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.2-10 There are still obstacles for gene therapy before it will become a routine treatment, but studies such as that by Martin 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 MCLs. 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 identity7 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...
The studies by Vegliante et al highlight the power of integrative analyses coupling PRDM1/BLIMP1 in B-cell development? are the SOX factors upstream of PAX5-regulatory axis in normal B cells? If so, what associated SOX11-PAX5-PRDM1/BLIMP1 a physiologic counterpart of the MCL-observed in mouse tumor xenografts? Is there antilymphoma effects of SOX11 inactivation are the specific mechanisms mediating the anti lymphoma 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 PRDM1/BLIMP1 in B-cell development? are the SOX factors upstream of PAX5-regulatory axis in normal B cells? If so, what associated SOX11-PAX5-PRDM1/BLIMP1 a physiologic counterpart of the MCL-observed in mouse tumor xenografts? Is there antilymphoma effects of SOX11 inactivation are the speci 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 anti lymphoma 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?

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**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. 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 al2). Why this explosion? Quite simply, communication. 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. But, as demonstrated by the Inamoto et al article, the order necessary for true basic and clinical advances is becoming evident.
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