Langerhans cells), and macrophages, are abundant within MF/SS-involved skin (see figure). A recently described subset of peripheral T-cell lymphomas expresses CCR4 as part of the transcriptional repertoire of GATA-3, the "master" transcriptional regulator driving Th2 differentiation. GATA-3 is not only expressed by Treg cells residing within barrier sites such as the skin, but also by MF/SS cells, and may drive CCR4 expression in these cells.[3,4] Furthermore, GATA-3–dependent cytokines produced by malignant T cells, particularly interleukin-4/interleukin-13, functionally polarize lymphoma-associated macrophages (LAMs). Polarized LAMs, in turn, produce CCL17 and CCL22, which interact with CCR4 on malignant T cells and facilitate tumor–microenvironment crosstalk. The CCL17/CCL22–CCR4 axis in MF/SS is further maintained by the absence of CD26, a dipeptydil peptidase that normally inactivates CCR4 ligands.

In addition to its role in regulating cell homing and trafficking, CCR4 engagement may also promote cell growth and survival. However, cells can become desensitized to CCR4 through receptor internalization, a homeostatic regulatory mechanism. Gain-of-function mutations in the CCR4 cytoplasmic domain inhibit CCR4 internalization and promote phosphatidylinositol 3-kinase/AKT activation. These mutations were recently described in ~25% of adult T-cell leukemia/lymphomas.[5] Clearly, CCR4 has a pathogenic role in MF/SS and other T-cell lymphoproliferative disorders and is an attractive therapeutic target.

Mogamulizumab depletes CCR4-expressing cells by antibody-dependent, cell-mediated cytotoxicity (ADCC). Defucosylation of its Fc region culminates in enhanced Fc receptor binding, permitting ADCC at lower antigen densities and at lower ratios of effector cells to target cells. Or, viewed in a different light, mogamulizumab completely cleared the peripheral blood of malignant T cells in >50% of patients at a concentration (1 mg/kg) that is approximately 1/10th that of rituximab (ie, 375 mg/m^2 or ~10 mg/kg). In addition to directly targeting malignant T cells expressing CCR4, mogamulizumab depletes Treg cells, an important therapeutic target in many human cancers because of their role in suppressing host antitumor immunity. In a recent companion study, Duvic and her colleagues observed a significant reduction in peripheral blood Treg cells following treatment with mogamulizumab.[6] A similar reduction in Treg cells was also observed in a mogamulizumab-treated cohort of peripheral T-cell lymphoma patients.[7] Therefore, in addition to directly targeting malignant T cells expressing CCR4, mogamulizumab may favorably influence the tumor microenvironment upon Treg depletion (see figure) without triggering clinically significant autoimmune complications. Given its dual mechanism of action, mogamulizumab may effectively "kill 2 birds with 1 stone" and may be rationally combined with other immunomodulatory agents in future studies. For example, immunomodulatory drugs and agonistic antibodies targeting T-cell costimulatory receptors, including CD137 (4-1BB),[8,9] may further augment ADCC and T cell–mediated immunity. Because PD-L1 is frequently expressed in MF/SS,[10] anti–PD-L1/PD-1 checkpoint blockade is a similarly attractive combinatorial approach. The clinically meaningful responses observed with mogamulizumab in a heavily pretreated cohort of MF/SS patients, and the possibility of future combinatorial strategies (see figure), suggest that we are witnessing the dawn of an exciting new era in MF/SS management.

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

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● ● ● LYMPHOID NEOPLASIA

Comment on Arribas et al, page 1922

DNA methylation in lymphoma: an opportunity?

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Epigenetic mechanisms, including DNA methylation, play an important role in not only the development and maturation of normal cells, but also the development and progression of malignant cells.[1] In this edition of *Blood*, Arribas et al show that DNA methylation profiling identifies 2 subtypes of splenic marginal zone lymphoma with different clinical and genetic features.[2] These findings provide an opportunity to better understand the biology of marginal zone lymphoma and optimize therapy by using demethylating agents to reverse the high-methylation phenotype and thereby target malignant B cells.

Splenic marginal zone lymphoma is an uncommon B-cell malignancy representing ~8% of all non-Hodgkin lymphomas.[3] This disease commonly arises in the context of autoimmune processes or chronic infectious diseases. Previous sequencing studies have identified recurrent mutations in key pathways in this disease, notably NOTCH2 mutations in approximately one-quarter of patients. Furthermore, loss of chromosome 7q31-32 is also frequently seen in marginal zone lymphoma.[4,5] Although many patients have a good prognosis, the outcome of this disease can vary, with some patients having a more aggressive disease course or disease transforming to a more aggressive phenotype. Arribas et al, by performing integrated genome-wide DNA-promoter methylation profiling and comparing this with gene-expression profiling, identified a cluster of patients with high promoter methylation who had a very poor outcome compared with others who had a much lower methylation profile. The prognostic relevance of this profile was tested in a discovery set and subsequently validated in an independent cohort of patients. These findings provide an opportunity for patients with marginal zone lymphoma who have a poor prognosis to be prospectively identified based on their methylation profile.

DNA methylation is an epigenetic mechanism that has been implicated in the pathogenesis of chronic inflammatory diseases as well as malignancies, by regulating the differentiation, apoptosis, proliferation, and activation of different cell types.[6,7] This is achieved through alteration of gene expression and regulation of cellular phenotype. The work by Arribas et al identifies methylation of 3 genes—*KLF4*, *CACNB2*, and *HTRA1*—as most important in defining the high-methylation cohort that is associated with a poor outcome. By integrating the methylation data with paired-gene-expression profiling data, they show an inverse correlation between methylation status and expression levels of these and other genes. They also show, using a functional network analysis, that methylation changes have a direct effect on transcription levels of a variety of key genes in the pathogenesis of marginal zone lymphoma. These include genes with significant roles in the fate and differentiation of cells, in cell communication and signal transduction, and in regulation of apoptosis.

These different methylation profiles in splenic marginal zone lymphoma present a further opportunity to treat patients in the high-methylation cohort with demethylating agents such as decitabine. In this study, the authors found that the use of decitabine could reverse the methylation profile in both cell lines and primary patient specimens. Decitabine has been approved for use in the treatment of patients with myelodysplastic syndromes, including previously treated and untreated, de novo, and secondary myelodysplastic syndrome.[8] Decitabine has been used to treat patients with lymphoma and chronic lymphocytic leukemia but has shown only modest clinical benefit.[9] The use of decitabine in patients with splenic marginal zone lymphoma, specifically those with a high methylation profile, may be an opportunity to treat a group of patients who have a poor outcome with standard treatment and yet may be more likely to respond to this agent. The rational use of hypomethylating agents in a cohort of marginal zone lymphoma patients who are most likely to benefit is a potential future treatment approach.

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

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● ● ● MYELOID NEOPLASIA

Comment on Savona et al, page 1857

Speaking a common language in MDS/MPNs

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In this issue of *Blood*, Savona and an international consortium of clinical investigators propose uniform response criteria for treatment trials enrolling adult patients with myelodysplastic/myeloproliferative neoplasms (MDS/MPNs).[1] Such a proposal is needed because new drugs are finally being tested in these rare "overlap" syndromes that have both dysplastic and proliferative pathological features, and neither the International Working Group (IWG) response criteria for myelodysplastic syndromes[2] nor the IWG Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) response criteria for myelofibrosis[3] or for other myeloproliferative neoplasms fit such patients well.

MDS/MPNs are clinically heterogeneous and biologically poorly understood, although some pathophysiological insights have begun to emerge from high-throughput genetic analyses and murine models.[4] Four somewhat distinct clinicopathological