5. Coiffier B, Pro B, Prince HM, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol*. 2012;30(6):631-636.

6. O'Connor OA, Horwitz S, Masszi T, et al. Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: results of the pivotal phase II BELIEF (CLN-19) study. *J Clin Oncol*. 2015;33(23):2492-2499.

7. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol*. 2012;30(18):2190-2196.

8. Iqbal J, Wright G, Wang C, et al; Lymphoma Leukemia Molecular Profiling Project and the International Peripheral T-cell Lymphoma Project. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. *Blood*. 2014;123(19):2915-2923.

DOI 10.1182/blood-2017-11-817734

HEMATOPOIESIS AND STEM CELLS

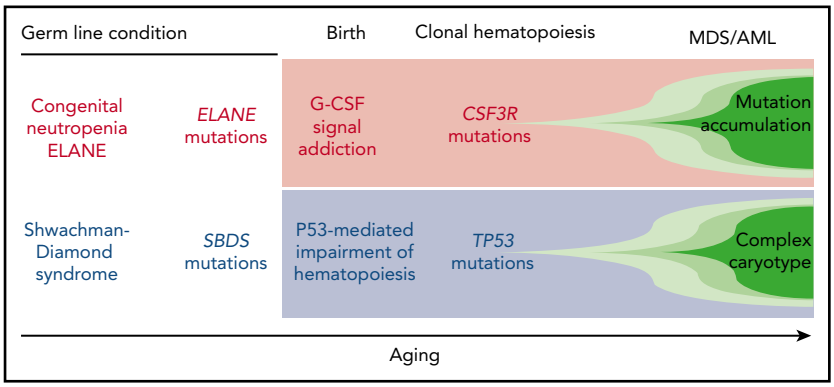
Comment on Xia et al, page 408

TP53 mutations: the dawn of Shwachman clones

Jean Donadieu[1] and François Delhommeau[2] | [1]APHP Hôpital Trousseau; [2]Sorbonne Université

In this issue of *Blood*, Xia et al[1] screened for an early onset of clonal hematopoiesis in 2 rare genetic syndromes characterized by chronic neutropenia and a high risk of leukemia, *ELANE* neutropenia and Shwachman-Diamond syndrome (SDS), and found acquired *TP53* mutations in SDS.

Revealing the steps in the divide between birth (the naive germ line situation) and leukemia (a clonal catastrophe) is the goal of many hematologists. Nobody reasonably thinks that a clonal catastrophe occurs in a single day, and we all think that it has to be preceded by a multistep mutational process.[2] Studying genetic diseases with a high risk of leukemia may offer both help for patients with such conditions and a better understanding of leukemogenesis. *ELANE* neutropenia[3] is an autosomal-dominant neutropenia caused by mutations in the *ELANE* gene. It is usually not associated with organ dysfunction. Neutropenia may be permanent (severe congenital neutropenia) or intermittent (cyclic neutropenia), requiring granulocyte colony-stimulating factor (G-CSF) to treat or to prevent infection. *ELANE* neutropenia exhibits a high risk of leukemia. SDS is an autosomal-recessive multisystem disorder characterized by exocrine pancreatic dysfunction, mild neutropenia, and various other organ dysfunctions.[4] SDS is caused by compound heterozygous mutations of the *SBDS* gene. The SBDS protein is an essential cofactor for elongation factor 1. Together they directly catalyze eIF6 release from nascent 60S subunits of the ribosome by a mechanism requiring both guanosine triphosphate binding and hydrolysis.[5] Mouse models have identified overstimulation of the p53 pathway[6] as a consequence of ribosomal stress.[7]



From germ line defects to clonal catastrophe in congenital neutropenia. Distinct germ line mutations induce specific hematopoiesis stresses, specific early somatic lesions in preleukemic clones, and specific MDS/AML.

Approximately 40% of patients develop major hematological complications.[8] Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are the main causes of early death in SDS. Although often treated by hematopoietic stem cell transplantation (HSCT), HSCT is often proposed too late in the course of the disease. So far, no risk factors for MDS/AML evolution have been clearly identified apart from the early diagnosis of clinical manifestations and mild chronic multilineage hematological abnormalities.[8]

The identification of initial clonal events is therefore a very important issue, because it may offer both a better understanding of leukemogenesis and tools for early monitoring of the preleukemic phase. By comparing the exomes of individual colonies grown from *ELANE* neutropenia and SDS patients, Xia et al show that there was no increase in somatic mutation burden compared with healthy cord blood or age-matched controls. This virtually excludes any "mutator" phenotype in the 2 diseases. Rather, this strongly suggests that in these patients, the observed somatic mutations and subsequent clonal hematopoiesis are the result of natural selection processes in a disease-specific hematopoietic context. In line with this, they show striking associations of specific mutations in each disease; ie, *CSF3R* mutations in ELANE neutropenia, which was previously established, and *TP53* mutations in SDS, which is a new observation. The remainder of this commentary will focus on this new observation of SDS and *TP53*.

