

the percentage of apoptotic cells. Corresponding changes were observed in B cells from wild-type and p66Shc knockout mice, further suggesting that the imbalance in Bcl-2 family protein expression in CLL B cells may be caused by p66Shc deficiency.

What remains unclear from this study is the mechanism through which p66Shc regulates the expression of Bcl-2 family proteins. One possibility is that p66Shc deficiency could lead to increased tonic BCR signaling, a phenomenon that was recently described in CLL and several other B-cell malignancies and was shown to contribute to the increased apoptosis resistance of the leukemic cells. In favor of this possibility is the observation of the authors that both ligand-dependent and ligand-independent phosphorylation of Syk is enhanced in the absence of p66Shc. However, recently published data suggest that in CLL cells, the antiapoptotic effect of constitutively active Syk is primarily related to changes in the expression of Mcl-1 and Bim, whereas expression of Bcl-2, Bcl-xL, and Bax does not appear to be affected.⁶ Alternatively, the mechanism through which p66Shc modulates Bcl-2 family protein expression could be related to some other function of this protein. Apart from its role as an adaptor, p66Shc is known to function also as a redox enzyme that enhances reactive oxygen species production by mitochondria.⁷ Production of reactive oxygen species results in mitochondrial dysfunction, cytochrome-c release, and activation of the caspase cascade, but has also been shown to affect Bcl-2 expression.⁸

A second unresolved question is the mechanism responsible for the reduced ex-

pression of p66Shc in CLL cells. The observation that p66Shc is expressed at higher levels in mutated CLL than in unmutated CLL cells can be taken to suggest that expression of this protein could be modulated by external stimuli from the microenvironment. Identification of stimuli that up-regulate p66Shc may possibly provide a new venue for CLL treatment.

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

REFERENCES

1. Capitani N, Lucherini OM, Sozzi E, et al. Impaired expression of p66Shc, a novel regulator of B-cell survival, in chronic lymphocytic leukemia. *Blood*. 2010;115(18):3726-3736.
2. Cimmino A, Calin GA, Fabbri M, et al. miR-15 and miR-16 induce apoptosis by targeting BCL2. *Proc Natl Acad Sci U S A*. 2005;102(39):13944-13949.
3. Messmer BT, Albesiano E, Efremov DG, et al. Multiple distinct sets of stereotyped antigen receptors indicate a role for antigen in promoting chronic lymphocytic leukemia. *J Exp Med*. 2004;200(4):519-525.
4. Stamatopoulos K, Belessi C, Moreno C, et al. Over 20% of patients with chronic lymphocytic leukemia carry stereotyped receptors: pathogenetic implications and clinical correlations. *Blood*. 2007;109(1):259-270.
5. Pacini S, Pellegrini M, Migliaccio E, et al. p66SHC promotes apoptosis and antagonizes mitogenic signaling in T cells. *Mol Cell Biol*. 2004;24(4):1747-1757.
6. Gobessi S, Laurenti L, Longo PG, et al. Inhibition of constitutive and BCR-induced Syk activation downregulates Mcl-1 and induces apoptosis in chronic lymphocytic leukemia B cells. *Leukemia*. 2009;23(4):686-697.
7. Giorgio M, Migliaccio E, Orsini F, et al. Electron transfer between cytochrome c and p66Shc generates reactive oxygen species that trigger mitochondrial apoptosis. *Cell*. 2005;122(2):221-233.
8. Shanafelt TD, Lee YK, Bone ND, et al. Adaphostin-induced apoptosis in CLL B cells is associated with induction of oxidative stress and exhibits synergy with fludarabine. *Blood*. 2005;105(5):2099-2106.

● ● ● IMMUNOBIOLOGY

Comment on Scott-Algara et al, page 3708

Changing lanes in ICL

Irini Sereti NATIONAL INSTITUTES OF HEALTH

In this issue of *Blood*, Scott-Algara and colleagues describe decreased surface expression with intracellular accumulation of CXCR4 in CD4⁺ T cells of 6 patients with ICL.¹ This was associated with decreased migratory responses to CXCL12 and was restored by both in vitro and in vivo IL-2.

