

CORRESPONDENCE

Mutation in *TET2* in Myeloid Cancers

TO THE EDITOR: The finding of Delhommeau and colleagues that *TET2* mutations occur in myeloid cancers (May 28 issue)¹ has been confirmed by others.²⁻⁵ The presence of single-copy and double-copy *TET2* defects and the frequent occurrence of frameshift, nonsense, or deletion mutations are consistent with the notion that *TET2* is a tumor suppressor. Delhommeau et al. suggest a role for *TET2* in disease progression. We looked into this possibility by studying stored, serial bone marrow samples from eight patients with myeloproliferative neoplasms. Mutant *TET2* was not detected in any of the follow-up samples, even though leukemic or fibrotic transformation occurred in three of these patients. These results are consistent with observations of similar frequencies of *TET2* mutations in chronic and advanced-phase myeloproliferative neoplasms.³ We therefore believe that it is difficult to assign a specific role in the pathogenesis or progression of myeloproliferative neoplasms to mutant *TET2*.

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THE AUTHORS REPLY: Recent reports support the designation of *TET2* as a tumor-suppressor gene, which probably also acts through haploinsufficiency. The detection of sequence variation in *TET2* is the only method of showing its inactivation. However, the absence of a mutation cannot preclude abnormal function of either copy of *TET2*. The inactivation of tumor-suppressor genes may contribute to the initiation and progression of the transformation process. Our data strongly support the occurrence of *TET2* mutations in the initial steps of myeloid diseases but do not exclude the possibility that such mutations can occur later in the course of these diseases. The sequence of events can differ within a single disease entity or even within the same patient.¹ It has been shown that mutation of the second copy of *TET2* may occur later in the course of the disease, preceding progression.^{2,3} We agree that the unambiguous assignment of a specific role for *TET2* mutations in the development of myeloid neoplasms is difficult and needs to be supported by experimental data.

THIS WEEK'S LETTERS

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Age, Neuropathology, and Dementia

TO THE EDITOR: Savva et al. (May 28 issue)¹ reported on the assessment of the pathologic features of 456 brains donated from older old persons with or without dementia. Although their results challenge the current idea that neuritic plaques and tangles are a hallmark of Alzheimer's disease in a younger old cohort, the results should still merit reexamining the detailed mechanisms of how these pathologic factors induce neuronal loss or dementia. Furthermore, it is essential to incorporate neuronal and synaptic loss into a quantitative evaluation of pathologic changes in both younger and older cohorts of persons with dementia; pathologic changes evidently occurred in the cerebral cortex of patients with Alzheimer's disease² and might result in the consistent brain atrophy seen in patients of increasing age in this study. In addition to age, mixed pathologic factors such as proteins associated with dysfunction, trophic factors (e.g., brain-derived

neurotrophic factor released in situ), and their interaction with neuronal and synaptic plasticity³⁻⁵ should be also taken into account when assessing the effects of intervention in patients with dementia.

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Autologous Stem-Cell Transplantation for Multiple Myeloma

TO THE EDITOR: In the last sentence of their review article, Harousseau and Moreau (June 18 issue)¹ state that the patient they describe had no adverse prognostic factors. However, the patient actually had three such adverse factors: a deletion of chromosome 13, a β_2 -microglobulin level of 2.8 mg per liter, and a hemoglobin level of 9.8 g per deciliter.² In a study of 110 patients undergoing autologous stem-cell transplantation for myeloma, the two most powerful adverse prognostic factors were a monosomy or deletion of chromosome 13 and a serum β_2 -microglobulin level of more than 2.5 mg per liter. Median survival for patients with none, one, or two of these adverse features were more than 111 months, 47 months, and 25 months, respectively.³ In another study, pa-

tients with a chromosome 13 deletion had a significantly decreased overall survival (24 months vs. >60 months) and rate of response to chemotherapy (41% vs. 79%).⁴ These are key factors to take into account during the decision-making process, since a drug such as bortezomib may abrogate the adverse prognostic effect of a chromosome 13 deletion and may be useful during induction therapy before transplantation.⁵

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