EUROPEAN HEMATOLOGY ASSOCIATION

Diffuse large B-cell lymphoma - Section 1

Oncogenic mutations that promote plasmacytic differentiation in diffuse large B-cell lymphoma

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Seminal studies using gene expression profiling classified diffuse large B-cell Lymphoma (DLBCL) into two main subgroups: the germinal center B-cell (GCB)-DLBCL, and the activated B-cell (ABC)-DLBCL.[1] A major difference between these two DLBCL subtypes is the enriched presence of genetic lesions leading to constitutive NF-kappaB activation in the ABC-DLBCL subtype.[2] However, it is well defined that NF-kappaB can directly induce the expression of genes responsible for B to plasma cell differentiation, such as BLIMP1 and IRF4, and that ABC-DLBCLs show features of plasmacytic differentiation without losing their B-cell phenotype.[3] These observations led to the hypothesis that a block of B-cell differentiation occurs in the pathogenesis of ABC-DLBCL. Consistently, a fraction of human ABC-DLBCLs displays inactivating mutations in the BLIMP1 gene, a key regulator of plasma cell differentiation, while another mostly non-overlapping fraction displays enforced BCL6 expression through chromosomal translocation.[4-6] Using mouse modeling we demonstrated that the disruption of BLIMP1 or the enforced expression of BCL6 in GC B-cells, the putative cells of origin of DLBCL, synergized with the activation of the NF-kappaB pathway in the development of B-cell lymphomas that resemble human ABC-DLBCL.[7-8] Iterations of the mouse model systems now reveal that oncogenic mutations present in human ABC-DLBCL cooperate with NF-kappaB activation to form tumors displaying plasma cell features and loss of the B-cell phenotype. These observations reinforce the concept that a block in plasma cell differentiation is essential for the development of ABC-DLBCL and demonstrate that the interplay between oncogenic mutations determines the phenotype of the emerging tumor. How these specific characteristics of the ABC-DLBCL can be therapeutically exploited to improve the poor prognosis this disease will be discussed.

References

*1. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000;403(6769):503-11.

Seminal work in which the cell of origin classification of DLBCL was first presented.

*2. Compagno M, Lim WK, Grunn A, Nandula SV, Brahmachary M, Shen Q, et al. Mutations of multiple genes cause deregulation of NF-kappaB in diffuse large B-cell lymphoma. Nature. 2009;459(7247):717-21.

First demonstration of widespread genetic mutations enforcing NF-kB in DLBCL.

3. Wright G, Tan B, Rosenwald A, Hurt EH, Wiestner A, Staudt LM. A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. Proc Natl Acad Sci U S A. 2003;100(17):9991-6.

4. Pasqualucci L, Compagno M, Houldsworth J, Monti S, Grunn A, Nandula SV, et al. Inactivation of the PRDM1/BLIMP1 gene in diffuse large B cell lymphoma. J Exp Med. 2006;203(2):311-7.

5. Tam W, Gomez M, Chadburn A, Lee JW, Chan WC, Knowles DM. Mutational analysis of PRDM1 indicates a tumor-suppressor role in diffuse large B-cell lymphomas. Blood. 2006;107(10):4090-100.

*6. Mandelbaum J, Bhagat G, Tang F, Mo T, Brahmachary M, Shen Q, et al. BLIMP1/PRDM1 is a tumor suppressor gene frequently disrupted in activated B-cell like diffuse large B cell lymphoma. Cancer Cell. 2010;18(6):568-79.

(Together with reference 7) First demonstration that BLIMP1 functions as a tumour suppressor.

*7. Calado DP, Zhang B, Srinivasan L, Sasaki Y, Seagal J, Unitt C, et al. Constitutive canonical NF-kB activation cooperates with disruption of BLIMP1 in the pathogenesis of activated B cell-like diffuse large cell lymphoma. Cancer Cell. 2010;18(6):580-9.

First demonstration of the cooperative activity between constitutive NF-kB signaling and blockade of terminal differentiation in DLBCL pathogenesis.

8. Zhang B, Calado DP, Wang Z, Fröhler S, Köchert K, Qian Y, et al. An oncogenic role for alternative NF-κB signaling in DLBCL revealed upon deregulated BCL6 expression. Cell Rep. 2015;11(5):715-26.