In this issue of *Blood*, Scott-Algara et al found that patients with idiopathic CD4 lymphocytopenia (ICL) had very low to undetectable levels of surface CXCR4 expression on CD4⁺ T cells and higher levels of intracel-

lular levels of CXCR4 and its ligand, CXCL12, compared with healthy controls. The abnormally low CXCR4 expression was seen exclusively in T cells (predominantly in CD4⁺) including both naive and memory sub-

sets. Overnight rest of the cells restored surface expression of CXCR4 to normal levels. In chemotaxis assays, it was shown that T cells from ICL patients had impaired chemotactic responses to CXCL12 and normal responses to CXCL8. Further experiments showed a slower reemergence of CXCR4 after ligand binding and internalization. Finally, in vivo interleukin-2 (IL-2) administration seemed to restore CXCR4 expression and responses to CXCL12 in 3 of 4 patients treated.

Seventeen years from the Centers for Disease Control and Prevention description and definition of ICL,² the etiology or etiologies of this syndrome are unknown. Few studies have addressed the pathways potentially involved in perturbed CD4⁺ T-cell homeostasis, such as decreased clonogenic capacity of lymphoid progenitors,³ increased susceptibility of CD4⁺ T cells to Fas-mediated apoptosis,⁴ or defective p56Lck activity of T cells.⁵ Unfortunately, because of the rarity of this syndrome and the variable clinical presentations and acuity, most studies have relied on a small number of patients without structured longitudinal follow-up. Despite the consensus that ICL is a heterogeneous syndrome in both etiology and clinical manifestations, many immunologic observations appear to be consistent among patients, raising the question of whether they relate more to cause or effect.⁶

The role of chemokines and their receptors expands from organogenesis, trafficking of cells between tissues, and establishment of functional lymphoid microenvironments supporting homeostasis. Dysfunction of chemokine receptors or signaling can affect susceptibility to infections. CXCR4 and CXCL12 could thus play an important role in idiopathic T-cell lymphocytopenia, in terms of both pathogenesis and susceptibility to infections. Cause and effect conundrum aside, decreased CXCR4 expression and CXCL12 responsiveness may contribute to perturbed trafficking and homeostatic signals, further hampering T-cell function or expansion.

The limitations of this study were the small number of patients and the fact that all patients had ICL with an underlying significant infection (there were no clinically asymptomatic ICL patients and no patients with chronic infections but normal CD4⁺ T-cell counts as controls). In addition, there was no systematic evaluation for potential soluble factors that could play a role in CXCR4 down-regulation. It is unclear why the patients in this cohort did

not have a decreased proportion of naive CD4⁺ T cells seen in previous studies^{3,4,6} that could have at least explained the decreased levels of CXCR4 expression.

Cytokine therapies (IL-2 and IFN γ) have been used to improve proliferation, increase survival of T cells, and facilitate clearance of infections with variable success in cases of ICL. The lack of clinical benefit, despite substantial CD4⁺ T-cell expansions with IL-2 therapy in HIV infection, has taught us that cytokine-induced CD4⁺ T-cell increases are not always clinically meaningful. Reversal of a specific T-cell defect in ICL would be a reasonable objective. Defects in chemokine receptors or signaling may thus represent a plausible immunotherapeutic target not investigated to date. Both IL-2 as shown here and IL-7 can up-regulate CXCR4 expression,⁷ so it will be important to determine whether the results of this study can be reproduced in other cohorts and whether clinical outcome correlates with these laboratory measurements. In conclusion, Scott-Algara et al have opened up a new area of investigation in ICL, both from the pathogenesis and etiology standpoint and from the therapeutic perspective. More data are needed to validate these findings in other cohorts and to further evaluate potential underlying genetic defects or soluble factors that may be responsible for these observations.

