

● ● ● NEOPLASIA

Comment on Roos et al, page 2246

Do short telomeres shorten CLL survival?

Thomas S. Lin THE OHIO STATE UNIVERSITY

Roos and colleagues demonstrate that telomere length correlates with known biological prognostic factors in CLL and may independently predict clinical outcome. These findings suggest that telomerase may be a useful pharmacological target in CLL.

Patients with chronic lymphocytic leukemia (CLL) exhibit greatly variable clinical behavior; some patients do not require therapy for years or decades, whereas others progress rapidly, respond poorly to therapy, and die within a few years. Over the past decade, significant advances in our understanding of the prognostic importance of cytogenetic abnormalities and other biological factors in the natural history of CLL have greatly improved clinicians' ability to identify patients who are likely to do poorly and may require more aggressive treatment. This risk stratification provides essential information on the percentage of high-risk patients in a clinical protocol, and is critical for interpretation of clinical trial results. Furthermore, risk stratification allows researchers to target high-risk populations in clinical studies of new regimens and agents in CLL.

Deletion of 17p13 and 11q22, corresponding to loss of the p53 and ataxia telangiectasia mutated (ATM) tumor suppressor genes, respectively, is associated with a need for earlier therapy and poor long-term prognosis. Similarly, patients with an unmutated immunoglobulin heavy chain variable region (IgV_H) have a markedly inferior prognosis compared with patients who have unmutated IgV_H. However, IgV_H mutational analysis is expensive and, until recently, reliable IgV_H mutational assessment was not available outside specialized academic centers. Therefore, investigators have examined prognostic factors such as CD38 and zeta-associated protein (ZAP)-70, whose expression correlates with unmutated IgV_H and inferior long-term survival.

In this issue of *Blood*, Roos and colleagues report an inverse correlation between telomere length and unmutated IgV_H status, ZAP-70 expression, and CD38 expression in a cohort of 152 patients with CLL. Furthermore, a solitary del(13q) cytogenetic abnormality,

which is associated with a favorable prognosis, was observed more frequently in patients with a telomere length above the median than in patients with short telomeres. In contrast, deletions of 11q or 17p, which confer an inferior prognosis, were more common in patients with short telomeres. More importantly, the authors demonstrate that telomere length correlates with clinical outcome. Patients with telomere lengths below the median had poorer long-term treatment-free and overall survival compared with patients with long telomeres. In fact, multivariate analysis using clinical stage, IgV_H mutational status, ZAP-70, CD38, and telomere length as variables identified only clinical stage and telomere length as inde-

pendent prognostic factors for treatment-free survival. These important findings indicate that telomere length may be a useful independent prognostic factor in the risk stratification of CLL patients, although further studies are needed to confirm these results.

These findings suggest that the enzyme telomerase, which is overexpressed in CLL and other hematologic malignancies, may be a target for novel anticancer therapies, particularly in those patients whose tumor cells feature shortened telomeres. The phosphorothioate oligonucleotide GRN163L targets telomerase and is in phase I clinical study at The Ohio State University and other institutions. Similar studies are planned for other diseases, such as multiple myeloma and myelodysplasia, with increased telomerase activity. Roos and colleagues' identification of telomere length as a biological prognostic factor in CLL provides further rationale for these clinical studies. Hopefully, targeting telomerase will translate into effective clinical therapy for CLL patients.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

● ● ● HEMOSTASIS

Comment on Dimberg et al, page 2015

New entry for angiostatic cancer treatment

Arjan W. Griffioen MAASTRICHT UNIVERSITY SCHOOL FOR ONCOLOGY AND DEVELOPMENTAL BIOLOGY

A member of the small heat shock protein family is found to regulate the formation of vasculature. A study by Dimberg and colleagues combines novel insights into the mechanisms of tumor angiogenesis with therapeutic opportunities for the treatment of cancer.

In their study, Dimberg and colleagues present α B-crystallin as a promoter of tumor angiogenesis, working through increasing endothelial-cell survival. An approach involving the proteomic screening of endothelial cells in a tubular morphogenesis assay led to the identification of this molecule, which was never before found to be involved in vessel formation or angiogenesis. α B-crystallin is up-regulated during tube formation of cultured endothelial cells in a 3-dimensional sprouting assay. Besides enhanced expression,

there is also activation of the molecule through phosphorylation during tube formation. siRNA knock-down experiments proved the specific role of α B-crystallin in tube formation through enhanced cleavage of caspase-3, leading to induction of apoptosis. α B-crystallin was shown to be overexpressed in a subset of blood vessels in human tumors, and knock-out mice were shown to have reduced angiogenesis and impaired function of the endothelium.

The identification of specific markers of tumor endothelium is an important field of

research that may reveal novel therapeutic targets based on angiogenesis inhibition. The neutralization of a central angiogenic factor, vascular endothelial growth factor (VEGF), has been shown to prolong the life expectancy of patients with colon, breast, and lung cancer. Although this approach has demonstrated proof-of-concept for clinical application of antiangiogenesis compounds, targeting VEGF is a way of treating the tumor cells, which may be difficult due to different means of resistance that can be acquired by virtue of the plasticity of those cells.^{1,2} A better strategy for angiogenesis inhibition is therefore the direct targeting of (pivotal determinants of the biology of) endothelial cells, leading to growth inhibition or cell death without tumor-cell interference. Such an approach would take advantage of the inherent attraction of angiogenesis inhibition—that is, that the endothelial-cell compartment is genetically stable and therefore unlikely to mutate into drug resistant variants, and thus could be a superior target compared with the tumor cell.

