The success of Nathwani et al in using gene therapy to establish long-term expression of factor IX in patients with hemophilia B is among a string of recent successes in human gene therapy, which have restored vision to the sightless and released immunodeficient patients from isolation.[8-10] There are still obstacles for gene therapy before it will become a routine treatment, but studies such as that by Martino et al are an excellent example of how bench to bedside and back to bench can help to overcome these obstacles.

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

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● ● ● LYMPHOID NEOPLASIA

Comment on Vegliante et al, page 2175

SOX11 is a mantle cell lymphoma oncogene

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In this issue of *Blood*, Vegliante et al establish for the first time the oncogenic role and mechanisms of SOX11 in mantle cell lymphoma.[1]

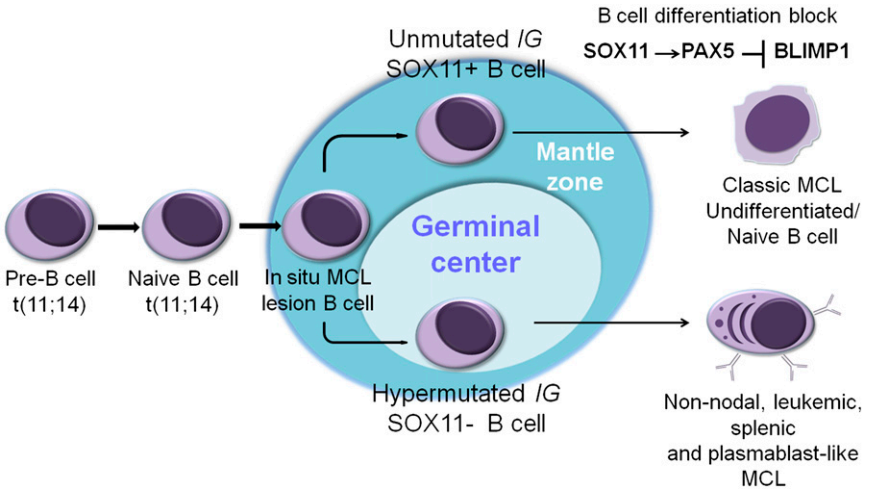
Mantle cell lymphomas (MCL) are CD5-positive mature B-cell lymphoid tumors derived from antigen-naive pregerminal center B cells located in the mantle zone surrounding normal germinal center follicles.[2,3] The t(11;14)(q13;q32), a chromosomal rearrangement driving overexpression of the cyclin D1 gene, is a hallmark of this disease.[2] Still, the full spectrum of genetic lesions involved in the pathogenesis of MCL remains to be established. MCLs are typically aggressive tumors associated with poor prognosis. However, recent studies have identified a distinct clinical group of t(11;14)(q13;q32)-positive MCL cases that show an indolent clinical course and prolonged survival.[4-6] Notably, smoldering MCLs show hypermutated immunoglobulin genes indicating that they originate from postgerminal center B cells. In addition, they characteristically lack expression of *SOX11*, a transcription factor aberrantly and universally expressed at high levels in aggressive classic MCL cells. Most notably, and in contrast with its high levels of expression in classic MCL, *SOX11* is not expressed in lymphoid progenitors and mature B-cell populations.

Based on these observations, Vegliante and coworkers proposed that aberrant expression of *SOX11* could play an oncogenic role in the pathogenesis of classic MCL. The underlying hypothesis is that SOX11 could sit atop of an oncogenic transcriptional network controlling critical effector target genes and pathways responsible for B-cell transformation and the aggressive clinical course typically associated with SOX11-high MCLs. Should this premise hold true, deciphering the structure of the SOX11-controlled oncogenic network in MCL could identify new therapeutic targets for the treatment of this disease.

Toward this goal, these investigators first addressed the identification of SOX11 direct target genes via chromatin immunoprecipitation microarray analyses using a promoter array platform. These experiments uncovered over 1000 promoter sequences occupied by SOX11 in MCL cells. In addition, and to establish the specific role of SOX11 in the control of gene expression in MCL, they analyzed the gene expression changes associated with *SOX11* small hairpin RNA knockdown. Despite the complexity of the data and the large number of genes controlled by SOX11 identified, 2 major findings stood out from these analyses. First, *SOX11* knockdown in MCL cells results in upregulation of gene expression signatures associated with plasma cell differentiation while suppressing the genetic programs characteristic of B cells. In addition, *PAX5*, a key transcription factor strictly required for the establishment of B-cell identity[7] and a major negative regulator of plasma cell differentiation,[8] stood out as one of the most significant direct target genes upregulated by SOX11 in MCL cells.

