To the editor:

Short telomeres in B-CLL: the chicken or the egg?

In their recent paper in Blood, Roos et al report a correlation between telomere length in B-CLL cells and the presence of complex chromosomal aberrations.1 Roos et al suggest that patients with poor-prognosis B-CLL have short telomeres at the time of malignant transformation, and that chromosomal aberrations follow. While this is one possible explanation for their findings, we feel an alternative explanation deserves further discussion. When debating the role of telomeres in pathophysiologic processes, it is important to consider cause versus effect. Thus the fundamental question is whether the short telomeres seen in B-CLL cells with complex chromosomal abnormalities are causative for the development of chromosomal aberrations, or whether the chromosomal aberrations led to the short telomeres.

In the first scenario, favored by Roos et al, the malignant B cell clone has a “preset” telomere length. Because telomeres function as protective “caps” for chromosomes, B-CLL cells with shorter telomeres are more prone to the development of complex chromosomal aberrations. Telomerase is up-regulated and thereby contributes to the fixation of the immortalized state of the malignant B cell clone. Up-regulation of telomerase activity may occur as a direct consequence of the chromosomal aberrations, or by the same mechanism as in rapidly dividing nonmalignant cells.2,3

In an alternative hypothesis, the short telomeres in B-CLL cells are not the cause, but the consequence of the complex chromosomal aberrations. In this scenario, the chromosomal aberrations directly result in a more rapid B-CLL cell turnover, and it is this rapid turnover that induces short telomeres. Several lines of indirect evidence support this scenario. Messmer et al found the cellular birth rate of B-CLL cells is significantly higher in patients who exhibit poor prognostic factors compared with other B-CLL patients.4 These findings were confirmed by a study of Longo et al that showed that the proliferative capacity of unmaturated B-CLL cells (poor prognosis) is significantly higher than that of mutated B-CLL cells.5 We found that B-CLL cells with complex chromosomal aberrations undergo spontaneous apoptosis more abundantly, and have lower intracellular bcl-2 levels, than B-CLL cells with good prognosis cytogenetics. We also found that serum lactate dehydrogenase levels, used as a surrogate marker of cell turnover, were significantly higher in patients with complex cytogenetics compared with other B-CLL patients.6

According to this alternative hypothesis, B-CLL cells with complex chromosomal aberrations (poor prognosis) have a higher turnover in vivo, including both greater proliferative activity and greater tendency to undergo spontaneous apoptosis. This higher turnover results in a more rapid attrition of telomeres, thereby causing shorter telomeres and up-regulation of telomerase.

Response

Or both?

We appreciate the comment given by Jahrsdörfer and Weiner arguing for the hypothesis that short telomeres in CLL are a consequence, rather than a cause, of complex chromosomal aberrations.

Clearly, the findings of Roos et al are an excellent addition to the growing list of predictive factors for risk stratification of B-CLL. However, the determination of causality may have significant therapeutic implications. If short telomeres precede complex chromosomal aberrations, a telomerase inhibitor might be of therapeutic value, because it would disrupt the vicious circle of increasing telomerase activity and cumulative complexity of chromosomal aberrations. If the alternative hypothesis is correct, inhibition of telomerase activity would have no further effect on rapidly dying B-CLL cells with short telomeres. In fact, such treatment could be detrimental, because such agents could inhibit the expansion of potentially arising B-CLL–specific T cells in these patients.2,6

In conclusion, more information is needed to understand how the relationship between complex chromosomal aberrations and telomeres impacts on clinical course. For example, no data exist on correlation of telomere length and prognosis in B-CLL patients with normal karyotype, a group not included in the study by Roos et al. Furthermore, it may be helpful to find out more about how different therapies impact telomere length in B-CLL. After all, a large, comprehensive study exploring clinical course, prognosis, telomere length, proliferative activity, apoptosis and various immunologic parameters, at multiple points during therapy of B-CLL, could help address many of the questions outlined above and may have therapeutic implications as well.

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References

To the editor:

Radiologic and nuclear events: the METREPOL severity of effect grading system

The US approach to optimizing medical preparedness to a mass nuclear irradiation disaster has been nicely outlined in Weinstock et al,1 and we thought it might be of interest, and relevance, to present in more depth the European approach referred to in the article. In March 2002, the European Group for Blood and Marrow Transplantation (EBMT) established a Nuclear Accident Committee (NAC) to determine whether the EBMT resource of more than 1000 patients could be optimized as a network for providing help in the event of a radiation disaster.2

In 2005, an EBMT International Consensus Meeting defined a unified basis for the medical management of radiation accident victims.3 The core of this consensus was the 2001 “METREPOL” (Medical Treatment Protocols for Radiation Accident) clinical grading of irradiated victims, based on data from the event of a radiation disaster.2 The genetic alterations leading to a bypass of M1 (senescence) are in CLL probably 11q− (ATM↓) and 17p− (p53↓).2 CLL cells with these aberrations in general have unmutated IGHV genes3,4 and it can also be assumed that these cells from the start have shorter telomeres than B cells with mutated IGHV genes.5,6 We also wrote “11q− or 17p− aberration in combination with overexpression of ZAP-70 and/or CD38 gives cells a survival advantage and facilitate cell cycle progression, one consequence of which is telomere attrition.”7p2250 In addition, we referred to the report showing a correlation between birth rate and disease activity,7 concluding that “[t]hese data suggest that cell kinetic characteristics can contribute to differences in telomere length.”7p2250

In summary, we argue that short telomeres can be a consequence of certain genetic aberrations leading to increased cell proliferation, and thus agree with Jahrsdorfer and Weiner, but we also believe that it is likely that the cell of origin differs in telomere length depending on its IGHV gene status. Critically short telomeres can thereafter induce a state of genetic instability leading to further genetic alterations.

Regarding the question “Short telomeres in B-CLL: The chicken or the egg?” we argue that the answer rather is “both,” which means that the short telomere phenotype is the result of many interacting factors as outlined in our paper. The “chicken” is the telomere length in the cell of origin, and the “egg” includes a number of possible events (11p−/17p−, ZAP70↑, CD38↑, and others) with effects on cell cycle progression and survival.

References

Response: Or both?

Göran Roos, Richard Rosenquist and Stephan Stilgenbauer