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Comment on Chng et al, page 2755

Gene expression relates WM to CLL

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Waldenström macroglobulinemia (WM) shares traits with both chronic lymphocytic leukemia (CLL) and multiple myeloma (MM). Chng and colleagues now demonstrate that by gene expression WM appears more closely related to CLL than MM.

Waldenström macroglobulinemia (WM) is a rare hematologic malignancy characterized by an IgM monoclonal gammopathy and bone marrow infiltration by small lymphocytes that can undergo plasmacytoid and plasma cell differentiation.[1] It has long been recognized that WM shows features suggestive of an intermediate process between chronic lymphocytic leukemia (CLL) and multiple myeloma (MM). WM cells express B-cell markers but not CD5 or CD23 in contradistinction to CLL. WM cells appear to derive from a postgerminal B cell that has undergone somatic hypermutation but not switch recombination. The clonal cells reside primarily in the bone marrow similar to MM but secrete an IgM paraprotein that causes many of the clinical sequelae. Effective therapeutic agents in WM are by and large the same as in CLL (see figure).

		CLL	WM	MM
Biologic and clinical characteristics	Clonal cell	Small, mature lymphocyte	Small & plasmacytoid lymphocyte, plasma cell	Plasma cell
	Immunoglobulin	Surface IgM	Surface & cytoplasmic IgM	Cytoplasmic IgG, IgA,
	VH gene mutation	Mutated & unmutated	Mutated	Mutated
	Isotype switching	No	No	Yes
	Immunophenotype	Pos: CD5, CD19, dim CD20, CD22, CD23	Pos: CD19, CD20, CD22 neg: CD5, CD23, CD138	Pos: CD38, CD138 neg: CD19, CD20
	Paraprotein	Rare, low level	IgM	IgG, IgA, light chain
	Clinical Characteristics	Lymphocytosis, autoimmunity	Hyperviscosity, peripheral neuropathy	Bone & renal disease
	Lymphadenopathy & splenomegaly	Common	Possible/common	No
	Preferred/active agents	Fludarabine, rituximab, chlorambucil	Fludarabine, rituximab, chlorambucil	Steroids, melphalan, bortezomib
Chng et al	Source of cells	Blood	Marrow	Marrow
	Purification of malignant cells	CD19	CD19 & CD138	CD138
	Gene Expression	SYK, CD52, CD79a, PAX5, CD19, VAV	SYK, CD52, CD79a, PAX5, CD19, VAV	DKK1, HGF, FRZB, MAF, IL-6-R
	Pathogenic role of IL-6 ?	No	Autocrine	(Paracrine)*

Summary of characteristics of WM, CLL, and MM and of methods and results from the study by Chng et al. See the complete figure in the article beginning on page 2755.

Gene expression profiling can establish molecular diagnoses and uncover or better define distinct diseases.[2] This approach has been especially successful when the clinical material was relatively homogeneous, for instance lymph node biopsies or purified leukemic cells. Chng and colleagues used genomic-scale gene expression analysis to investigate the relationship between WM, CLL, and MM. Such a comparison is no easy undertaking due to distinct expression of cell-surface markers, differences in anatomic distribution, and the variable degree of blood or marrow involvement. The malignant cells studied here were obtained from peripheral blood (CLL) or bone marrow (WM, MM) and purified for CD19 (CLL), CD138 (MM), and combined CD19 and CD138 (WM) expression. The nature of the diseases and the approach chosen introduced confounding factors, notably differences in gene expression apparently contributed by contaminating cells, and made the use of statistical filters necessary. Nevertheless, the authors made several interesting observations (see figure).

Gene expression among the 23 WM cases appeared homogeneous, supporting the concept of a common biology despite the morphologic variability of the clonal cells. WM shared expression of typical B-cell markers with CLL and by hierarchic clustering analysis most WM samples aligned with the CLL samples. A small set of genes that interestingly included IL-6 and CD1c were overexpressed in WM. A role for IL-6 in WM has been previously suggested by the observation of IL-6–induced differentiation of the clonal B cells into plasma cells and the secretion of IL-6 by WM cells in vitro.[3] The current study thus provides a valuable confirmation of IL-6's potential pathogenic role in WM. The CD1 family of MHC-like glycoproteins presents glycolipids to antigen-specific T cells and plays important roles in innate immunity and autoimmunity.[4] Because WM cells often produce IgM paraproteins reactive with phospholipids, it is tempting to speculate that phospholipid antigens could contribute to the pathogenesis of WM.

