A new mutant at the end: TPP1, telomeres, and BMF

Alison A. Bertuch  Baylor College of Medicine

In this issue of Blood, Guo et al identify a mutation in ACD, which encodes the protein TPP1, as the underlying cause of short telomeres and bone marrow failure (BMF) in a family. They show that the mutation results in a defect in the recruitment of telomerase to telomeres.

Approximately 15 years ago, the first link between telomeres—the specialized DNA-protein structures localized to the ends of chromosomes—and the inherited bone marrow failure syndrome dyskeratosis congenita (DC) was made. Since then, a constitutional defect in the ability to maintain telomere length has been found to underlie a spectrum of disorders from DC and its severe forms Hoyeraal-Hreidarsson and Revesz syndromes to some forms of familial aplastic anemia, myelodysplastic syndrome, and idiopathic pulmonary fibrosis (IPF). As reflected by most of these syndromes, the hematopoietic system is particularly sensitive to telomere length defects. Consistent with this, hematopoietic stem cells are among the few somatic cell types in which the enzyme responsible for the addition of telomeric repeat sequences onto chromosome ends, telomerase, is expressed.

Before the Guo et al report, mutations in 9 genes were found to be associated with the telomere biology disorders or telomeropathies; all 9 are linked to telomere maintenance or stability, including genes encoding components of telomerase or factors required for its biogenesis. Despite these advances, approximately 40% of patients who are diagnosed with a telomere biology disorder today lack a mutation in one of the known genes. These genetically uncharacterized patients are of great interest to researchers around the world, who hope to uncover the identities of the remaining genes. As expected, such discoveries are being facilitated by the application of whole exome sequencing. Although the telomere biology disorder genes identified in this fashion have been low-hanging fruit (ie, genes previously implicated in telomere biology through basic science research), the mutations identified in these patients’ genes have provided compelling corroboration of what has been learned through model organism and human cell line research. The Guo et al report is a prime example.

TPP1 is a component of the telomere-specific shelterin complex. Shelterin performs numerous essential functions. These include facilitating the replication of the double-stranded telomeric DNA tracts by conventional DNA replication machinery; protecting the telomeric end from unregulated DNA repair activities, which can lead to genomic instability; and regulating the access and activity of telomerase at the chromosome terminus. Shelterin consists of 6 distinct polypeptides and, until now, only the TN2 component had been implicated in the telomere biology disorders. Previous candidate gene sequencing in a cohort of 25 individuals with DC or short telomeres and BMF did not reveal damaging or deleterious variants in the other shelterin components. Nonetheless, mutations in ACD/TPP1 were highly anticipated because prior work demonstrated that TPP1’s direct interaction with the telomerase catalytic subunit, TERT, was crucial for the recruitment of telomerase to telomeres.

Strikingly, the mutation identified in the family reported by Guo et al was localized to the specific region of TPP1 required for TERT interaction. Thus, this suggests that a reduced recruitment of telomerase to the telomere via a heterozygous mutation in ACD/TPP1 is sufficient to lead to shortened telomeres and the BMF phenotype that frequently manifests in telomere biology disorders.

From a clinical perspective, the family reported by Guo et al highlights several important aspects of evaluating patients with BMF. First, a detailed family history can provide important clues that a constitutional telomere biology disorder underlies a patient’s BMF diagnosis. A family history of aplastic anemia, myelodysplastic syndrome, or leukemia is obviously suggestive of an inherited BMF disorder; however, a history of carcinoma of the tongue, as observed in the reported family (see Figure 1A in the article by Guo et al), may be missed as clinically significant. It is quite important, however, because individuals with DC are known to have a >1000-fold increased risk of tongue squamous cell carcinoma compared with the general population. A family history of IPF or cryptogenic liver disease may also provide an important clue. Indeed, the cooccurrence of BMF and IPF in an individual or family is highly predictive for the presence of a telomerase gene mutation.

