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## **R-CHOP strikes again with survival benefit in follicular lymphoma**

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oligosaccharide ligands on Th1 cells was shown by functional assays (ie, T-cell rolling on monolayers of cells expressing E- or P-selectin). This functional approach allowed identification of ST3Gal-VI ( $\alpha$  2,3-sialyltransferase VI) as a novel glycosyltransferase involved in synthesis of selectin ligands on Th1 cells. More important, these investigators' past and current work are now synthesized in a model integrating signaling from T-cell and interleukin 12 (IL-12) receptors with transcriptional regulation resulting in coordinated expression of 4 different glycosyltransferases that create functional selectin ligands on cell surface glycoproteins (see figure).

In the emerging field of glycobiology, mechanistic connection of cell signaling to the synthesis of specific oligosaccharide ligands during differentiation is an exciting and important advance. As oligosaccharides on glycoproteins and glycolipids cover much of the

surface of mammalian cells and regulate cell adhesion, migration, proliferation, and survival, future studies will no doubt demonstrate that signals regulating cellular glycosylation are critical for the differentiation and function of all hematopoietic cells. ■

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#### CLINICAL OBSERVATIONS

Comment on Hiddemann et al, page 3725

## R-CHOP strikes again with survival benefit in follicular lymphoma

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Hiddemann and colleagues demonstrate improved response duration and overall survival with the addition of rituximab to CHOP, compared with CHOP alone, in symptomatic patients with untreated advanced-stage follicular lymphoma.

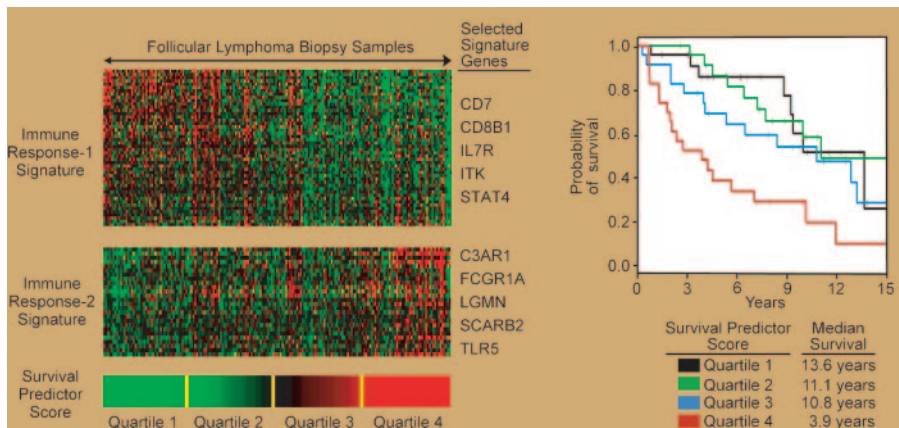
The arrival of rituximab (R) onto the therapeutic landscape heralded a new era in the treatment of B-cell lymphoma and provided a

rational basis for its combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Czuczman et al<sup>1</sup> first demon-

strated the benefits of R-CHOP in indolent lymphomas, but the broad applicability of their findings was uncertain due to limited sample size and absence of a control group. A recent 9-year follow-up of their study and the results of the present report, however, provide new evidence for the merits of R-CHOP and reshape treatment recommendations.<sup>2</sup>

In this issue of *Blood*, Hiddemann and colleagues report the results of a randomized study of CHOP versus R-CHOP in 428 patients with advanced-stage follicular lymphoma of grade I or II histology and requiring treatment. Responding patients younger than 60 years of age were offered a second randomization following CHOP or R-CHOP of either intensification with stem cell support or long-term interferon- $\alpha$  maintenance, whereas older patients received interferon- $\alpha$  maintenance. At the median follow-up time of 18 months (range, 1-38 months), the risk of treatment failure was reduced by 60% in the R-CHOP arm with benefit observed in patients younger or older than 60 years and with low or high international prognostic index scores. The time to next therapy also demonstrated an advantage for R-CHOP. Of great interest was the significant improvement in overall survival with R-CHOP, albeit only modest at the relatively short follow-up time. A justifiable caveat to a broad embrace of these findings is found in the secondary treatment requirement. It is reassuring that the secondary randomizations were stratified for risk and that the R-CHOP benefit was irrespective of interferon- $\alpha$  maintenance. It is notable though that the R-CHOP benefit was not observed among patients randomized to stem cell consolidation, suggesting that enhanced treatment efficacy and not the unique biologic attributes of rituximab may underlie the benefits of R-CHOP. It should also not escape notice that differential access to rituximab containing salvage treatment for patients on the 2 arms could account for the survival advantage of R-CHOP. Nevertheless, these results as well as those of Czuczman et al,<sup>2</sup> where the observation time is quite mature, raise the specter of survival advantage, if not cure, with R-CHOP in follicular lymphoma. While many opinions might favor the notion that rituximab combined with CHOP delays relapse in follicular lymphoma, the prospect of cure should be considered with appropriate circumspection.

