Comment on Gentles et al, page 3158

Stem cell mimicry: key to transformation?

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In this issue of Blood, Gentles and colleagues used a computational model to investigate FL and transformed DLBCL, and identified the acquisition of an ESC-like signature as a key feature of transformation.1

Although follicular lymphoma (FL) is an indolent tumor, up to one-third of cases can progress to a more aggressive and usually fatal disease, with most cases transforming to diffuse large B-cell lymphoma (DLBCL). Transformation appears to be a complex process involving genomic, transcriptional, and epigenetic mechanisms that have lent themselves to whole-genome screening approaches. Unfortunately, analysis of gene expression to date has largely been restricted to the expression of single genes and cannot take into account the full complexity of the disease. Newer computational models analyze the biology of tumors by considering gene interaction networks and molecular pathways rather than separate genes. These approaches have already been applied to other epithelial tumors identifying signatures that drive cancer progression.2 In their paper, Gentles and colleagues performed a re-analysis of gene expression data from a study of FL-transformed DLBCL3 and generated a network that focused on the gene expression programs relevant to the transformation process. The

Schematic model of the possible patterns of evolution of FL. The cell of origin of FL and transformed DLBCL could be a cell that has already acquired the t(14;18) chromosomal aberration. After migrating from the bone marrow to the lymph node, this cell could acquire further genetic changes (gc) and subsequently the epigenetic aberrant methylation of the PcG genes (ec) before progressing to tumor (A). Alternatively, epigenetic changes of PcG target genes can occur in the BM (B) or in the lymph node (C) and subsequently evolve into FL or DLBCL after additional genomic events.
power of models such as these is that they can capture modules—a group of genes regulated in concert by a shared regulation program—and thus the key events regulating transformation. It is reassuring to see that, within the module network, they also captured events already known to be important in the transformation process.

They first observed that multiple modules contained genes expressed in embryonic stem cells (ESCs). Further validation comes from the finding that the ESC1 module is a predictor of survival associated with propensity for transformation and that the ESC-like module was enriched for genes induced specifically by MYC overexpression in a transgenic mouse model of lymphoma. Finally, they derived a 3-module model. Two modules had an ESC-like related signature and one a stromal signature. These models were able to stratify the patients in 2 different cohorts that discriminated FL patients prone to transform to DLBCL from those with a better clinical course. The value of such models is that they allow hypothesis generation regarding pathways important in lymphomagenesis that may enable better use of available therapies and help to identify putative targets of novel therapies.

The ESC-like signatures are in support of a model of a lymphoma precursor cell, which may arise at an earlier stage of B-cell development than the germinal center. Of particular relevance to the process of FL transformation is whether the transformed lymphoma arises directly from FL, or might arise from additional genetic events in a lymphoma progenitor cell. Such a model is supported in findings by Carlotti et al.4 and those of Ruminy et al.5 wherein intracranial diversity, as defined by the patterns of somatic hypermutation occurring in FL and transformed lymphoma, is more complex than previously described.

Among the core signatures identified in their analysis on modules closely associated with histologic transformation were enrichment for genes usually repressed in ESC through targeting by polycomb group (PcG) complexes. The role of PcG target genes in FL and transformation is further supported by the recent finding that these target genes are significantly overrepresented among aberrantly hypermethylated genes in FL.6 and in aggressive lymphomas.7 The similarities in the patterns of methylation in sequential biopsies taken from FL and subsequent transformed lymphoma suggest that the widespread methylation represents an early event in lymphomagenesis.8 Intriguingly, such a model is also supportive of a PcG-regulated process of lymphoma generating changes arising in an earlier precursor cell, whereby the methylation of these genes is an early event that “locks in” the stem cell–like phenotype. These findings suggest that alterations in methylation represent a common feature of the initiating events in lymphoma.

The genetic/epigenetic characteristics of the precursor cell, the sequential steps leading to its transformation into a lymphoma cell, the genes driving these processes, and the anatomical sites where the lymphoma precursor cells originate are still a matter of speculation. As outlined in the figure, future studies performed on purified populations of cells or single cells should show whether these B precursors have features of an immature cell or whether they have already acquired additional genetic lesions or an aberrant methylation of PcG target genes, clarifying their role in tumor progression and transformation.

Comment on Campeau et al, page 3181

Mesenchymal gaucho homing on the range

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GD1 is a disorder whose pathophysiology is manifested primarily in tissue macrophages.1 In this issue of Blood, Campeau and colleagues demonstrate that lysosomal glucocerebrosidase deficiency in GD1 bone marrow MSCs is associated with increased cellular glucosylceramide and up-regulation of inflammatory mediators that may promote bone mineral loss and hematologic malignancy.2

Type 1 (nonneuronopathic) Gaucher disease (GD1) is caused by an inherited deficiency of glucocerebrosidase. The clinical manifestations are heterogeneous and include hematologic cytopenias, hepatomegaly, splenomegaly, and sometimes disabling skeletal pathology. Pharmacologic treatments (intravenous enzyme replacement therapy and oral substrate depletion therapy) ameliorate the hematologic, visceral, and skeletal manifestations of GD1 with resultant gains in quality of life.1 Attention has now focused on the long-term morbidity including late-emerging Parkinsonian syndromes, persistent osteopenia/osteoporosis, and GD1-associated malignancies, particularly myeloma and lymphoma. Defining the complex impact of glucocerebrosidase deficiency and abnormal glycosphingolipid metabolism on the ecology of the skeletal microenvironment is essential for development of effective treatment and prevention strategies for patients with GD1.

The cause of bone mineral loss in GD1 patients is unclear. There are no consistent abnormalities in OPG-RANKL or in the classic markers of bone formation and resorption. Although most GD1 patients have had bone marrow biopsies, histomorphometry is rarely done. Reduced numbers of CD8 cells reportedly correlate with GD1
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