development as indicated by the recent identification of a mutation in the RPS19 gene in a case of hydrops fetalis along with other cases of hydrops fetalis in DBA families.

The present study by Garçon and colleagues represents the first step in what should prove to be a long and productive journey toward a comprehensive understanding of the role of ribosomes in normal and disordered hematopoiesis and in evaluating new therapeutic options for the treatment of DBA.

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

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 Comment on Gertner-Dardenne et al, page 922

Inhibiting inhibitory pathways in human γδ T cells

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In this issue of Blood, Gertner-Dardenne et al show that B- and T-lymphocyte attenuator (BTLA) functions as an inhibitory receptor on γδ T cells and suggest that disruption of this inhibitory pathway in tumor-reactive γδ T cells may result in enhanced antitumor responses.1-2

Unlike αβ T cells, which recognize specific peptide antigens presented by major histocompatibility complex molecules, γδ T cells in contrast appear to recognize generic determinants expressed by cells that have become dysregulated as a result of either malignant transformation or viral infection. It is now generally accepted that as a result of dysregulation, tumor cells may display a variety of antigens that, although neither tumor-specific nor tumor-derived per se, can nonetheless serve as recognition determinants for cytolytic γδ T cells.3-5 It is this innate ability to recognize and kill a broad spectrum of tumor cell types—in a manner that does not require the existence of bona fide tumor-specific antigens—that has made the study of γδ T cells particularly appealing in the context of developing novel cell-based therapies directed against a variety of human cancers.6

Critical to any strategy intended to exploit either adaptive or innate antitumor immune responses is the development of an understanding of the mechanisms by which tumor cells can subvert, evade, or reshape such otherwise protective antitumor immune responses. To highlight this particular point, one need only consider the recent reports showing that antibody blockade of programmed death 1 (PD-1) inhibitory receptor pathways can lead to clinical responses in patients with a wide variety of tumors.7-8

BTLA is a more recently described inhibitory receptor that shares both structural and functional similarities with PD-1 and cytotoxic T lymphocyte–associated antigen 4 (CTLA-4).2 Although the function of BTLA as an inhibitory receptor on conventional αβ T cells is well established,9 its role in the regulation of human γδ T cells has remained unrecognized until now.

In the report by Gertner-Dardenne et al published in this issue of Blood,1 the authors establish that, through its interaction with herpes virus entry mediator (HVEM), BTLA expressed on human γδ T cells can moderate the activation, proliferation, and differentiation of Vγ9Vδ2 T cells, the predominant γδ T-cell subset found in human peripheral blood. Taken as a whole, this report provides evidence in support of a model in which the BTLA-HVEM interaction must now be counted as an important—and potentially targetable—inhibitory pathway that should be considered in the design of strategies intended to exploit the innate antitumor properties of human γδ T cells.

The authors first establish that BTLA and the T-cell receptor (TCR) colocalize within Vγ9Vδ2 T cells after mitogen stimulation. Importantly, this physical association was shown to negatively regulate TCR-mediated signaling because stimulation of Vγ9Vδ2 T cells through the TCR in the presence of blocking antibodies to BTLA resulted in increased phosphorylation of TCR-associated signaling molecules. Moreover, when Vγ9Vδ2 T cells were stimulated in the presence of HVEM-Ig (a soluble fusion protein that functionally engages BTLA), a significant reduction in Vγ9Vδ2 T-cell proliferation was observed. Conversely, when Vγ9Vδ2 T cells were stimulated in the presence of blocking antibodies directed against either BTLA or HVEM, substantially increased Vγ9Vδ2 T-cell proliferation occurred.

The authors conclude their report by presenting results obtained using more clinically relevant models. First, Vγ9Vδ2 T cells from healthy donors were stimulated in the presence of human lymphoma cell lines...
that express HVEM. As predicted, Vγ9Vδ2 T cells proliferated to a greater extent in the presence of antibodies that blocked BTLA-HVEM interactions. Finally, upon careful examination of patient-derived lymph node samples, Vγ9Vδ2 T cells from within these cancerous lymph nodes were found to proliferate to a significantly greater extent when stimulated in the presence of blocking antibodies directed against either BTLA or HVEM.

The major contribution of this work is its demonstration for the first time that BTLA-HVEM interactions can significantly inhibit the activation and proliferation of Vγ9Vδ2 T cells. However, the findings from this report also allow one to pose several important questions—particularly when one considers the dynamic nature of the expression of both BTLA and HVEM and the correspondingly complex interactions that may occur between these 2 molecules in vivo.9 Several interesting questions stand out in this regard. What, for example, is the significance of the findings that the expression of BTLA varies depending on the developmental status of Vγ9Vδ2 T cells where naive Vγ9Vδ2 T cells express higher levels of BTLA when compared with more differentiated, antigen-experienced Vγ9Vδ2 T cells? In a related point, what is the significance of the findings that BTLA-HVEM interactions can diminish the transition of Vγ9Vδ2 T cells from less differentiated (naive and central memory) to more differentiated effector phenotypes? In this regard, does the BTLA-HVEM interaction actually regulate Vγ9Vδ2 T-cell differentiation? If this is indeed the case, could this provide insight into the mechanisms by which tumor cells—particularly those that express HVEM—might escape from antitumor immunosurveillance provided by Vγ9Vδ2 T cells? In addition, because HVEM itself is expressed on a wide variety of cell types, including γδ T cells themselves, just which cells in the tumor microenvironment are expressing functionally relevant HVEM that interacts with BTLA on Vγ9Vδ2 T cells? These and related questions can surely be addressed in future studies.

To date, the therapeutic potential of human γδ T cells still remains largely unrealized. Beginning with the early pioneering attempts to exploit the antitumor properties of endogenous human γδ T cells in patients with hematolymphoid malignancies,10 to more recent efforts targeting a broader spectrum of tumors,6 clinical responses although clearly evident, have been modest at best. The findings of this current report provide a strong rationale for moving forward with more intensive studies designed to understand how the blockade of the BTLA-HVEM inhibitory pathway might potentiate the in vivo antitumor activity of human γδ T cells. Such efforts could soon enough lead to the design of exciting new clinical trials—provided the appropriate clinical-grade antibodies can be developed in a timely and economically feasible manner.

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

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