score[2] into a new high-risk group, resulting in 2 groups: low-risk (median survival, 109 months) and high-risk (median survival, 26 months).

External validity and discriminating power are the main attributes of any prognostic classification. Unfortunately, both remain unsolved,[3,4] probably because statistical validity does not always mean clinical value. For this reason, we assembled an unprecedented large number of PMF patients and worked only with variables with previously demonstrated prognostic value. It should be noted that the proportional hazards assumption was checked in all Cox models and the discriminating power of the classification tested not only by the C index of Harrell but also by calculating the model's accuracy to predict actual survival (supplemental Figure 2 in our article). Obviously, because no PMF series as large as the one of the IWG-MRT was available to test the prognostic classification, we relied on resampling, which is a convenient approach for external validation of prognostic models of diseases with low prevalence,[5] as recently acknowledged by Morel and Duhamel.[6] Moreover, we tested the discriminating power of the new classification to predict relative survival, a method less sensitive to the changes in baseline life expectancy occurring over long time periods.

The Lille score has been an important tool in PMF prognostic stratification. However, it was unsatisfactory due to the high proportion of patients in the low-risk group and the poor separation between the intermediate- and high-risk categories, a fact actually acknowledged by Morel and Duhamel when proposing combination of the latter 2 categories. The weakness of the Lille score lies on the fact that it is based on only 2 prognostic factors: hemoglobin less than 10 g/dL and leukocyte count. Because leukocyte values greater than 30×10^9/L are rare in PMF (7.6% of patients in the IWG-MRT series), whereas leukopenia is also infrequent (11% of patients), the score relies mostly on hemoglobin. PMF is not a disease of black or white, certainly not with regard to prognosis, where survival is not a matter of long and short survivors and the spectrum of possibilities is wide. In identifying prognostic variables, the chances of capturing all variables with prognostic relevance substantially increase with larger sample sizes. This was the case of the IWG-MRT study, in which we could demonstrate that other variables also easily available at presentation are important to assess PMF prognosis.

In recent years, considerable advances have been achieved in the molecular characterization of the classic myeloproliferative neoplasms. At clinical level, progress will likely come from collaboration between different investigators. This seemed to be the opinion of other members of the Lille group, who helped to make possible the new PMF prognostic score by contributing to the study.

Francisco Cervantes
Hematology Department, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain

Arturo Pereira
Hemotherapy & Hemostasis Department, Hospital Clinic, Barcelona, Spain

Ayalew Tefferi
Hematology Department, Mayo Clinic, Rochester, MN

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Francisco Cervantes, MD, Hospital Clinic, Villarroel 170, Barcelona 08036, Spain; e-mail: fcervan@clinic.ub.es.

References

1. Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. *Blood.* 2009;113(13):2895-2901.
2. Dupriez B, Morel P, Demory JL, et al. Prognostic factors in agnogenic myeloid metaplasia: a report on 195 cases with a new scoring system. *Blood.* 1996; 88(3):1013-1018.
3. Graf E, Schmoor C, Sauerbrei W, Schumacher M. Assessment and comparison of prognostic classification schemes for survival data. *Stat Med.* 1999; 18(17-18):2529-2545.
4. Altman DG, Royston P. What do we mean by validating a prognostic model? *Stat Med.* 2000;19(4):453-473.
5. Harrell FE, Lee KL, Mark DB. Multivariate prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med.* 1996;15(4):361-387.
6. Morel P, Duhamel A, Gobbi P, et al. International prognostic scoring system for Waldenström macroglobulinemia. *Blood.* 2009;113(18):4163-4170.

To the editor:

Chemokine receptors as therapeutic tools in Hodgkin lymphoma: CCR4 and beyond

We read with great interest the paper by Di Stasi and colleagues[1] demonstrating that enforced expression of the chemokine receptor CCR4 improves the homing of CD30-specific chimeric antigen receptor (CAR-CD30)–modified effector T cells to thymus- and activation-regulated chemokine/CC chemokine ligand 17 (TARC/CCL17)–producing $CD30^+$ Hodgkin lymphoma (HL) cells, thereby promoting their antitumor effects in vivo. This elegant work indicates a possible way to exploit the peculiar chemokine milieu of HL for therapeutic purposes.