These results are of sufficient measure to reshape the debate from "if" to "when"



Molecular prognostic model of follicular lymphoma based on signatures of infiltrating "immune" cells.

patients should receive R-CHOP for the initial treatment of advanced-stage disease, not to mention its role in early-stage disease. Questions of who will benefit from treatment with R-CHOP, versus less “hair-razing” regimens like R-CVP (rituximab–cyclophosphamide, vincristine, and prednisone), will occupy the minds of oncologists and patients.<sup>3</sup> Gene expression profiling, while providing insight into tumor biology, is also a powerful prognostic tool that may help identify beneficiaries of such treatment. This technology has revealed a central biologic role for infiltrating “reactive” cells, termed the immune reaction (IR), within the malignant lymph node on the survival of follicular lymphoma.<sup>4</sup> The relative expression of 2 signatures, termed IR-1 and IR-2, that differentially express genes related to T-cell markers, macrophages, and/or dendritic cells, can be used to predict survival (see figure). It is not unreasonable, given the early benefits of rituximab on survival, to hypothesize that rituximab may impact tumors that predominantly express IR-2, as this signature is associated with short survival. Indeed, a recent study on gene expression associated

with rituximab responsiveness suggested the relevance of immune cells albeit as negative predictors.<sup>5</sup> The prospective application of these technologies to future trials is vital for understanding outcome biology and to guide the rational clinical development and use of new treatments. ■

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tion, and subcellular compartmentalization have been extensively studied in cultured endothelial cells using simple flow protocols.<sup>2</sup> Other in vitro flow studies have attempted to simulate the complex flow characteristics associated with sites of lesion susceptibility in the arterial circulation.<sup>3</sup> Such regions correlate with decreased eNOS transcript expression even in lesion-free animals<sup>4</sup> but the relationship between cause (complex flow) and effect (eNOS expression and localization) had not been established in vivo.

To address these issues, the Rotterdam group generated transgenic mice that express human eNOS in fusion with green fluorescent protein (GFP) as a reporter of eNOS protein expression.<sup>5</sup> To demonstrate hemodynamic cause-effect, gradations of  $\tau$  and separations of flow were created by placement of a tapered cast around the midportion of the left common carotid artery, resulting in a corresponding gradual narrowing of the artery lumen over a length of several millimeters. This is normally a region of pulsatile laminar flow without flow separation and where  $\tau$  forces are unidirectional. It is also a site resistant to atherosclerotic lesion development. Since  $\tau$  is proportional to  $1/(\text{diameter})^3$ , shear stress increases rapidly throughout the length of the cast. Downstream of the cast, the lumen widens to create a short region of oscillating separated flow similar to that recorded at atherosclerosis-susceptible locations elsewhere. Within 24 hours following placement, the hemodynamics were spatially mapped to face cell responses. Cheng and colleagues report that eNOS gene and protein expression was elevated as  $\tau$  increased within the tapered cast consistent with shear stress experiments in vitro and that the intracellular redistribution of eNOS, including its activated form (serine 1177 phosphorylation), was significantly increased both by elevated  $\tau$  and oscillatory flow, although the fraction of total eNOS that was phosphorylated remained unaltered.

The studies are encouraging for investigations both in vivo and in vitro. They suggest that flow-related mechanisms of eNOS regulation identified in reductionist experiments in tissue culture also occur in vivo, albeit with subtleties imparted by a more complex environment. Furthermore, studies of flow disturbance in relation to localized endothelial phenotype in vivo can now be cautiously interpreted as cause-and-effect mechanisms rather than simply correlative. ■

#### ● ● ● HEMOSTASIS

Comment on Cheng et al, page 3691

## Hemodynamic manipulation of eNOS in vivo

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In this issue of *Blood*, Cheng and colleagues at Erasmus University in Rotterdam demonstrate that arterial eNOS expression in eNOS-GFP transgenic mice is responsive both to hemodynamic flow characteristics and to the magnitude of shear stress forces ( $\tau$ ). These experiments provide important in vivo validation of numerous in vitro studies of the flow-eNOS relationships and reveal the spatial sensitivity of hemodynamic characteristics in the regulation of eNOS in intact arteries.

**H**emodynamic regulation of vascular physiology occurs through convective mass transport and through forces imparted to the vessel wall. Flow is also a pathologic determinant of the localization of atherosclerotic lesions that originate at sites of geometric (and hemodynamic) complexity. A particular target of flow forces is the arterial endothelium, an interface that is sensitive to the local (frictional) shear stress.<sup>1</sup> An important physiologic example of  $\tau$ -endothelial interactions is flow-

mediated generation of nitric oxide (NO) by activation of endothelial nitric oxide synthase (eNOS). Regulation of this enzyme is considered to be of major physiologic and pathologic importance. Its activities play a dominant role in vasodilatation by relaxing the smooth muscle cells of arteries to reduce blood pressure. NO also inhibits platelet aggregation, leukocyte adhesion to the endothelium, and cell migration. The effects of  $\tau$  on eNOS transcription, translation, posttranslational activa-