Intensive immunosuppressive therapy, typically with antithymocyte globulin and
cyclosporine, is the mainstay of treatment of children and adults younger than age 40 years with severe aplastic anemia who lack a histocompatibility locus antigen-matched related donor. However, as reported for the proband in the Guo article and suggested by numerous cases in the literature, severe aplastic anemia resulting from a constitutional defect in telomere length maintenance is not responsive to immunosuppressive therapy. Thus, the prompt recognition of an underlying telomere biology disorder can spare patients from ineffective and risk-associated immunosuppressive therapy. In addition, if a matched related donor is available, he or she can be screened for the underlying telomere biology disorder, thereby avoiding transplantation with similarly affected hematopoietic stem cells.

Telomere length testing at the time of BMF presentation may provide the laboratory-based data needed to arrive at a telomere biology disorder diagnosis. Multiple methods for telomere length testing have been developed, and an assay that combines flow cytometry with fluorescent in situ hybridization (Flow-FISH) is available as a clinical test. When examined using the Flow-FISH assay, individuals with DC have very short telomere length across leukocyte populations has been observed, as determined by Flow-FISH, is both highly sensitive and specific for DC. Whereas some patients have profoundly short telomeres, others may have telomere lengths that hover around the first percentile, as did the proband in Guo et al. Additionally, telomere length slightly below the first percentile across lymphocyte populations has been observed, albeit rarely, in patients with inherited bone marrow failure syndromes other than DC, such as Fanconi anemia, Diamond-Blackfan anemia, and Shwachman-Diamond syndrome. Thus, short telomeres and BMF alone may be insufficient to arrive at a diagnosis of an underlying telomere biology disorder.

Ultimately, gene mutation data, as obtained by Guo et al., can provide the essential support for an underlying telomere biology disorder. Thus, continuing efforts to arrive at the full repertoire of genes associated with the telomere biology disorders is of particular importance as we strive to accurately diagnose and provide optimal care to patients with BMF.

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REFERENCES

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Comment on Scheinberg et al, page 2820

Cyclophosphamide in severe aplastic anemia?

Régis Peffault de Latour ASSISTANCE PUBlique DES HÔPitaux DE PARIs

In this issue of Blood, Scheinberg et al investigate moderate-dose cyclophosphamide (120 mg/kg) in treatment-naïve patients with severe aplastic anemia (SAA). The study was stopped for safety reasons. 1

SAA is a rare but serious form of bone marrow failure related to an immune-mediated mechanism that results in severe pancytopenia, a high risk of life-threatening infection, and hemorrhage. Allogeneic bone marrow transplantation (BMT) from an HLA-identical sibling donor is the treatment of choice for young patients, leading to an 80% to 90% chance of survival, with no or few complications in the long term. 2 In the absence of an HLA-identical sibling donor or in older patients, excellent outcomes can be achieved with the current gold standard first-line immunosuppressive therapy (IST) consisting of antithymocyte globulin (ATG) plus cyclosporine (CsA; 60-70% response rate and 70-80% long-term survival). 3 After IST, only one-third of the patients are cured, one-third are dependent on long-term administration of CsA, and one-third will either relapse or develop a clonal disorder (myelodysplastic syndrome or acute myeloid leukemia); the latter complications are usually rare after BMT. Additional immunosuppressive drugs (ie, high-dose corticosteroids, mycophenolate mofetil, or sirolimus) have been added to the ATG/CsA backbone with the objective of decreasing relapse and secondary clonal disease, but thus far, no improvement in outcome has been observed. 3 The use of rabbit ATG, a more potent immunosuppressant drug than horse ATG, did not improve the rate of hematological recovery and was associated with a detrimental effect on overall survival, justifying the recommendation to prioritize horse ATG in this setting. 5

Cyclophosphamide is as an alternative immunosuppressive drug in treatment-naïve patients with SAA, which may improve outcome but has already generated considerable controversy. A single phase 2 study conducted at the Johns Hopkins University testing high-dose cyclophosphamide (200 mg/kg) was updated in 2010 and an editorial in this journal
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