EUROPEAN HEMATOLOGY ASSOCIATION

Mantle cell lymphoma - Section 1

Pathology and molecular pathogenesis of mantle cell lymphoma

German Ott

Department of Clinical Pathology, Robert-Bosch-Krankenhaus, Stuttgart, Germany

For a long time, mantle cell lymphoma (MCL) was viewed as a malignant lymphoid neoplasm with strikingly unique morphological, genetic and biological features and a uniformly aggressive clinical behavior. More recently, however, this attitude has changed. In the Istanbul Lymphoma Workshop jointly organized by the European Association of Haematopathology and the Society of Hematopathology, the cases presented illustrated MCL as a lymphoma with a broad spectrum from indolent to very aggressive, and with varying biological and genetic features, the most important seems to be proliferation.[1] The existence of Cyclin D1 negative MCL was now firmly established, and these cases can now reliably be identified by the recognition of SOX11 overexpression and frequently harbor Cyclin D2 translocations.[2] The rare occurrence of MCL with a long-term indolent behavior is a new concept[3,4] and the indolent behavior of MCL in these cases was linked to downregulated expression of the transcription factor SOX11 and confers particular morphological and biological traits to tumors.[5] More interesting, SOX11 has now been identified as an important partner to CyclinD1 overexpression in inducing the malignant phenotype via downregulation of PAX5 expression mediated by BCL6 and blocked of terminal B cell differentiation.[6,7] Finally, next generation sequencing studies begun to unravel the nature and impact of genetic aberrations in this type of lymphoid cancer.[8] Mantle cell lymphoma, therefore, represents a malignant lymphoma with discrete primary genetic alterations, cooperating mechanisms in disease progression and a limited spectrum of genetic alterations ultimately defining the fate of the patient (Figure 1).

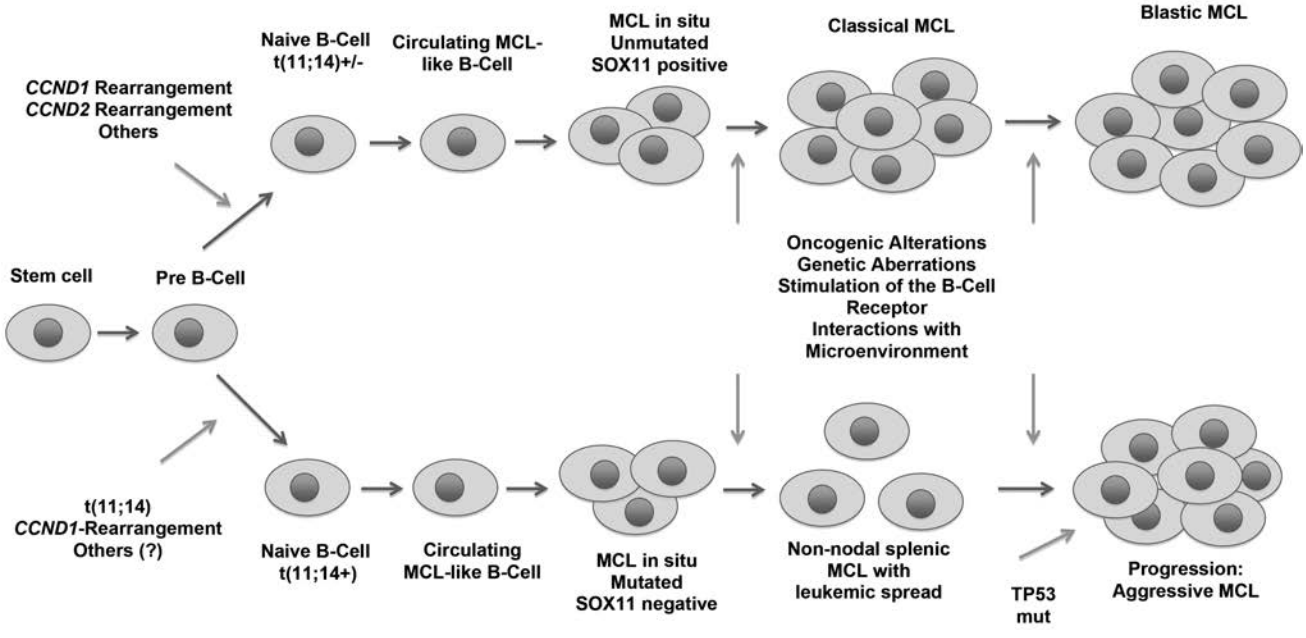

Figure 1. A hypothetical scheme of MCL development and evolution.

Mantle cell lymphoma - Section 1

References

*1. Sander B, Quintanilla-Martinez L, Ott G, Xerri L, Kuzu I, Chan JK, et. al. Mantle cell lymphoma-a spectrum from indolent to aggressive disease. Virchows Arch. 2016;468(3):245-57.

An overview on varying morphological and biological features in MCL.

*2. Salaverria I, Royo C, Carvajal-Cuenca A, Clot G, Navarro A, Valera A, et al. CCND2 rearrangements are the most frequent genetic events in cyclin D1(-) mantle cell lymphoma. Blood. 2013;121(8):1394-402.

A large series of Cyclin D1 negative MCL and the importance of Cyclin D2 aberrations.

*3. Fernàndez V, Salamero O, Espinet B, Solé F, Royo C, Navarro A, et al. Genomic and gene expression profiling defines indolent forms of mantle cell lymphoma. Cancer Res. 2010;70(4):1408-18.

Description of the biological basis of indolent MCL.

4. Navarro A, Clot G, Royo C, Jares P, Hadzidimitriou A, Agathangelidis A, et al. Molecular subsets of mantle cell lymphoma defined by the IGHV mutational status and SOX11 expression have distinct biologic and clinical features. Cancer Res. 2012;72(20):5307-16.

5. Ribera-Cortada I, Martinez D, Amador V, Royo C, Navarro A, Beà S, et al. Plasma cell and terminal B-cell differentiation in mantle cell lymphoma mainly occur in the SOX11-negative subtype. Mod Pathol. 2015;28(11):1435-47.

*6. Vegliante MC, Palomero J, Pérez-Galán P, Roué G, Castellano G, Navarro A, et al. SOX11 regulates PAX5 expression and blocks terminal B-cell differentiation in aggressive mantle cell lymphoma. Blood. 2013;121(12):2175-85.

Identification of SOX11 as an important co-factor in inducing the malignant phenotype in MCL.

7. Palomero J, Vegliante MC, Eguileor A, Rodríguez ML, Balsas P, Martínez D, et al. SOX11 defines two different subtypes of mantle cell lymphoma through transcriptional regulation of BCL6. Leukemia. 2015; [Epub ahead of print]

*8. Beà S, Valdés-Mas R, Navarro A, Salaverria I, Martín-Garcia D, Jares P, et al.Landscape of somatic mutations and clonal evolution in mantle cell lymphoma. Proc Natl Acad Sci U S A. 2013;110(45):18250-5.

An extensive NGS study deciphering secondary mutations in MCL.