● ● ● LYMPHOID NEOPLASIA

Comment on Kühnl et al, page 3737

Getting to the root of (it) ALL

Jacob M. Rowe RAMBAM HEALTH CARE CAMPUS

As shown in an elegant study of patients treated on GMALL trials in this issue of *Blood*, Kühnl and colleagues report that the *Brain And Acute Leukemia Cytoplasmic (BAALC)* gene provides a new marker identifying a population of B-lineage ALL patients whose cells express an immature leukemic phenotype and whose outcome is associated with a poor overall response to standard therapy.¹

The overall survival of adults with acute lymphoblastic leukemia (ALL), in sharp contrast with childhood ALL, has not changed significantly over the past 3 decades, with 5-year survival rates between 30% and 40%.² For far too long the therapy of ALL in adults has been based on largely arbitrary and non-

Acknowledgments: The author would like to thank Drs Philip M. Murphy and Michail S. Lionakis for interesting discussions. This work was supported by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

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

REFERENCES

1. Scott-Algara D, Balabanian K, Chakrabarti LA, et al. Idiopathic CD4⁺ T-cell lymphocytopenia is associated with impaired membrane expression of the chemokine receptor CXCR4. *Blood*. 2010;115(18):3708-3717.
2. Smith DK, Neal JJ, Holmberg SD. Unexplained opportunistic infections and CD4⁺ T-lymphocytopenia without HIV infection: an investigation of cases in the United States. The Centers for Disease Control Idiopathic CD4⁺ T-lymphocytopenia Task Force. *N Engl J Med*. 1993;328(6):373-379.
3. Isgro A, Sirianni MC, Gramiccioni C, Mezzaroma I, Fantauzzi A, Aiuti F. Idiopathic CD4⁺ lymphocytopenia may be due to decreased bone marrow clonogenic capability. *Int Arch Allergy Immunol*. 2005;136(4):379-384.
4. Laurence J, Mitra D, Steiner M, Lynch DH, Siegal FP, Staiano-Coico L. Apoptotic depletion of CD4⁺ T cells in idiopathic CD4⁺ T lymphocytopenia. *J Clin Invest*. 1996;97(3):672-680.
5. Hubert P, Bergeron F, Ferreira V, et al. Defective p56Lck activity in T cells from an adult patient with idiopathic CD4⁺ lymphocytopenia. *Int Immunol*. 2000;12(4):449-457.
6. Zonios DI, Falloon J, Bennett JE, et al. Idiopathic CD4⁺ lymphocytopenia: natural history and prognostic factors. *Blood*. 2008;112(2):287-294.
7. Beq S, Rozlan S, Gautier D, et al. Injection of glycosylated recombinant simian IL-7 provokes rapid and massive T-cell homing in rhesus macaques. *Blood*. 2009;114(4):816-825.

leukemia (AML), where cytogenetics have been at the core of therapy for more than 25 years and molecular targeting has come into place over the past 15 years. Thus, it is often difficult to define the prognosis of patients with ALL, leading to either undertreatment or overtreatment.

Age remains the single most important prognostic factor determining outcome. However, this is likely to be, at least in part, a surrogate for intrinsic unfavorable biologic features, such as the Philadelphia chromosome, and is also driven by the inherent inability to tolerate the intensive therapies considered crucial for the management of adults with ALL.³ High white blood cell (WBC) count at presentation, another time-honored prognostic factor, is also associated with known poor prognostic features, such as t(4;11)(q21;q23). Conversely, aberrations such as the t(12;21)(p13;q22), known to confer a better prognosis, are associated with low WBC counts. Apart from the “Burkitt leukemia” mature B-cell ALL, morphology has had no prognostic value in ALL. Time to CR, shorter or longer than 4 weeks, has been used in therapeutic stratification for several decades, although the significance of this has not been demonstrated in a recent very large trial.⁴ Detection of minimal residual disease at various time points is becoming increasingly incorporated into the management of adult ALL and, much like childhood ALL, is likely to be a mainstay in the future determination of the appropriateness of intense therapies in this disease, such as allogeneic hematopoietic stem cell transplantation.⁵ Although immunophenotyping has been considered crucial in the classification of ALL, its discriminatory impact on prognosis and therapy has been marginal and often conflicting. It is only with the detection of specific molecular abnormalities present in either T- or B-lineage ALL, or specific molecular targeting, such as monoclonal antibodies for B-lineage ALL or novel drugs for T-lineage ALL, such as nelarabine, that immunophenotyping is likely to have a significant role in the management of ALL. Only recently have cytogenetics been recognized as having a major role in the classification of Philadelphia chromosome-negative ALL in adults. In addition to the previously recognized t(9;22)(q34;q11), an analysis from the UKALLXII/ECOG2993 study, with the largest prospective cytogenetic database, has