Consistently, *SOX11* knockdown cells showed transcriptional and immunophenotypic changes consistent with repression of the B-cell program and upregulated *PRDM1/BLIMP1*, a transcription factor tumor suppressor gene involved in the termination of the B-cell program during plasma cell differentiation.[9] Notably, *PRDM1/BLIMP1* is a known direct target gene repressed by PAX5.[8] Moreover, xenograft studies demonstrated a marked loss of tumorigenic potential in *SOX11* knockdown cells.

The relevance of these findings was then elegantly highlighted by integrative analyses of *SOX11* small hairpin RNA knockdown induced signatures with those derived from a panel of well-characterized MCL clinical samples. These studies showed significant



Hypothetical models of SOX11-possitive vs SOX11-negative MCL. The naive B cell carrying the t(11;14) colonizes the mantle zone of the lymphoid follicle and generates an in situ MCL lesion. Most MCLs evolve from these cells in the marginal zone with no or limited *IGHV* somatic mutations and SOX11 expression. SOX11 overexpression in conventional MCL may block the cells in a mature B-cell stage, preventing their further differentiation thought the SOX11-PAX5-PRDM1/BLIMP regulatory axis. Alternatively, some cells with the t(11;14) may enter the germinal center, undergo *IGHV* somatic hypermutation, and lack expression of SOX11. SOX11 may modulate the mature B-cell and early plasma cell differentiation program in MCL.

enrichment of SOX11 upregulated genes in SOX11-positive tumors and SOX11 downregulated transcripts in SOX11-negative lymphomas, respectively. Consistently, SOX11-positive MCL signatures were enriched in B-cell vs plasmablast and PAX5 activated gene sets, whereas the SOX11-negative MCL program was characteristically enriched in plasmablast-associated transcripts. Moreover, histologic and flow cytometry examination showed signs of focal plasmacytic differentiation and downregulation of B-cell marker expression in SOX11-negative tumors.

Overall, these results demonstrate an essential role for SOX11 in the growth of MCLs in vivo and support a role for the SOX11-PAX5-PRDM1/BLIMP1 regulatory axis in the maintenance of B-cell features and suppression of plasma cell differentiation programs in MCL. Still, several questions remain to be elucidated: What drives the aberrant expression of SOX11 in MCL? What are the specific mechanisms mediating the antilymphoma effects of SOX11 inactivation observed in mouse tumor xenografts? Is there a physiologic counterpart of the MCL-associated SOX11-PAX5-PRDM1/BLIMP1 regulatory axis in normal B cells? If so, what are the SOX factors upstream of PAX5-PRDM1/BLIMP1 in B-cell development?

The studies by Vegliante et al highlight the power of integrative analyses coupling carefully crafted mechanistic studies, genomic analyses, and expert histopathologic examination of clinical samples to uncover basic mechanisms underlying the biology of MCL.

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● ● ● TRANSPLANTATION

Comment on Inamoto et al, page 2340

Order out of chaos

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In all chaos there is a cosmos, in all disorder a secret order. (Carl Jung)

In this issue of *Blood*, Inamoto et al show that chronic graft-versus-host disease (cGVHD) has emerged from the chaos as a distinct disease with validated staging and response criteria. Inomata et al also show that there is order in steroid refractory cGVHD that can be exploited to better design and interpret therapeutic trials.[1]

Basic and clinical interest in chronic graft-versus-host disease (cGVHD) has exploded since the publication of the National Institutes of Health (NIH) Consensus Criteria for cGVHD in 2005-2006 (summarized in Pavletic et al[2]). Why this explosion? Quite simply, communication. Instead of each investigator living in his or her own parallel universe and having no effective way of communicating the extent of disease or the response to treatment, investigators now have a common language they can use to work with each other. Admittedly, much of the initial published work has been in validating and refining the NIH criteria.[3,4] But, as demonstrated by the Inamoto et al article, the order necessary for true basic and clinical advances is becoming evident.