

3. Barton NW, Brady RO, Dambrosia JM, et al. Replacement therapy for inherited enzyme deficiency—macrophage-targeted glucocerebrosidase for Gaucher's disease. *N Engl J Med.* 1991;324(21):1464-1470.
4. Elstein D, Dweck A, Attias D, et al. Oral maintenance clinical trial with miglustat for type I Gaucher disease: switch from or combination with intravenous enzyme replacement. *Blood.* 2007;110(7):2296-2301.
5. Robertson PL, Maas M, Goldblatt J. Semiquantitative assessment of skeletal response to enzyme replacement therapy for Gaucher's disease using the bone marrow burden score. *AJR Am J Roentgenol.* 2007;188(6):1521-1528.
6. Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med.* 2006;355(12):1233-1243.

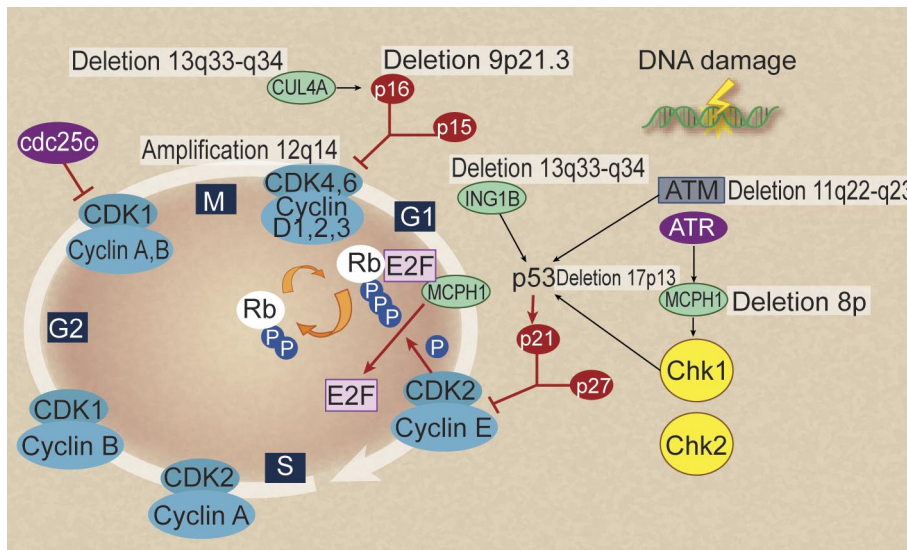
● ● ● LYMPHOID NEOPLASIA

Comment on Hartmann et al, page 953

# Discovery of Hippo in MCL

Rebecca Auer BARTS AND THE LONDON SCHOOL OF MEDICINE

In this issue of *Blood*, Hartmann and colleagues report on the results of a high-resolution genomic profiling study in a large series of MCL. Copy number alteration and expression data are amalgamated with clinical outcome. Their data confirm the critical role of the cell-cycle and DNA damage-response pathways to MCL and also identify novel target genes within these. Specifically, Hippo signaling is recognized as a potentially novel pathogenetic pathway.<sup>1</sup>



**Figure 1.** Schematic diagram summarizing the cell-cycle and DNA damage response alterations in MCL, highlighting specific genomic copy number variations. The t(11;14)(q13;q32) translocation results in up-regulation of cyclin D1, an important regulator of the G1 phase of the cell cycle with its catalytic partner cyclin-dependent kinase 4 (CDK4). Overexpression of cyclin D1 maintains retinoblastoma (Rb) in a phosphorylated state leading to its inactivation and release of its suppression on the transcription factor E2F. E2F transactivates numerous S-phase gene promoters (cyclins D, E, A) and thus instigates DNA synthesis. Alterations described by Hartmann et al may act in the following ways. CUL4A binds to CDKN2A/p16 causing p16 activation. Loss of CUL4A prevents cell-cycle inhibition through p16. ING1 increases p21 expression by up-regulating the DNA damage-response gene p53. The loss of ING1 enhances cell-cycle progression through the G1/S checkpoint by removing the p21 brake. In MCL, MCPH1 is down-regulated resulting in increased cell cycling and a failure of apoptosis. Professional illustration by Debra T. Dartz.

