Telomerase regulation in HTLV-I infection

Hinh Ly  Emory University School of Medicine

In this issue of Blood, Bellon and Nicot describe an elegant mechanism used by HTLV-I to up-regulate telomerase gene expression and function in the absence of the viral tax oncoprotein.

Adult T-cell leukemia was first reported as an entity in Blood in 1977. Three years later, Gallo et al identified the human T-cell leukemia/lymphoma virus-I (HTLV-I), a deltaretrovirus, as the causative agent for this debilitating disease. Currently, the estimated number of people infected with HTLV-I worldwide is between 15 and 25 million. However, due to insidious characteristics of this virus, most HTLV-I–infected individuals remain asymptomatic for at least 20 to 30 years before developing HTLV-related clinical disorders. Besides causing adult T-cell leukemia and lymphoma (ATLL), HTLV-I has been associated with other human diseases, including a neurologic disorder known as HTLV-I–associated myelopathy/tropical spastic paresis, and perhaps other hematologic and nonhematologic disorders.

HTLV-I has been intensely studied, primarily because it has the capacity to transform primary human T cells in vitro and in vivo. To convert a normal T cell to a leukemic cell, the HTLV-I tax oncoprotein must participate in several cellular pathways in order to overcome innate cellular barriers to transformation. To achieve clonal expansion in the early phase of viral infection, HTLV-I–infected cells also acquire an increased capacity to replicate DNA. The complete replication of linear chromosomal DNA relies on the enzymatic activity of a specialized cellular RNA-dependent DNA polymerase (telomerase) that synthesizes telomeric sequences at the 3’ ends of linear chromosomes. The tax protein of HTLV-I has been shown to up-regulate expression of the catalytic protein subunit of telomerase (hTERT) in infected cells, via the nuclear factor κB (NF-κB) signaling pathway. Clonal expansion of HTLV-I–infected cells is also dependent on the presence of interleukin-2 (IL-2), as this cytokine is required for the differentiation and long-term proliferation of T cells. However, as noted by Bellon and Nicot, expression of tax protein in IL-2–dependent cells and in primary tissues of ATLL patients is almost undetectable, yet these cells retain high levels of telomerase enzymatic activity. These observations suggest an alternative mechanism for telomerase activation, independent of the viral tax protein.

To establish a link between IL-2 and telomerase activation, the authors withdraw this growth factor in cultures of immortalized HTLV-I–infected cells and show that telomerase activity is reduced. By using known pharmacological inhibitors of PI3K, a downstream target of the IL-2 receptor complex, and of its immediate downstream target Akt, the authors show that these inhibitors can also reduce telomerase activity, suggesting that the PI3K/Akt pathway is involved in activating telomerase in virus-infected cells. Perhaps more importantly, the authors provide data to show that PI3K regulates telomerase gene expression at a transcriptional level independent of Akt, which increases telomerase activity by phosphorylating hTERT posttranscriptionally, and that IL-2 results in sequestration of a known transcriptional repressor of the hTERT gene, WT1, in the cytoplasm, thereby increasing telomerase gene expression and function.

One potential problem with this approach is that the 2 small molecule inhibitors of PI3K/Akt activity used in the study may have other targets in the cell that are not specific to the PI3K/Akt pathway. It would next be important to investigate whether the same effects are seen in cells deficient for components of the PI3K/Akt pathway (eg, knockout or knockdown cells) or in cells expressing dominant negative mutants of some components in this signaling pathway. In addition, as the authors have correctly pointed out, it is not known if PI3K is directly responsible for WT1 cytoplasmic retention or whether additional IL-2R signaling pathways are activated.

A model of how HTLV-I can up-regulate telomerase gene expression and function in the absence of the viral tax oncoprotein. Upon IL-2 stimulation, PI3K transcriptionally up-regulates telomerase (hTERT) gene expression, whereas Akt increases telomerase function by phosphorylating hTERT protein. LY29 and AKTII, known pharmacological inhibitors of PI3K and Akt, respectively, reduce telomerase activity, confirming the involvement of the PI3K/Akt pathway in activating telomerase function. IL-2 stimulation also results in sequestration of WT1, a known transcriptional repressor of hTERT gene, in the cytoplasm of the cell, thereby increasing telomerase gene expression and function.
and/or repressed in order to increase telomerase functions in ATLL patients.

