for GVHD, a common immune-mediated complication of allogeneic transplantation. Allogeneic NST regimens for autoimmune diseases must, therefore, be designed to prevent GVHD. Prevention of GVHD may be accomplished by donor lymphocyte and antigen-presenting cell (APC) depletion and/or costimulatory blockade using methods such as ex vivo CD34⁺ selection, in vivo depletion of donor lymphocytes with alemtuzumab, or, as demonstrated by Flierman et al, costimulatory blockade with anti-CD40L (ligand) to induce anergy. When combining an NST regimen with donor lymphocyte depletion or costimulatory blockade it is likely that the result will be mixed chimerism (ie, coexistence of both donor and recipient hematopoiesis). This raises several questions. (1) What NST regimen maximizes donor engraftment without clinical GVHD? (2) Is mixed chimerism sufficient to prevent autoimmune disease recurrence? (3) What percentage of donor chimerism is required to prevent autoimmune disease relapse? (4) Is mixed chimerism durable or will either recipient or donor hematopoiesis eventually be rejected? These questions remain unanswered and require further research.

REFERENCES

Comment on Lu et al, page 2924

Showing the way: large cell lymphoma

Michael M. Quigley  NAVAL MEDICAL CENTER SAN DIEGO

In this issue of Blood, Lu and colleagues clearly show how the identification of biologically meaningful patterns of gene expression can guide the molecular dissection of the mechanisms that give rise to neoplastic phenotypes.

In the field of oncology, microarray technology holds great promise for improved diagnostic categorization of tumors, for more precise prognostic groupings, and for the identification of specific molecular targets for therapy. However, mRNA expression profiles cannot easily identify differences in cellular states that exist due to variable activation and localization of cellular proteins. For this reason, array data will have to be combined with more classical cell biology techniques to understand the molecular mechanisms that drive neoplastic cellular behavior.

Diffuse large B-cell lymphoma (DLBCL), long recognized as a heterogenous diagnostic category, was one of the first tumors to be investigated by gene expression profiling. This analysis defined 2 subgroups of DLBCLs: activated B-cell–like (ABC-like) and germinal center B-cell–like (GCB-like). Subsequent studies showed that interleukin 4 (IL-4) target genes are differentially expressed in the DLBCL subtypes and that some of these genes correlate with survival differences. Lu and colleagues hypothesize that these divergent responses may result from inherent differences in the 2 molecularly defined DLBCL subtypes. IL-4 cellular effects are partially mediated by the JAK-STAT (Janus kinase–signal transducers and activators of transcription) signaling pathway. One major thread of their manuscript examines STAT6 signaling in cell lines of the 2 tumor types. In a stepwise fashion, the authors explore the cellular mechanisms that account for the differences in response to IL-4. They show that the GBCL-like cell lines accumulate phosphorylated STAT6 (pSTAT6) in the nucleus in response to IL-4 whereas ABC-like cells do not. This difference is presumably responsible for the dichotomous transcriptional responses.

Experiments using tyrosine phosphatase inhibitors and proteasome inhibitors show that pSTAT6 dephosphorylation and degradation are responsible for the lack of nuclear pSTAT6 accumulation in ABC-like cells. These data led the authors to postulate the existence of a specific tyrosine phosphatase activity in the ABC-like cells. Where better to look for potential candidate phosphatases than the published DLBCL microarray studies? Candidate phosphatases that showed significantly higher expression in ABC-like cells were identified and evaluated for cellular localization and known target protein specificities. Two enzymes, protein tyrosine phosphatase nonreceptor type 2 (PTPN2) and PTPN1, were shown to be expressed only in ABC-like cells (in the nucleus and cytoplasm, respectively). An additional experiment showed that both are capable of dephosphorylating pSTAT6. The authors suggest that PTPN2 and PTPN1 may be responsible for the distinct responses to IL-4 in the tumor cell lines. A further intriguing result described is that IL-4 also leads to distinct proliferative responses in the 2 tumor subtypes.

This paper demonstrates the power of combining information derived from microarray analysis with insightful experimental manipulation. Through the use of molecular cell biology techniques, Lu et al arrive at a satisfying explanation for differences in IL-4 responses in the ABC-like and GCB-like cell lines. More importantly, this paper begins to validate the rationale that array data can define the critical cellular pathways that underlie a neoplastic phenotype.