It is important to recall that no early somatic mutations have been identified in SDS between the germ line mutation (the initial event putting patients at risk of malignancy) and the catastrophic clonal events (ie, MDS or AML). This gap was examined on one side (the malignant stage) in a recent study by Lindsley et al,[9] who screened 1514 patients with MDS who underwent HSCT. *TP53* mutations were found in 289 patients (19%). Among them, 7 young patients with a particularly

poor response after HSCT had SDS with compound *SBDS* mutations.[3] This study clearly pointed that in SDS patients, MDS/AML with *TP53* acquired mutations was significant. The present paper examines the other end of the problem (the early stage). They report a cross-sectional appraisal of the prevalence of *TP53* mutations in their cohort that includes 27 patients with SDS. None of the patients with SDS had evidence of MDS at time of sampling. In this analysis, clonal hematopoiesis due to one or several mutations in *TP53* was observed in 48% (13/27) of patients with SDS. By contrast, no *TP53* mutations were observed in the ELANE neutropenia cases. Despite the lack of longitudinal follow-up (only 1 patient had >1 evaluation), the study shows that the prevalence of *TP53* mutations increases with age. The allelic frequency of *TP53* mutants was mostly very low (between 0.1% and 7% [mean, 0.1%]), meaning that only a small proportion of cells carry the mutations without evidence of MDS, and no correlation between hematological parameters and somatic status could be drawn.

The involvement of *TP53* mutations at the onset of clonal hematopoiesis and at time before evidence of MDS strongly suggests that hematopoietic stem cells with such somatic mutations have a fitness advantage over their nonmutated counterparts in the SDS bone marrow. The precise mechanisms of this selection process need to be elucidated, but the mutations may attenuate a TP53-mediated impairment of hematopoietic stem cell function induced by ribosomal stress and microenvironment defects.[6] Likewise, the initiation of the clonal preleukemic state in ELANE neutropenia may also result from a natural selection process where G-CSF signal addiction would provide a fitness advantage to *CSF3R* mutant hematopoietic stem cells (see figure).

Do these findings have implications for the monitoring of patients with SDS in clinical practice? The detection of *TP53* mutations as an early sign of clonal hematopoiesis may become a useful tool. In the present paper, the authors claimed to detect *TP53* mutations at similar frequencies in blood and bone marrow samples from distinct patients with SDS. It would be premature to state, on this basis, that the evaluation of *TP53* mutation burden is equivalent in the blood and bone marrow. This must be demonstrated by the comparison of paired bone marrow and blood samples.

In the future, it will be crucial to develop not only cross-sectional studies but also longitudinal studies[10] to unravel the missing steps between the initial faulty but benign hematopoiesis in SDS and the hematological malignancy. Deciphering the mechanisms of the natural selection processes and understanding clonal dynamics will offer powerful tools to prevent catastrophic complications in such patients.

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

REFERENCES

1. Xia J, Miller CA, Baty J, et al. Somatic mutations and clonal hematopoiesis in congenital neutropenia. *Blood*. 2018;131(4):408-416.
2. Hirsch P, Zhang Y, Tang R, et al. Genetic hierarchy and temporal variegation in the clonal history of acute myeloid leukaemia. *Nat Commun*. 2016;7:12475.
3. Germeshausen M, Deerberg S, Peter Y, Reimer C, Kratz CP, Ballmaier M. The spectrum of ELANE mutations and their implications in severe congenital and cyclic neutropenia. *Hum Mutat*. 2013;34(6):905-914.
4. Dror Y, Donadieu J, Koglmeier J, et al. Draft consensus guidelines for diagnosis and treatment of Shwachman-Diamond syndrome. *Ann N Y Acad Sci*. 2011;1242(1):40-55.
5. Finch AJ, Hilcenko C, Basse N, et al. Uncoupling of GTP hydrolysis from eIF6 release on the ribosome causes Shwachman-Diamond syndrome. *Genes Dev*. 2011;25(9):917-929.
6. Zambetti NA, Ping Z, Chen S, et al. Mesenchymal inflammation drives genotoxic stress in hematopoietic stem cells and predicts disease evolution in human pre-leukemia. *Cell Stem Cell*. 2016;19(5):613-627.
7. Golomb L, Volarevic S, Oren M. p53 and ribosome biogenesis stress: the essentials. *FEBS Lett*. 2014;588(16):2571-2579.
8. Donadieu J, Fenneteau O, Beaupain B, et al; Associated investigators of the French Severe Chronic Neutropenia Registry. Classification of and risk factors for hematologic complications in a French national cohort of 102 patients with Shwachman-Diamond syndrome. *Haematologica*. 2012;97(9):1312-1319.
9. Lindsley RC, Saber W, Mar BG, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. *N Engl J Med*. 2017;376(6):536-547.
10. Donadieu J, Martignoles JA, Beaupain B, et al. Frequency and evolution of TP53 mutant clones in Shwachman-Diamond syndrome. A cohort study from the French severe chronic neutropenia (SCN) registry [abstract]. *Blood*. 2017;130(suppl 1). Abstract 780.

DOI 10.1182/blood-2017-11-815431