Reed-Sternberg (RS) cells produce large amounts of TARC/CCL17 and macrophage-derived chemokine (MDC)/CCL22, 2 chemokines capable of recruiting CCR4-expressing cell subsets, including type 2 T helper (Th2) cells and regulatory T cells (Tregs). The relevance of both of these chemokines to the pathobiology of HL is reinforced by the presence of elevated serum levels of TARC and MDC in the great majority of HL patients.[2] Although TARC and MDC have been regarded as important determinants of T-cell migration within the HL microenvironment, $CCR4^-$ Th2 and Tregs cells are overwhelming in HL lesions, and only a minority of $CCR4^+$ T cells can be usually found by immunohistochemistry in HL-involved tissues.[1,3,4] Accordingly, only 11% (± 9%) of peripheral blood T cells from HL patients with active disease expressed CCR4 and slightly migrated in the presence of HL cell lines' supernatants.[1]

The expression of CCL5/regulated on activation normal T-cell expressed and secreted (CCL5/RANTES) and its receptor CCR5 by RS cells has been recently documented.[5] CCL5/RANTES is a chemokine capable of attracting CCR3- and CCR5-expressing cells, including Tregs and Th2 cells, eosinophils, and mast cells.[5,6] HL cell lines produce a functional CCL5 capable of inducing a remarkable migration of purified $CD4^+$ T cells, eosinophils, and mast cells.[5,6] Interestingly, both CCR3 and CCR5 are expressed on T cells of the HL microenvironment but not on T lymphocytes residing

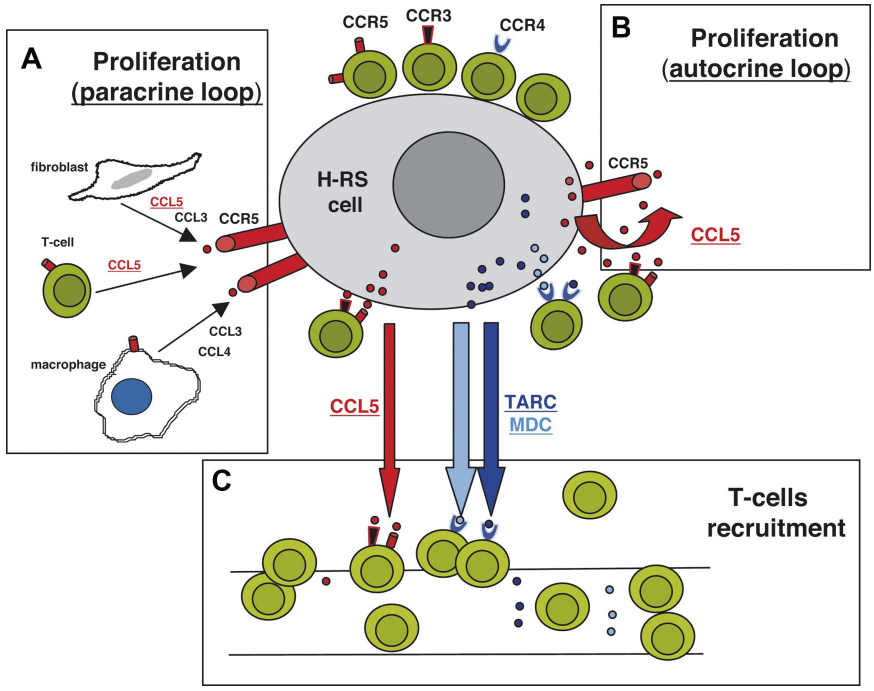

Figure 1. Schematic illustration showing the involvement of TARC, MDC, and CCL5 in microenvironment formation and RS cell growth. (A) The production of CCR5 ligands (CCL5, CCL3, and CCL4) by T cells, macrophages and fibroblasts may contribute to RS cells' proliferation (paracrine loop). (B) CCL5 produced by RS cells may represent an autocrine growth factor. (C) CCL5 produced by RS cells, together with TARC and MDC, may recruit CCR5$^+$, CCR4$^+$, or CCR3$^+$ T cells.

in normal lymph nodes.[7] CCR3 is evenly distributed among CD4$^+$ and CD8$^+$ cells, whereas CCR5, like CCR4, is mostly expressed by CD4$^+$ cells.[7,8] It is, therefore, tempting to speculate that enforced expression of CCR5 might, in turn, maximize homing of CAR-CD30–modified effector T lymphocytes to RS cells.[1]