**A**lthough the hallmark of mantle cell lymphoma (MCL) is overexpression of cyclin D1 related to the t(11;14) translocation, it is clear that there are a number of biologic factors synergizing in the disease process. Their identification has contributed to the provision of prognostic molecular markers, and such

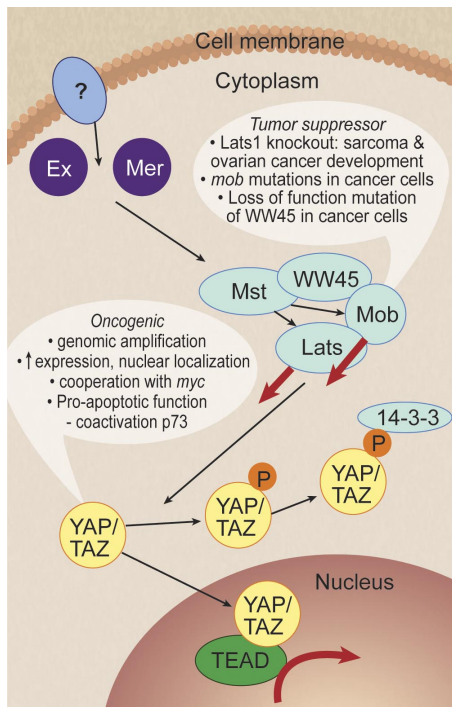
secondary genomic alterations are likely to account for the highly variable clinical behavior of MCL and may permit better risk stratification at diagnosis. Most of the additional abnormalities identified to date perturb the cell-cycle machinery and interfere with the cellular response to DNA damage.<sup>2</sup> Our

knowledge, however, of the biology of this disease is by no means complete. There have been a number of studies exploring copy number alteration.<sup>3,4</sup> This research paper presents the largest dataset to date, using high-resolution techniques to power this study to combine genome-wide copy number alteration with gene expression and clinical data in a cohort of primary MCL cases. Importantly, this permitted identification of new survival-associated genetic alterations affecting prognosis and revealed potential new pathogenetic pathways.

This report confirms the complexity of the secondary genomic imbalances that occur in MCL. The few cases of cyclin D1-negative MCL included were found to carry the same types of abnormalities and complexity as cyclin D1-positive cases, confirming again that these represent the same pathogenic entity and raising the possibility that genetic profiling could be used as an aid to diagnosis when difficulties exist by providing a robust means of identifying this particular disease subtype.

By incorporating clinical survival with genomic data, this study nicely highlighted those genomic alterations that were most likely to influence the clinical course of the disease. Previous studies have identified key alterations relating to the genes that control cell cycle and response to DNA damage and these are confirmed here (summarized in Figure 1). Genomic amplification of cyclin-dependent kinase 4 (*CDK4*), deletion of cyclin-dependent kinase inhibitor 2A/p16 (*CDKN2A*), and overexpression of *BIMI* (a transcriptional repressor of p16) all contribute to increasing the protein drive on cell cycling and proliferation.<sup>2</sup> Loss of response to DNA damage through *ATM* and *TP53* mutations further promotes cell cycling. Here Hartmann and colleagues provide good evidence that the regions of common loss are characterized by survival genes, associated with the proliferation signature<sup>5</sup> that is critical to MCL pathogenesis. In this way, these data also suggest that subsets of genes encompassed by minor common regions of change impact on patients' outcome and have prognostic value. MCL is a "spectrum of diseases" with no clear best method for risk stratification besides continuous variables including MCL International Prognostic Index and Ki67. By identifying different molecular subsets this provides new clinically relevant prognostic stratification

Downloaded from <http://ashpublications.net/blood/article-pdf/116/6/861/1460049/zh803210000861.pdf> by guest on 08 June 2024



**Figure 2. The Hippo pathway.** In mammalian cells, the Hippo pathway kinase cascade inhibits YAP by direct phosphorylation of YAP by Lats to generate a 14-3-3-binding site that induces YAP cytoplasmic translocation and inactivation. Evidence to support the role of YAP as an oncogene is listed. Ex indicates Expanded; Mer, Merlin, also called NF2; Mst, Mst1/2, also called STK4 and STK3, Hpo homolog; WW45, Sav homolog; Mob, Mps 1 binder kinase activator-like 1A/B, MOBKL1A/B, Mats homolog; Lats, Lats1/2, Wts homolog; YAP, Yes-associated protein, Yki homolog; TAZ, transcriptional coactivator with PDZ-binding motif, also called WWTR1, Yki homolog; and TEAD, TEA domain family member 1/2/3/4. Dashed arrows indicate unknown biochemical mechanism and question marks denote unknown components. Adapted from Zhao et al<sup>7</sup> with permission. Professional illustration by Debra T. Dartez.

analogous to that seen with activated B cell-like and germinal center B cell-like gene array-identified subtypes of diffuse large B-cell lymphoma and may be an important basis for future clinical trial design.

