Burkitt Lymphoma: Much More than MYC

David Dominguez-Sola[1] and Riccardo Dalla-Favera[1,*]
[1]Institute for Cancer Genetics, Columbia University, New York, NY 10032, USA
*Correspondence: rd10@columbia.edu
http://dx.doi.org/10.1016/j.ccr.2012.07.018

Chromosomal translocations causing deregulated c-MYC expression are detectable in most Burkitt lymphoma cases. However, little is known about the additional lesions necessary for lymphomagenesis. Now, two independent studies, one of which was performed by Sander et al. in this issue of *Cancer Cell*, identify constitutive PI3K signaling and CyclinD3 mutations as cooperating lesions in both mice and humans. The results have directly actionable therapeutic implications.

Burkitt lymphoma (BL) arises from the malignant transformation of germinal center (GC) B cells and displays heterogeneous epidemiological features (Magrath, 2012). Although BL can occur sporadically in any population (sporadic BL [sBL]), it is endemic in several equatorial regions typically in Africa (endemic BL [eBL]) and can also develop at significant frequency in HIV-infected individuals (hivBL) (Magrath, 2012). The etiology of BL is associated with Epstein-Barr virus (EBV) infection, and in the case of eBL, with malaria, although the pathogenic significance of these associations is still unclear. For instance, EBV infection of tumor cells is detectable in all eBL but is detectable in only 30% of sBL and hivBL cases. Moreover, most EBV transforming genes are not expressed in the tumor cells (Magrath, 2012). Intensive chemotherapeutic regimens can cure the majority of BL cases but cannot be used in developing countries due to their toxicity and limited availability.

BL has garnered intense attention because of its unusual epidemiological distribution, which suggests complex biological interactions with the host and the environment (Magrath, 2012). Furthermore, it represents a landmark in tumor biology research, being among the first tumors for which a genetic alteration of clear pathogenic significance was discovered (Dalla-Favera et al., 1982; Taub et al., 1982). In fact, chromosomal translocations that involve the c-MYC (MYC) proto-oncogene and the immunoglobulin loci and lead to deregulated MYC expression are detectable in virtually all BL cases. Substantial evidence indicates that MYC deregulation elicits a range of cancer-causing effects that include aberrant cell proliferation, metabolic reprogramming, and genomic instability.

As for most cancer types, BL is likely to develop through multiple genetic alterations. Numerous studies have established that MYC deregulation is not sufficient for malignant transformation but that additional lesions are required. Yet, except for inactivation of p53, which is detectable at variable frequencies in the different BL subtypes (Gaidano et al., 1991), little is known about the cooperating lesions that lead to BL development. Now, however, two independent studies (Sander et al., 2012 [in this issue of *Cancer Cell*]; Schmitz et al., 2012), remarkably complementary in their findings in mice and humans, provide fundamental insights into the pathogenesis of BL with important and directly actionable therapeutic implications.

In this issue of *Cancer Cell*, researchers in the laboratory of Klaus Rajewsky, in collaboration with long-standing BL experts in Europe, have identified novel genetic lesions that cooperate with MYC deregulation in generating BL in the mouse (Sander et al., 2012). Based on their previous work implicating the PI3K pathway in the survival of mature B cells (Srinivasan et al., 2009), Sander et al. (2012) engineered mice expressing deregulated MYC and constitutively-active PI3K specifically in GC B cells, the putative BL cell of origin. These mice develop lymphoid malignancies strikingly similar to human BL, indicating that PI3K signaling can cooperate with MYC in the development of BL. Compared with previous attempts to model human BL in mice, the present one stands out for its faithful recapitulation of BL in terms of the activating pathways commonly deregulated in this lymphoma, the site of activation of these lesions (GC), and the resulting tumor phenotype, which displays all the characteristics of human BL in terms of histology, cell surface markers, expression of key transcription factors, and immunological history (Sander et al., 2012). Furthermore, co-activation of MYC-PI3K often selects for stabilizing mutations in cyclin D3, a key regulator of cell cycle progression in GC B cells (Peled et al., 2010). Importantly, similar mutations are reported in a small survey of human BL, further confirming this mouse model as an accurate phenocopy of human BL.

While the synergy between PI3K signaling and MYC deregulation was suspected based on normal B cell biology (Kumar et al., 2006) and confirmed by the phenotype of the new BL mouse model, it remained unclear whether and how the PI3K pathway contributes to human BL. However, an independent team led by Louis Staudt has now resolved this issue and determined the essential regulatory pathways that cooperate with MYC in BL pathogenesis (Schmitz et al., 2012). By comprehensive high-throughput RNA sequencing, they identified a cadre of somatic coding mutations in a large panel of BL cases and then examined which of the mutated genes/pathways was required to maintain the BL phenotype. Remarkably, they found that 70% of sBL display constitutive activation of PI3K signaling caused by mutations that either deregulate the activity of the transcription factor TCF3 (E2A) or inactivate its negative regulator ID3. The E2A/PI3K association in BL is especially intriguing in light of recent reports that this "module" has essential functions in B cell fate and GC biology (Kwon et al., 2008; Lin et al., 2010).

