since reactive oxygen species can damage stem cell DNA and may accelerate clonal evolution of abnormal stem cell clones in late stages of MDS and low blood counts in early stage/low-grade MDS. Elimination of normal stem cell clones can undergo apoptosis, leading to ineffective hematopoiesis in low-grade MDS and potentially restore normal hematopoiesis. Adapted from Zhou et al with permission.1

Proposed model of pathogenesis of stem cell apoptosis in MDS. A mutation in a stem cell compartment can give rise to a malignant clone. Interactions of the abnormal stem cell clones with the bone marrow microenvironment can lead to increased proinflammatory cytokine production in the bone marrow. Normal stem cell clones can undergo apoptosis, leading to ineffective hematopoiesis and low blood counts in early stage/low-grade MDS. Elimination of normal stem cells and clonal evolution of abnormal stem cell clones in late stages of MDS lead to development of leukemia. p38 MAPK inhibition can disrupt cytokine-driven apoptosis in low-grade MDS and potentially restore normal hematopoiesis. Adapted from Zhou et al with permission.1

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

REFERENCES

Comment on Rimsza et al, page 3425

**Blocks to paraffin get the CHOP, +R**

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In this issue of Blood, Rimsza and colleagues present an embarrassment of riches. They report the use of a multiplex quantitative nucleic acid protection assay to measure, in FFPET, prognostic genes for DLBCL in patients treated with rituximab. Their approach overcomes 3 significant problems in the field, namely the difficulty of working with FFPET, the requirement for a simple method for clinical measurement of prognostic genes, and the need for a prognostic gene signature applicable to patients treated in the rituximab era.

Microarray gene expression profiling has resulted in an exponential increase in the understanding of cancer. It has also identified a plethora of putative novel diagnostic and prognostic biomarkers. These are increasingly important as traditional markers, either clinical or cellular, are beginning to lose discriminatory power, especially in the emerging era of personalized medicine. However, almost all diagnostic material is in the form of formalin-fixed paraffin embedded tissue (FFPET), in which gene expression profiling is compromised by RNA degradation and cross-linking, and this has hindered translation of microarray-identified biomarkers to clinical practice.1 Several groups have sought to overcome this, either by use of modified RNA extraction and labeling for microarray analysis,2 by measurement of candidate prognostic genes by real-time PCR3 or by bead-based approaches, such as the DASL platform.4 These studies demonstrate the feasibility of gene expression profiling in FFPET but admit reduced sensitivity compared with fresh/frozen tissue, though Malumbres and colleagues reported successful measurement of a 6-gene model in FFPET in diffuse large B-cell lymphoma (DLBCL) patients treated with R-CHOP.5 Additionally, while real-time PCR is possible in FFPET, there remains a need for multiplex measurement of several genes, particularly as the power of prognostic gene signatures is often based on more than one gene. Furthermore, identification of specific prognostic groups often suggests new drug targets, increasing the importance of FFPET-based studies capable of extending the range and depth of clinical material for translational study.

The biology and behavior of DLBCL is highly heterogeneous. Several gene expression profiling studies have provided greater prediction of disease behavior, separating DLBCL into at least 2 distinct molecular subtypes: a favorable germinal center B-cell type (76% 5-year survival) and an unfavorable activated B-cell type (16% 5-year survival).6 Rituximab has dramatically altered outcome in DLBCL and its introduction has been contemporaneous with these studies. Therefore, their results must be tempered by their analysis of patients treated in the pre-rituximab era, with some reports of loss of prognostic distinction between germinal center (GC) and non-GC types in patients treated with rituximab.7 Monti et al addressed this problem by unsupervised analysis of samples of DLBCL from untreated patients to determine an a priori biological signature predictive of new therapeutic targets,8 demonstrating the importance of identifying a prognostic gene signature in patients treated with rituximab.

The paper by Rimsza et al uses an elegant novel methodology to solve, at a single stroke, the multiple problems outlined above. The
**REFERENCES**


**CONFLICT OF INTEREST**

The author declares no competing financial interests.

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**Donor dendritic cells dance the do-si-do in allogeneic transplantation**

Edmund K. Waller and Jian-Ming Li

**EMORY UNIVERSITY**

In this issue of *Blood*, Taylor and colleagues studied the effect of CpG oligonucleotide ligands for TLR9 on host and donor APCs in a murine model of allogeneic bone marrow transplantation. The article describes an unexpected result: administration of CpG activated both donor and host DCs, resulting in enhanced rates of graft rejection and accelerated GVHD.

The current paradigm for understanding engraftment in allogeneic hematopoietic progenitor cell transplantation is that donor T cells facilitate engraftment by donor stem cells, host dendritic cells (DCs) activate donor T cells and induce graft versus host disease (GVHD), and host T cells mediate graft rejection. The role for donor DCs has been neglected due, in part, to their scarcity in bone marrow grafts, assumptions of limited survival in allogeneic recipients after transplantation, and the overwhelming larger numbers of host DCs that are capable of directly presenting alloantigen to donor T cells. A novel finding in the report by Taylor et al relates to a role for donor DCs in modulating engraftment. The study is also of some interest to transplant immunologists, since it suggests caution in using...
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Richard Byers