expressed independently of Aire. The results reveal a previously unappreciated role for p53 in the expression of many TRAs that appears distinct from known functions of Aire and Fez2.

The loss of TRA expression is predicted to result in autoimmunity, and indeed, the authors report autoimmune defects in p53cko animals, including increased infiltration of lymphocytes into salivary and lacrimal glands resulting in inflammatory lesions. One potential cause of autoimmunity is a reduction in the number or function of Tregs, and the authors showed that when p53cko-derived thymocytes were transferred to T-cell deficient mice, the mice developed autoimmune symptoms, including diarrhea and accelerated weight loss. Thus, T cells educated by p53–deficient mTECs are not appropriately self-tolerant.

It is unclear whether and how these newly identified functions of p53 in mTECs align with the well-established roles it plays in response to cellular stress. Past work indicates that Aire in mTECs associates with proteins implicated in the DNA damage response, including Ku80, DNA-PKcs, γH2AX, and PARP-1.7 One possibility is that mechanisms driving transcription of otherwise repressed genes in mTECs result in DNA damage and so stabilize p53 protein in a subpopulation of mTECs. An alternative possibility derives from the observation that p53 can function as a transcriptional activator in cells without stress.8 An intriguing possibility is that some transcription factors, including p53, may promote the expression of the same gene targets in mTECs as they do in other tissues. The absence of a given transcription factor specifically in mTECs would result in altered expression of its respective target genes in mTECs, but not other tissues, resulting in tissue-specific autoimmunity. A prediction of this model is that mice that lack activity of the transcription factor in all tissues would not display such autoimmune symptoms. Indeed, the autoimmune phenotypes reported here for mice lacking p53 in TECs have not been previously reported in mice with germ line deficiency of p53.3 Whatever the mechanism, it will be fascinating to determine how this versatile transcription factor contributes to self-tolerance.

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**REFERENCES**


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**LYMPHOID NEOPLASIA**

Comment on Balsas et al, page 501

**SOX11 holds mantle cell lymphoma’s key to home**

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In this issue of *Blood*, Balsas et al define a SOX11-driven program supporting key cellular processes (cell adhesion, homing, and invasion) underlying some of the aggressive clinical and biological features of mantle cell lymphoma (MCL).1

**MCLs** are lymphoid malignancies with aggressive clinical features and poor prognoses. Typically, MCLs are characterized by widespread dissemination and poor response to therapy, which may explain the disproportionate contribution of this rare lymphoma type to overall lymphoma mortality.2 In fact, the extension to extranodal sites (ie, gastrointestinal tract) and bone marrow (up to 60% of cases) implies a natural tendency for dissemination and homing to different tissue compartments, which in turn can affect cell survival and sensitivity to therapy.3 Previous studies had related this ability of MCL cells to home in different tissues to the expression of certain molecules involved in cell adhesion and cellular crosstalk, including CXCR4, VLA-4, CCL4, and TNFSF9,4 but the underlying mechanism remained largely unexplained.

Within the clinical spectrum of MCL, there is a small fraction of patient cases with indolent clinical behavior. These indolent MCL cases feature cyclin D1+ clonal B-cell populations with the hallmark t(11;14)(q13;q32) rearrangement found in a vast majority of MCLs but have a rather unusual clinical presentation, with prominent leukemic, non-nodal distribution and a nonprogressive clinical course that is in stark contrast to that of typical MCL.5,6 Most notably, they also lack expression of SOX11, a transcription factor that is overexpressed in MCL but not other B-cell non-Hodgkin lymphomas and is believed to play a prominent role in the biology of these malignancies.7,8 Reasonably, these observations prompted Balsas et al to investigate the possibility that SOX11 could also be responsible for the apparent differences in tissue dissemination between these 2 MCL groups.