The identification of α B-crystallin as a target for therapy may provide a tool for directly targeting the tumor endothelium. The proteomic screen as performed by Dimberg and coworkers, as well as previously published

genomic screenings of tumor endothelium,^{3,4} may help pinpoint even more markers for direct targeting of tumor endothelium.

It is interesting to note that α B-crystallin is also overexpressed in other cells that are under continuous stress. This includes the tumor cells, in which the molecule was earlier described as a novel oncogene and, when present in human tumors, a predictor of poor survival. The dual targeting of endothelium and tumor cells is an attractive approach that may be possible with a single molecule that blocks α B-crystallin. The present challenge is to develop small-molecule, peptide, or antibody-based α B-crystallin blocking compounds and test them in animal models of cancer.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Griffioen AW. Therapeutic approaches of angiogenesis inhibition: are we tackling the problem at the right level? *Trends Cardiovasc Med.* 2007;17:171-176.
2. Carmeliet P. Angiogenesis in life, disease and medicine. *Nature.* 2005;438:932-936.
3. St Croix B, Rago C, Velculescu V, et al. Genes expressed in human tumor endothelium. *Science.* 2000;289:1197-1202.
4. van Beijnum J, Dings RP, van der Linden E, et al. Gene expression of tumor angiogenesis dissected; specific targeting of colon cancer angiogenic vasculature. *Blood.* 2006;108:2339-2348.

premature mortality in FA, remains equally unclear.

It has been previously observed that patients with FA³ as well as patients with idiopathic aplastic anemia⁴ have raised levels of tumor necrosis factor- α (TNF- α) and γ -interferon (γ -IFN). TNF- α is a cytokine with important biological roles in hematopoiesis and apoptosis.⁵ Soluble mature TNF- α is released from cells by the TNF- α -converting enzyme (TACE) or by the matrix metalloproteinase 7 (MMP-7). The binding of TNF- α to its receptors results in activation of both the mitogen-activated protein kinase (MAPK) stress signaling cascade and the NF- κ B transcription factor. Activation of these 2 pathways plays an important role in the recruitment of many other effector molecules, including TNF- α . TNF- α has been shown to have inhibitory effects on normal hematopoietic progenitors, and it has been observed that raised levels of TNF- α are found in several hematopoietic disorders, including idiopathic aplastic anemia and FA. These observations suggest that TNF- α could be a key player in the pathophysiology of bone marrow failure (and other abnormalities) in FA.

In this issue of *Blood*, Briot and colleagues provide new and exciting data regarding the origin of TNF- α overproduction in FA. Their studies show that biallelic FA mutations result in aberrant activation of 2 major stress-signaling pathways: NF- κ B and MAPK. Using both molecular and pharmacological inhibitors, they show that the ERK pathway, 1 of the 3 major players within the MAPK pathway, is activated and is responsible for the elevated expression of MMP-7 in FA cells. This, in turn, leads to a high rate of TNF- α shedding from the cytoplasmic membrane. Conversely, they show that MMP-7 inhibition normalizes TNF- α levels.

These new data therefore suggest that one of the important aberrations in FA cells is the increased activation of the MAPK–MMP-7–TNF- α axis (see figure). Further studies are necessary to determine the overall net contribution of the up-regulated MAPK–MMP-7–TNF- α axis in the pathophysiology of FA. As it is possible to inhibit this pathway pharmacologically, these new observations provide a putative rationale for developing a new therapeutic approach to the treatment of FA patients based on drugs

● ● ● HEMATOPOIESIS

Comment on Briot et al, page 1913

Dissecting “stress” in Fanconi anemia

Inderjeet Dokal BARTS AND THE LONDON, SCHOOL OF MEDICINE AND DENTISTRY

Briot and colleagues provide compelling evidence that aberrant activation of the MAPK stress-signaling cascade, which results in TNF- α oversecretion, plays an important role in the pathophysiology of Fanconi anemia.

Fanconi anemia (FA) is an inherited bone marrow failure syndrome characterized by a variable number of developmental abnormalities, genomic instability, and an increased predisposition to malignancy.¹ It is genetically heterogeneous, with 13 subtypes/complementation groups (FA-A, FA-B, FA-C, FA-D1, FA-D2, FA-E, FA-F, FA-G, FA-I, FA-J, FA-L, FA-M, and FA-N) currently recognized. The genes responsible for these subtypes (*FANCA*, *FANCB*, *FANCC*, *FANCD1*, *FANCD2*,

FANCE, *FANCF*, *FANCG*, *FANCI*, *FANCF*, *FANCL*, *FANCM*, and *FANCN*, respectively) have all been identified.

Studies from several research groups over the last 15 years suggest that the proteins encoded by the FA genes are important in DNA repair and therefore in the maintenance of genomic stability.² However, the precise role of these proteins in the repair of DNA lesions still needs to be fully defined. The molecular mechanism underlying bone marrow failure, the major cause of