancies, these were rare. Subsequent analyses of three *TET2*-mutant samples indicated that *TET2* mutations were somatic rather than germline mutations. Deep exome sequencing of a T cell lymphoma sample revealed that mutations in cysteine-rich transmembrane BMP regulator 1 (*CRIM1*), zinc finger and BTB domain containing 16 (*ZBTB16*) and zinc finger protein 774 (*ZNF774*) occurred in addition to mutations in *TET2*. Other mutations, including those targeting the second *TET2* allele, occurred at a later stage of lymphoma development.

Together, these papers indicate that TET2-mediated hydroxylation of methylcytosine is an important epigenetic modification, the loss of which has pleiotropic effects on haematopoietic lineage commitment and the development of haematological malignancies.

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ORIGINAL RESEARCH PAPERS Moran-Crusio, K. *et al.* *Tet2* loss leads to increased hematopoietic stem cell self-renewal and myeloid transformation. *Cancer Cell* **20**, 11–24 (2011) | Quivoron, C. *et al.* TET2 inactivation results in pleiotropic hematopoietic abnormalities in mouse and is a recurrent event during human lymphomagenesis. *Cancer Cell* **20**, 25–38 (2011)

FURTHER READING Pronier, E. *et al.* Inhibition of TET2-mediated conversion of 5-methylcytosine to 5-hydroxymethylcytosine disturbs erythroid and granulo-monocytic differentiation of human hematopoietic progenitors. *Blood*, 6 Jul 2011 (doi:10.1182/blood-2010-12-324707)