The authors first used an integrative computational approach, revisiting previously published SOX11 chromatin immunoprecipitation microarray analysis and gene expression data,9 in combination with pathway analysis computational tools. Using this strategy, they found that cell migration and stromal stimulation signatures correlated with the expression of SOX11 and that CXCR4 and PTK2 (encoding for focal adhesion kinase [FAK]), 2 genes with known roles in these
processes, were most prominent among all direct SOX11 gene targets (see figure). They further confirmed the latter observation in a series of MCL cell lines, where SOX11 expression was artificially manipulated through the constitutive expression of SOX11 or RNA interference with short hairpin RNAs. Interestingly, expression of the CXCR4 chemokine receptor had been previously reported to be elevated in a large fraction of MCL cell lines and had been shown to mediate cell migration and nurture crosstalk interactions between MCL cells and bone marrow stromal cells.4

Through a set of carefully crafted in vitro and in vivo experiments using engineered MCL cell lines and chemical inhibitors of CXCR4 and FAK activity, Balsas et al further confirmed and extended these fundamental observations. More importantly, they showed that expression of these programs depends (although not uniquely) on SOX11. Specifically, manipulation of SOX11 expression in xenografted MCL cell lines or, alternatively, chemical inhibition of CXCR4 and FAK signaling can alter the tissue distribution of the cancerous MCL cells. This results in contrasting patterns of widespread disease (bone marrow and lymph nodes) or disease significantly confined to peripheral blood, akin to that of patients with indolent MCL (see figure). These findings have obvious conceptual and translational implications, because they mechanistically explain how differential expression of SOX11 in the MCL disease spectrum may actually explain the exclusively leukemic, non-nodal presentation of SOX11–indolent MCL cases and their benign clinical behavior.

These results can also be translated into notable therapeutic considerations. Particularly, and as previously suggested by others,4 their findings may offer a foundation for a much-needed alternative approach to MCL treatment. Consistent with previous studies, Balsas et al showed that inhibition of the CXCR4/FAK axis prevented homing and crosstalk of MCL cells with peripheral tissue niches and that this effect resulted in increased sensitivity to conventional therapeutic agents like bortezomib by counteracting cell adhesion–mediated drug resistance. Cell adhesion–mediated drug resistance is a cytoprotective response supported by cell–cell interactions between cancerous and marrow stromal cells and has also been found in multiple myeloma and other hematologic malignancies that typically home in the bone marrow, like chronic myelogenous leukemia.10

Thus, in principle, blockade of MCL–stroma interactions with specific molecules would facilitate the mobilization of the cancerous cells into peripheral blood and away from protective tissue microenvironments, thereby increasing the therapeutic efficacy of conventional MCL therapies.

In summary, the study by Balsas et al provides an important and clarifying piece to the puzzle of MCL biology and further highlights SOX11 as a key driver of critical aspects of this disease. Furthermore, as occurs with all exciting science, it also raises some notable questions. Which other genes and programs are involved in the tissue homing and microenvironment interactions of MCL cells? To what extent are these programs controlled by SOX11? Are there any natural feed-forward signaling loops between lymphoid cells and the microenvironment that reinforce SOX11 expression? And if so, is the lack of SOX11 expression in indolent MCL cases a result of undiscovered defects in adhesion molecules or chemokine receptors? Finally, given the remarkable similarities between lymphoid and neuronal cells, one wonders if these programs may be reminiscent of those controlled by SOX11 during early neurogenesis and tissue remodeling. Overall, the findings of Balsas et al will keep many researchers busy with efforts that could further improve our understanding of MCL biology and could translate into unprecedented diagnostic and therapeutic strategies much needed for these patients.2

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REFERENCES
Comment on Kamata et al, page 514

**KRAS**G12D, pulmonary LCH, and atorvastatin

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In this issue of *Blood*, Kamata et al elegantly demonstrate in mice that (1) **KRAS**G12D (but not **BRAF**V600E) mutation transfection in pulmonary myeloid cells induces an isolated pulmonary (IP)-Langerhans cell histiocytosis (LCH)–like neoplasm, via phosphatidylinositol 3-kinase (PI3K) activation, and that (2) atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor that inhibits RAS interaction of PI3K, reduces tumor burden in vivo.

