Profiling is a good thing (at least in the clinic)

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Monti and colleagues take the next step in the molecular characterization of diffuse large B-cell lymphoma (DLBCL).

Despite remarkable advances in the immunology and genetics of lymphoma, predicting response to therapy and survival is still difficult, even with old foes such as diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). While the International Prognostic Index (IPI) and the Follicular Lymphoma IPI (FLIPI) allow robust risk stratification on clinical grounds, they are not biologically insightful.

Gene expression profiling using microchip platforms representative of the array of genes expressed by normal lymphocytes and cDNA from tumor tissue identified 3 subsets of DLBCL, distinguished by a cell-of-origin signature: germinal center B-cell (GCB) type, activated B-cell (ABC) type, and type-3.1

Remarkably, these 3 genetic signatures correlate with survival regardless of the IPI, indicating that biologic determinants of outcome cannot be inferred from clinical differences. Other studies of gene expression profiling in DLBCL using a supervised approach, that is arranging data according to known end points, confirmed the existence of outcome-associated signatures2,3 and identified a more limited set of genes sufficient to predict survival.4 Problems with this approach remain, however, as illustrated by the lack of overlap between the sets of predictive genes in the different studies. Furthermore, expression profiling according to the cell-of-origin paradigm fails to provide information about host-related factors, such as inflammatory response and antitumor immunity that may be important in determining outcome.

In this issue of Blood, Monti and colleagues describe the use of a genome-wide platform of 33,000 genes to identify novel transcriptional profiles in DLBCL, thus broadening our view of the molecular complexity of this disorder. Through multiple clustering methods, 3 “functional” subsets of DLBCL were identified. The OxPhos signature includes genes involved in oxidative phosphorylation, suppression of apoptosis, and mitochondrial and proteasome function. This subset is more frequently associated with the translocation t(14;18), affecting the antiapoptotic gene Bcl-2. The BCR/proliferation subset is enriched for genes involved in cell-cycle regulation, DNA repair, cell division, and B-cell–receptor (BCR) signaling and is associated with Bcl-6 gene rearrangements. The third subset, host response (HR), is enriched for genes involved in T-cell–receptor signaling (ZAP70, LAT), natural killer (NK) cell activation (NKp30), complement cascade, cytokine signaling (IRF1-7), dendritic cell maturation (LAG3/CD223), and T-cell adhesion and chemotaxis (LFA1, CXCR6). Interestingly, the HR subset displays high numbers of tumor-infiltrating lymphocytes (TILs), suggestive of an ongoing immune response, and overlaps with the variant of DLBCL called T-cell–rich B-cell lymphoma.

Those hoping for a simple, intuitive correlation between “functional” DLBCL signatures and outcome, however, will be disappointed. The survival of the OxPhos and BCR/proliferation subsets, with signatures suggesting disruption or piracy of key cellular circuits, was no different from that of the HR subset, rich in messages associated with immune activation. This observation aligns gene expression profiling with the inconclusive literature on the correlation between the type and number of infiltrating T cells and outcome in DLBCL. It also highlights the difference with FL where a “microenvironment” signature is clearly associated with improved survival.5 Further studies of the diversity and clinical impact of the host–response signatures in FL and DLBCL will need to make the difficult transition from transcriptional to functional analysis. The work of Monti et al and of a number of other investigators, however, holds the key for beginning to understand the role of the host’s immune response in DLBCL.

REFERENCES


“You break it, you fix it”

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Nonrandom chromosomal translocations are considered to be causal events leading to leukemic transformation. However, the mechanism(s) that cause these translocations are poorly understood. Libura and colleagues report exciting new findings on the mechanism(s) that lead to chromosomal translocation.

A novel variant of the “Pottery Barn rule” was invoked during the recent US presidential election. This rule (“you break it, you fix it”) also applies to the repair of mammalian DNA. It has been estimated that approximately 50 DNA double-strand breaks occur during S phase of a normal cell division cycle, and additional breaks may occur during other phases of the cell cycle. Moreover, a large number of environmental insults, including...