In summary, Bellon and Nicot provide experimental evidence to explain a seemingly paradoxical phenomenon, in which even in the absence of the HTLV-I tax protein, a strong inducer of telomerase gene expression, telomerase activity remains elevated in IL-2-dependent cells and ATLL patient samples. This is consistent with the fact that after HTLV-I–infected cells become transformed, they no longer require tax protein or IL-2 stimulation. For the first time, these authors show that the PI3K/Akt signaling pathway is invoked by HTLV-I to effect telomerase activation and long-term proliferation of infected cells. This study underscores the importance of this signaling pathway in regulating telomerase function in cancer cells, as both telomerase and PI3K/Akt functions are commonly found to be activated in cancer cells.3

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REFERENCES

TRANSPLANTATION

Comment on Stern et al, page 2990

Mother and child reunion

Jan J. Cornelissen  ERASMUS UNIVERSITY MEDICAL CENTER

While the graft–versus-leukemia effect of T-cell–depleted haploidentical family stem–cell transplantation is considered to be largely based on NK–cell alloreactivity, T–cell alloreactivity might still play an important role. In this issue of Blood, Stern and colleagues show that recipients of haploidentical stem–cell grafts may experience better outcome if the mother rather than the father serves as stem–cell donor, an effect that occurred independent of NK–cell alloreactivity.

Although the probability of finding at least one HLA–A, –B, –C, –DR, –DQ matched donor for a Caucassian patient is currently high (70%-80%), finding a match for HLA–A, –B, –C, –DR, and –DQ is considerably less (35%-40%) and even lower for non–white patients (www.bmdw.org). Recently, the selection of donors with preferably no more than 1 mismatched allele out of 8 was advocated.1 If that criterion is adhered to and if the number of patients who may progress during the search process is taken into account, only approximately 50% of patients with an indication for unrelated donor allogeneic stem cell transplantation (alloSCT) may ultimately receive the intended allograft.2 That percentage may be even lower for patients with a nonwhite background. Therefore, alternative donors and stem–cell sources are urgently needed, and currently, both haploidentical family donors as well as unrelated cord blood (UCB) stem cell sources are being applied with increasing frequency.

Family mismatched donor alloSCT, as has been developed by the Perugia team,1 is associated with a high rate of engraftment, low incidence of graft–versus-host disease (GVHD), and an event–free survival of approximately 45% to 50% for patients receiving their transplant in remission. The antileukemic activity is based on both an intensified preparatory regimen and the possibility of a donor–versus–recipient natural killer (NK)–cell alloreactivity,4 whereby a strong graft–versus–leukemia (GVL) effect may be exerted by NK–mismatched family donors. As with cord blood, haploidentical family donor alloSCT offers the advantage of immediate availability, which compares favorably to the 2 to 3 months needed to identify and prepare for a matched unrelated adult donor.

While the antileukemic effect of haploidentical family donor alloSCT is predominantly based on an NK–alloreactive effect, the residual low number of donor T cells present in the T–cell–depleted allograft may also be involved in the GVL effect. In this issue of Blood, Stern and coauthors present results from a retrospective study evaluating whether donor gender might influence outcome after parental donor haploidentical alloSCT. While reproducing the observation of a lower relapse rate associated with KIR–ligand mismatch, they also observed a lower relapse rate significantly associated with recipients of a maternal graft, independent of NK alloreactivity. This lower relapse rate may result from minor–antigen–specific memory T cells that were induced long ago during pregnancy by transplacental leukocyte trafficking. Minor rather than major HLA–antigen specificity is suggested by absence of more GVHD. These results compare well with earlier observations by Kolb et al, who observed the same phenomenon in a series of recipients of haploidentical stem cell grafts, which were less severely depleted of T cells using anti–CD6 antibodies.5 Meanwhile, investigators from the European Group of Blood and Marrow Transplantation (EBMT) have very recently shown that the GVL effect associated with UCB alloSCT may not be restricted to alloreactive T cells, but may also involve KIR–ligand–mismatched NK cells.6 Collectively, these results highlight the stronger GVL effect that may be associated with alternative donor alloSCT, but also evoke the urgent question of which alternative donor is to be preferred.

First, based on the results by Stern and Kolb, it may seem reasonable that an NK–cell nonalloreactive haploidentical transplant from a father, brother, or sister should be avoided for recipients with acute leukemia in remission and in need of an alternative donor. Second, if a nonmyeloablative regimen is indicated, such as in older patients, 1 or 2 adequately sized UCB transplantations may be preferred,7 due to the higher risk of nonengraftment associated with a full haplotype–mismatched donor. Third, the benefits and risks of UCB alloSCT...
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