Although 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.3 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.3,4 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).

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, MCHP1 is down-regulated resulting in increased cell cycling and a failure of apoptosis. Professional illustration by Debra T. Dartez.
This report is of interest because it identifies Hippo pathway dysfunction 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. Its role in cancer is increasingly being recognized with key components of the pathway acting as both oncogenes and tumor suppressors. 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 *MOBI* 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 lymphogenesis. 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.

**REFERENCES**


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**Another Link to STAT activation**

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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.1

**Human** 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...
Discovery of Hippo in MCL

Rebecca Auer