

Comment on *Stremenova Spegarova et al*, page 1055

# Human *TET2* bridges cancer and immunity

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**In this issue of *Blood*, Stremenova Spegarova et al report 3 patients with biallelic loss-of-function (LOF) *TET2* mutations.<sup>1</sup> These patients suffered from infections, autoimmunity, and lymphoma, demonstrating 3 of the 5 potential phenotypes seen in inborn errors of immunity. *TET2* encodes ten-eleven translocation methylcytosine dioxygenase 2 (TET2), 1 of the 3 members of the TET family of epigenetic regulators responsible for converting 5-methylcytosine to 5-hydroxymethylcytosine (5hmC) and subsequent oxidation products in an active DNA demethylation pathway. *TET2* is ubiquitous, with particularly strong expression in hematopoietic cells. Somatic LOF *TET2* mutations were first reported in patients with myeloproliferative disorders and hematologic cancers over 10 years ago.<sup>2</sup> *TET2* haploinsufficiency has also recently been reported in families with myeloid or lymphoid cancers. Intriguingly, some of these patients also presented signs of enhanced monocyte- and macrophage-mediated inflammatory responses, together with atherosclerotic plaque development, which has been associated with increases in NLRP3 inflammasome activation.<sup>3,4</sup> Thus, the tumor suppressor role of *TET2* has been extensively documented, especially in myeloid lineages.**

This elegant report of patients with autosomal-recessive complete *TET2* deficiency not only confirms the role of *TET2* as a tumor suppressor, but also highlights its function in immunity (see table). The infections observed in the patients included recurrent viral respiratory tract infections and persistent Epstein-Barr virus (EBV) viremia. The principal autoimmune manifestations were thrombocytopenia and anemia, accompanied by hepatosplenomegaly. The leukocyte subsets of these patients were reminiscent of

the autoimmune lymphoproliferative syndrome seen in patients with inborn errors of the Fas pathway, with high levels of CD4<sup>+</sup>CD8<sup>-</sup> double-negative T cells, low levels of T helper 17 (Th17), Th1, and follicular helper T (Tfh) cells, and low levels of class-switched memory B cells. Fas ligand-mediated apoptosis was also found to be impaired in 2 of the 3 patients. Nonhematopoietic clinical features, including developmental delay and hypothyroidism, were also reported.

The spectrum of hemato-immunological and clinical phenotypes in patients bearing myeloid LOF, germline monoallelic LOF, and germline biallelic LOF indicates the existence of a cell-type effect (from myeloid to lymphoid, from hematopoietic to nonhematopoietic) and a gene-dosage effect (from monoallelic to biallelic). The discovery of mono- and biallelic germline mutations also suggests that somatic *TET2* mutations act as a “first hit” in some myeloid cancers. Moreover, that the same germline and somatic mutations are associated with the same type of cancer provides strong evidence for a crucial role of the mutated gene in tumorigenesis. A similar situation has been reported for germline *NRAS* (lymphoproliferative diseases), germline *CARD11* (congenital B-cell lymphocytosis), and somatic *CARD11* (diffuse large B-cell lymphoma) mutations.<sup>5,6</sup> Thus, these germline mutations define promising drug targets for the corresponding tumors.

That article neatly illustrates the rapid growth of the field of inborn errors of immunity in many unexpected directions, at least partly due to the unpredictable impact of mutations in housekeeping or highly specialized genes.<sup>7</sup> In recent years, many new genetic defects have been shown to be caused by mutations of genes encoding proteins with basic biochemical functions that are essential to a broad range of cellular processes and are often ubiquitous. Examples include *TPPII*<sup>8</sup> for amino acids, *PGM3*<sup>9</sup> for glycosylation, and *DBR1* for RNA lariat metabolism.<sup>10</sup> Defects in these genes result in surprisingly narrow, and sometimes unique, phenotypes that could not be predicted from mouse models or biochemical studies.