In summary, this study adds further evidence that WM constitutes more a B-cell than a plasma cell malignancy and that WM is more closely related to CLL than MM. The unique gene expression profile of WM can provide a framework for further studies and focus attention on the possible pathogenic role of IL-6 production by the malignant clone. ■

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Comment on Han et al, page 2796, and comment on Fawal et al, page 2780

ALK-mediated oncogenesis: mechanisms that matter

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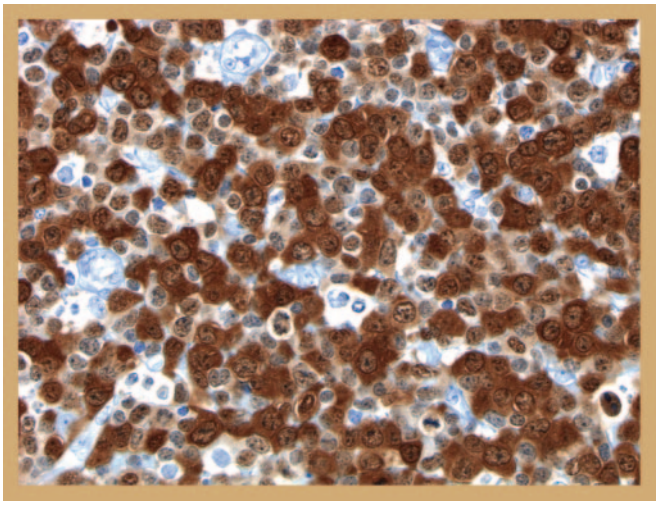
Two reports in this issue of *Blood* provide new insights into the lymphomagenic mechanisms used by ALK fusions, one highlighting the effects of loss of expression of the tyrosine phosphatase SHP1 that occurs in the majority of ALK-positive lymphomas and the other describing a heretofore unappreciated role for ALK fusions in the enhancement of mRNA stability.

Primary systemic anaplastic large cell lymphoma (ALCL) can be subdivided into 2 biologic subtypes based on the presence or absence of oncogenically transforming fusions of the anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase truncated and fused to a variety of N-terminal, activating partner proteins—the most common chimeric form being nucleophosmin (NPM)–ALK—in these lymphomas.[1] The distinction between the so-called ALK-negative and ALK-positive ALCLs (the latter colloquially known as ALKomas) is relevant both from basic research and clinical standpoints. For example, a substantial body of basic research data suggest ALK-positive ALCLs to be "ALK addicts" that are exquisitely dependent upon the continuous growth-promoting cellular signals conferred by chimeric ALK proteins, making ALK a very attractive target for the development of directed therapies for future clinical use such as small molecules analogous to the BCR-ABL inhibitors imatinib and dasatinib that have revolutionized chronic myeloid leukemia treatment. Two articles published in this issue of *Blood* report important basic research data that help to further elucidate the downstream cellular signaling mechanisms that modulate oncogenic transformation by ALK fusions and that may ultimately permit identification of additional targets for therapeutic intervention in the clinic for ALK-positive ALCLs.



Anti-ALK immunostain of a typical NPM-ALK–positive anaplastic large-cell lymphoma. Illustration by Dr Mihaela Onciu, St Jude Children's Research Hospital.

Han and colleagues report studies that follow up on earlier data from this group showing that almost all ALK-positive ALCLs experience silencing of the nonreceptor tyrosine phosphatase SHP1 due to methylation of the *SHP1* gene promoter. SHP1 phosphatase is normally abundant in hematopoietic cells, but is silenced in many hematologic cancers; the biologic importance of SHP1 is exemplified by the phenotype of so-called moth-eaten mice, in which absent or markedly reduced Shp1 expression causes abnormal myeloid cell development and function as well as a propensity for lymphomagenesis.[2] Using ALK-positive ALCL cell lines and primary tumor samples, Han et al show that reintroduction of *SHP1* expression into lymphoma cells that had silenced the gene produces marked reductions in the phosphorylation and activation of JAK3 (a known dephosphorylation target for SHP1) and STAT3 and down-regulation of the STAT3 transcriptional targets cyclin D3, MCL1, and BCL2.

Intriguingly, re-establishment of SHP1 expression in ALCL tumor cells also resulted in marked decreases in the levels of both JAK3 and NPM-ALK, an effect due to enhanced proteasome-mediated protein degradation by a yet-to-be defined mechanism. The biologic consequences of SHP1 re-expression were noteworthy: Karpas-299 and SU-DHL-1 ALCL cells experienced significant cell-cycle arrest and impaired growth upon introduction of exogenous SHP1. These data, as well as recent corroborating results from others,[3] demonstrate that SHP1 loss contributes to the growth of ALK-positive ALCLs by allowing enhanced, unregulated phosphorylation and activation of JAK3/STAT3 and by permitting increased levels of JAK3 and NPM-ALK protein expression due to decreased proteasome degradation. Taken collectively, these results provide impetus for additional preclinical studies to examine the feasibility of therapeutic efforts for the clinical management of ALCL (and other SHP1-silenced cancers) that are designed to reawaken SHP1 expression by the inhibition of *SHP1* promoter methylation.[4]

In a second ALK-related study, Fawal and colleagues report a novel oncogenic signaling mechanism—enhancement of mRNA stability by a fusion tyrosine kinase. These investigators discovered the physical interaction of NPM-ALK with AUF1/hnRNPD, one of the family of AU-binding proteins (AU-BPs) that regulates the half-lives of many mRNAs by directly interacting with A+U–rich elements (AREs) found in their 3′ untranslated regions.[5,6] AUF1/hnRNPD was shown to be hyperphosphorylated due to its association