Furthermore, as observed in the mouse model above, a sizable fraction of human BLs carried somatic mutations that increase the stability of the E2A direct target cyclin D3, probably driving cell cycle progression. Pharmacological or genetic inactivation of either PI3K signaling or cyclin D3 function is toxic to BL cells, indicating that these lesions are required for tumor cell viability (Schmitz et al., 2012). Overall, these results demonstrate that the synergy between deregulated MYC, PI3K and cyclin D3 experimentally observed in mice is a naturally occurring pathway of BL lymphomagenesis in humans.

These new results raise a number of intriguing questions and opportunities. The transcriptome analysis of human BL samples clearly indicate that a substantial number of additional, recurrent, genetic lesions of potential functional significance are present in the coding genome of human BL (Schmitz et al., 2012). No doubt, additional analyses will be necessary to ascertain which of these are more relevant and/or required for full transformation. Given its remarkable mechanistic similarity to human BL, the new mouse model (Sander et al., 2012) should facilitate a systematic evaluation of these lesions in BL development. In addition, the initial analysis of human BL suggests that the eBL subtype may carry at least partially distinct lesions from sBL and hivBL (e.g., a much lower frequency of cyclin D3 mutation). Although this observation is still preliminary due to the limited number of eBL cases examined, it would be consistent with the distinctive features of eBL, including different chromosomal breakpoints and a much higher frequency of EBV infection of tumor cells. As such, eBL may arise from pathogenic pathways that are partially distinct from those driving sBL and hivBL. Finally, both the mouse and human tumors conclusively show that BL is a genetically distinct entity from other aggressive B cell lymphomas, especially diffuse large B cell lymphoma. These findings may therefore help in their differential diagnosis in cases in which the histologic pattern is not clearly discriminating.

Despite more than three decades of research, no effective drugs have yet been developed to counter the oncogenic consequences of MYC deregulation. Thus, a particularly welcome outcome of the new studies is their identification of feasible targets for BL therapy. Indeed, several approved drugs are already available to either inactivate PI3K signaling or cyclin D3 function, and preliminary results show that some of these are active against BL. If validated in appropriate clinical trials, these drugs would be far less toxic than currently available chemotherapeutic regimens for BL. If confirmed, these therapeutic developments could improve the already high rate of cure of sBL. But more importantly, they could change the still ominous clinical history of eBL and hivBL in developing countries. The availability of a faithful preclinical model of the disease, clearly identified targets, and continuously emerging new drugs suggest that important changes in the diagnostic, prognostic, and therapeutic management of BL may appear in the textbooks in the not so distant future.

REFERENCES

Dalla-Favera, R., Bregni, M., Erikson, J., Patterson, D., Gallo, R.C., and Croce, C.M. (1982). Proc. Natl. Acad. Sci. USA *79*, 7824–7827.

Gaidano, G., Ballerini, P., Gong, J.Z., Inghirami, G., Neri, A., Newcomb, E.W., Magrath, I.T., Knowles, D.M., and Dalla-Favera, R. (1991). Proc. Natl. Acad. Sci. USA *88*, 5413–5417.

Kumar, A., Marqués, M., and Carrera, A.C. (2006). Mol. Cell. Biol. *26*, 9116–9125.

Kwon, K., Hutter, C., Sun, Q., Bilic, I., Cobaleda, C., Malin, S., and Busslinger, M. (2008). Immunity *28*, 751–762.

Lin, Y.C., Jhunjhunwala, S., Benner, C., Heinz, S., Welinder, E., Mansson, R., Sigvardsson, M., Hagman, J., Espinoza, C.A., Dutkowski, J., et al. (2010). Nat. Immunol. *11*, 635–643.

Magrath, I. (2012). Br. J. Haematol. *156*, 744–756.

Peled, J.U., Yu, J.J., Venkatesh, J., Bi, E., Ding, B.B., Krupski-Downs, M., Shaknovich, R., Sicinski, P., Diamond, B., Scharff, M.D., and Ye, B.H. (2010). Cell Res. *20*, 631–646.

Sander, S., Calado, D.P., Srinivasan, L., Köchert, K., Zhang, B., Rosolowski, M., Rodig, S.J., Holzmann, K., Siebert, R., Bullinger, L., et al. (2012). Cancer Cell *22*, this issue, 167–179.

Schmitz, R., Young, R.M., Ceribelli, M., Jhavar, S., Xiao, W., Zhang, M., Wright, G.W., Shaffer, A.L., Hodson, D.J., Buras, E., et al. (2012). Nature. Published online August 12, 2012. http://dx.doi.org/10.1038/nature11378.

Srinivasan, L., Sasaki, Y., Calado, D.P., Zhang, B., Paik, J.H., DePinho, R.A., Kutok, J.L., Kearney, J.F., Otipoby, K.L., and Rajewsky, K. (2009). Cell *139*, 573–586.

Taub, R., Kirsch, I., Morton, C., Lenoir, G., Swan, D., Tronick, S., Aaronson, S., and Leder, P. (1982). Proc. Natl. Acad. Sci. USA *79*, 7837–7841.