In the case of *TET2* deficiency, the preservation of most hematopoietic lineages in the patients, despite the profound

## Phenotypes of somatic, monoallelic, and biallelic *TET2* deficiencies

	Immunological phenotype	Hematopoietic phenotype	Other phenotypes
Somatic		Myeloid cancer	
Monoallelic	High levels of activated B cells and low levels of effector memory T cells	Lymphoid and myeloid cancer	Toxic thyroid adenoma with hyperthyroidism, testicular agenesis with hypergonadotropic hypogonadism, atherosclerosis
Biallelic	Viral infections (EBV, CMV, RSV), autoimmune cytopenia, high levels of DNTs, low levels of Th17 and Th1 cells, absence of Tfh cells, decreased class-switched B cells	Lymphoid cancer	Developmental delay, hypothyroidism

CMV, cytomegalovirus; DNT, double-negative T cells; RSV, respiratory syncytial virus.

increase in DNA methylation in the blood, is also surprising. These 3 patients, together with patients presenting haploinsufficiency for TET2, provide fascinating opportunities to study DNA methylation, particularly for 5hmC, in humans. Studies of the transcriptomes of different cell lineages from these patients will undoubtedly provide insight into methylation-dependent gene regulation. Stremenova Spegarova et al have already differentiated hematopoietic lineages from the patients' induced pluripotent stem cells and have shown this differentiation to be correlated with DNA hypermethylation. More detailed studies of these cells might also reveal the genomic distribution of 5hmC, related gene activity, and their influence on hematopoietic lineages. They might also differentiate the function of TET2 from those of TET1 and TET3 while also identifying TET2-specific targets and TET2-dependent tissues. It is reasonable to expect that, in the near future, following the identification of a larger number of patients, studies of TET2 deficiency will reveal a number of new DNA methylation targets and important cellular functions associated with them.

**Conflict-of-interest disclosure:** The authors declare no competing financial interests. ■

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## THROMBOSIS AND HEMOSTASIS

Comment on Bradbury et al, page 1091

# Thrombosis in the modern era of multiple myeloma

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**In this issue of *Blood*, Bradbury et al report on behalf of the United Kingdom Medical Research Council (MRC), the results of a pooled, secondary analysis of thrombotic events in the Myeloma IX and XI trials, which tested immunomodulatory agents (IMiDs; thalidomide and lenalidomide) as treatments for newly diagnosed multiple myeloma (MM). The authors found that thrombosis was common, but generally not associated with inferior longer-term outcomes such as overall survival.<sup>1</sup>**

This study is the latest chapter in the long story of thrombosis in MM, and examining the broader context is instructive. Myeloma IX and XI collectively constitute some of the largest interventional studies completed in MM; follow-up of subjects is long, and both stem cell transplant candidates and noncandidates were eligible. Prior publications regarding these trials have informed myriad other dimensions of MM management, such as chemotherapy selection and the use of both bisphosphonates and transplantation. MRC investigators deserve substantial kudos for trial design; these studies are an elegant model of trial efficiency, wherein each individual study sheds light on not one, but many areas of clinical equipoise.

Although illuminating, the generalizability today of the study currently under discussion is somewhat limited by the obsolescence of the regimens tested. Almost all of the arms on these trials incorporated “high-dose dexamethasone,” or repeated 4-day courses of dexamethasone 20 to 40 mg daily followed by a break. “Low-dose dexamethasone,” meaning 20 to 40 mg roughly once weekly, has arguably supplanted high-dose dexamethasone as standard of care since Rajkumar

et al published a classic clinical example of “less is more” in MM over a decade ago, namely a randomized study in which high-dose dexamethasone induced higher response rates than low dose, but also more thromboses and worse overall survival.<sup>2</sup> Bradbury et al’s data regarding the cytotoxic (ie, IMiD-lacking) regimens are of similarly limited contemporary relevance. These comments are meant not to criticize the selection of regimens used on Myeloma IX and XI, but simply to reflect on the challenge of applying mature clinical trial data within the rapidly evolving landscape of MM therapeutics.

Despite that caveat, the authors substantiate a number of known findings and add vital new ones:

1. Clots are common in MM. The high incident rate of thrombosis observed by Bradbury et al is far higher than that seen in the general population and fits with other studies showing the same.<sup>3</sup> The pathophysiological interplay between thrombosis and MM is complex and incompletely understood, but in many patients multiple risk factors for thrombosis can be identified and even trichotomized for conceptual purposes (see figure). Reflecting upon the individual