LCH is a rare and heterogeneous disease that has been called by several names, including “histiocytosis X,” which emphasizes the ambiguity of its cellular origin and pathogenesis. Clinical presentation and prognosis are highly variable. For example, in young adults, the disease often involves a single organ, has a favorable prognosis, and often resolves spontaneously. In infants, the disease presents as a systemic leukemia-like disease that requires chemotherapy. Therefore, age of onset roughly characterizes 2 distinct clinical forms of the disease with distinct etiologies. In adults, 2 additional presentations of the disease are a “systemic” form with single or multiorgan involvement with symptoms such as weight loss and fever or the IP-LCH, in which smoking is a significant risk factor. IP-LCH appears, therefore, as a distinct disease with a worse response to treatment than the usual adult systemic disease. The reasons for these differences are not known.

The study by the authors addressed many of these issues by exploring the pathophysiology revealing a new therapeutic option in IP-LCH. Recently, molecular defects have been shown to be involved in both LCH and Erdheim-Chester disease (ECD), a non-Langerhans cell histiocytosis, which share close pathogenic mechanisms and can be found in the same patient and even in the same biopsy site. **BRAF**V600E and NRAS molecular defects, leading to RAF/IRAS/MEK/extracellular signal-regulated kinase activation, have been described in both diseases, leading to their classification as myeloid inflammatory tumors possibly treatable with targeted anti-**BRAF** or anti-MEK molecules.3,4

The study by Kamata et al clearly shows that IP-LCH and systemic LCH have distinct cellular origins and oncogenic mechanisms in their mouse model. Indeed, the authors demonstrated that IP-LCH originates from pulmonary resident cells that correspond to myeloid and not dendritic cells. Moreover, they showed that only **KRAS**G12D, but not **BRAF**V600E expression, is able to induce tumorigenesis in these monocytic cells, probably via PI3K pathway activation. These findings separate IP-LCH from systemic LCH that originates in dendritic cells acquiring the **BRAF** mutation leading to oncoprotein **BRAF**V600E expression, which activates the MEK/extracellular signal-regulated kinase pathway. **KRAS** mutations have been researched but never described in LCH.3,4 In ECD, only 2 patients with **KRAS** mutations have been identified, corresponding to a **KRAS**G12D defect present at baseline in 1 patient and a **KRAS**G12D defect in the context of acquired resistance to an anti-**BRAF** treatment in the other.3,5 Several authors found concordance among tissue, plasmatic, and/or urinary cell-free DNA for the various mutations involved in ECD or LCH, including the ECD patient with the posttreatment acquired **KRAS**G12D defect. Finally, the **KRAS** mutation could be a specific molecular defect of IP-LCH among all untreated histiocytic disorders; it could even be a hallmark of IP-LCH if other MAPK (**MAP2K1** and **NRAS**) and PI3K pathway (**PIK3CA**) genes are proven to not induce this single disease location, as shown for **BRAF** mutation by the study authors. In the literature, supposed IP-LCH cases have been described in young children with secondary extrapulmonary involvement; however, because “systemic” LCH is a relapsing disorder characterized by wide temporal and anatomical distribution of organ involvement over decades, pulmonary-onset LCH is not necessarily IP-LCH. The term “primary pulmonary LCH”6 is a better name than IP-LCH to avoid any potential confusion.

The in vivo demonstration by the authors of IP-LCH–like disease control with atorvastatin is of clinical interest. Indeed, smoking cessation is frequently the only therapeutic intervention in IP-LCH, but actual efficacy of smoking cessation is unknown and patients do not always accurately report their smoking history. Indeed, smoking cessation is sometimes insufficient to control pulmonary function decline, with a need then for steroids and various cytotoxic drugs.2,7 Unlike pediatric LCH for which vinblastine and steroids are the validated initial treatment, a validated first-line chemotherapy regimen is not available for adult LCH. We recently showed in a retrospective study that vinblastine and steroids is an...
SOX11 holds mantle cell lymphoma's key to home

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