Putative novel target genes were also identified on the basis of the frequency of their occurrence rather than effect on survival. In this way another layer of complexity has been added to the cell-cycle dysregulation inherent to MCL and further demonstrates how critical this is to this disease process (Figure 1). *CUL4A*, *ING1*, and *MCPH1* have not previously been ascribed a role in lymphomagenesis, although they are known to have important functions in regulating the DNA damage-response pathways (see Figure 1 for a potential role in MCL cell-cycle dysregulation).

This report is of interest because it identifies Hippo pathway dysregulation for the first time in lymphoma. The Hippo pathway was originally discovered in *Drosophila* through its regulation of body and organ size by inhibiting cell proliferation and promoting apoptosis.<sup>6</sup> Its role in cancer is increasingly being recognized with key components of the pathway acting as both oncogenes and tumor suppressors.<sup>7</sup> Hartmann et al provide 2 lines of evidence to support a role for Hippo in MCL pathogenesis. This is an exciting development because it identifies for the first time the Hippo pathway as tumor suppressor genes contributing to lymphoma tumorigenesis. Decreased expression of Hippo members *MOBK1A*, *MOBK1B*, and *LATS2* was associated with inferior survival. Second, loss of the genomic regions where these 3 genes are located was observed in almost 40% of MCL cases. *MOBK1A*, *MOBK1B* are homologues of the *MOB1* gene that interacts with LATS in inhibition of YAP, a potent growth promoter. Evidence is growing to support the function of YAP as an oncogene as well as a tumor-suppressor function for its inhibitory upstream Hippo pathway components (see Figure 2 for summary of Hippo pathway). Thus, the findings of decreased expression of some of the Hippo members paves the way for further investigation of the Hippo pathway in lym-

phomagenesis. Is it perturbed in other B-cell lymphomas? This would be an interesting question to answer as well as raising the distinct possibility of a new therapeutic target, potentially with broad application.

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

## REFERENCES

- Hartmann EM, Campo E, Wright G, et al. Pathway discovery in mantle cell lymphoma by integrated analysis of high-resolution gene expression and copy number profiling. *Blood*. 2010;116(6):953-961.
- Fernández V, Hartmann E, Ott G, Campo E, Rosenwald A. Pathogenesis of mantle-cell lymphoma: all oncogenic roads lead to dysregulation of cell cycle and DNA damage response pathways. *J Clin Oncol*. 2005;23(26):6364-6369.
- Beà S, Salaverria I, Armengol L, et al. Uniparental disomies, homozygous deletions, amplifications, and target genes in mantle cell lymphoma revealed by integrative high-resolution whole-genome profiling. *Blood*. 2009;113(13):3059-3069.
- Schraders M, Jares P, Beà S, et al. Integrated genomic and expression profiling in mantle cell lymphoma: identification of gene-dosage regulated candidate genes. *Br J Haematol*. 2008;143(2):210-221.
- Rosenwald A, Wright G, Wiestner A, et al. The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. *Cancer Cell*. 2003;3(2):185-197.
- Edgar BA. From cell structure to transcription: Hippo forges a new path. *Cell*. 2006;124(2):267-273.
- Zhao B, Lei QY, Guan KL. The Hippo-YAP pathway: new connections between regulation of organ size and cancer. *Curr Opin Cell Biol*. 2008;20(6):638-646.

## ● ● ● MYELOID NEOPLASIA

Comment on Oh et al, page 988

# Another Lnk to STAT activation

Kevin D. Bunting EMORY UNIVERSITY

Aberrant JAK-STAT activation characterizes human myeloproliferative neoplasms. The study by Oh and colleagues in this issue of *Blood* identifies STAT activation through loss of negative feedback by novel mutations of the adapter protein Lnk.<sup>1</sup>

**H**uman myeloproliferative neoplasms (MPNs) result from dysregulated cytokine signaling. Further understanding of the key signaling nodes and relevant driver mutations in these disorders is biologically and clinically important. The best example of this targeted approach has been the treatment of chronic myelogenous leukemia (CML). The Philadelphia chromosome translocation t(9;22) product BCR-ABL was identified in the 1980s in CML cells. The aberrant protein phosphorylation due to the activated kinase

activity of the BCR-ABL fusion protein led to remarkably successful new drugs targeting the kinase domain. The patients lacking BCR-ABL were essentially without a genetic explanation for many years but this is starting to change quickly. In these disorders, one common feature has been cytokine-independent proliferation due to constitutive activation of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway (see figure). Significant advances in genetic analysis beyond metaphase