Most interestingly, recent reports demonstrated that chemokines play a critical role also in tumor growth and survival.[9,10] In this regard, we and others have shown that RS cells express CCR5 both in vivo and in vitro,[5,8] and that its ligand CCL5 has a direct effect on RS cells survival and proliferation (Figure 1).[5] This finding reflects a peculiar property of CLL5 since, differently from TARC and MDC, this chemokine was shown to directly regulate growth and survival of tumor cells also in other experimental models, including prostate and breast cancer.[9,10] Then CCR5 targeting by effector T cells, through the modalities described by Di Stasi et al,[1] may maximize the activity of adoptively transferred antitumor T cells through interference with the autocrine and paracrine growth regulatory loops between RS cells and CCL5.[5]

Donatella Aldinucci
Experimental Oncology 2, Centro di Riferimento Oncologico, Istituto Di Ricovero e Cura a Carattere Scientifico (IRCCS), Aviano, Italy

Antonio Pinto
Hematology-Oncology and Stem Cells Transplantation Unit, Istituto Nazionale Tumori, Fondazione "G. Pascale," IRCCS, Naples, Italy

Annunziata Gloghini
Department of Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy

Antonino Carbone
Department of Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy

Acknowledgments: This work was supported in part by the Associazione Italiana per la Ricerca sul Cancro (AIRC), Milan, Italy and the Ministero della Salute, Ricerca Finalizzata FSN, IRCCS, Rome, Italy (D.A. and A.P.) and by a grant from the Ministero della Salute, Rome, within the framework of the Progetto Integrato Oncologia-Advanced Molecular Diagnostics "Multidimensional characterization of tumors" project, and the Ministero della Salute, Ricerca Finalizzata FSN, IRCCS, Rome, Italy (A.C.).

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Donatella Aldinucci, Experimental Oncology 2, Centro di Riferimento Oncologico, IRCCS, via F. Gallini, 2, 33081 Aviano (PN), Italy; e-mail: daldinucci@cro.it.

References

1. Di Stasi A, De Angelis B, Rooney CM, et al. T lymphocytes coexpressing CCR4 and a chimeric antigen receptor targeting CD30 have improved homing and antitumor activity in a Hodgkin tumor model. *Blood.* 2009;113(25):6392-6402.
2. Niens M, Visser L, Nolte IM, et al. Serum chemokine levels in Hodgkin lymphoma patients: highly increased levels of CCL17 and CCL22. *Br J Haematol.* 2008;140(5):527-536.
3. Ohshima K, Tutiya T, Yamaguchi T, et al. Infiltration of Th1 and Th2 lymphocytes around Hodgkin and Reed-Sternberg (H&RS) cells in Hodgkin disease: relation with expression of CXC and CC chemokines on H&RS cells. *Int J Cancer.* 2002;98(4):567-572.
4. Vermeer MH, Dukers DF, ten Berge RL, et al. Differential expression of thymus and activation regulated chemokine and its receptor CCR4 in nodal and cutaneous anaplastic large-cell lymphomas and Hodgkin's disease. *Mod Pathol.* 2002;15(8):838-844.
5. Aldinucci D, Lorenzon D, Cattaruzza L, et al. Expression of CCR5 receptors on Reed-Sternberg cells and Hodgkin lymphoma cell lines: involvement of CCL5/Rantes in tumor cell growth and microenvironmental interactions. *Int J Cancer.* 2008;122(4):769-776.
6. Fischer M, Juremalm M, Olsson N, et al. Expression of CCL5/RANTES by Hodgkin and Reed-Sternberg cells and its possible role in the recruitment of mast cells into lymphomatous tissue. *Int J Cancer.* 2003;107(2):197-201.
7. Buri C, Körner M, Schärli P, et al. CC chemokines and the receptors CCR3 and CCR5 are differentially expressed in the nonneoplastic leukocytic infiltrates of Hodgkin disease. *Blood.* 2001;97(6):1543-1548.
8. Machado L, Jarrett R, Morgan S, et al. Expression and function of T cell homing molecules in Hodgkin's lymphoma. *Cancer Immunol Immunother.* 2009;58(1):85-94.
9. Vaday GG, Peehl DM, Kadam PA, Lawrence DM. Expression of CCL5 (RANTES) and CCR5 in prostate cancer. *Prostate.* 2006;66(2):124-134.
10. Murooka TT, Rahbar R, Fish EN. CCL5 promotes proliferation of MCF-7 cells through mTOR-dependent mRNA translation. *Biochem Biophys Res Commun.* 2009;387(2):381-386.