Summary

At the molecular level mantle cell lymphoma (MCL) is characterized by a specific translocation t(11;14) leading to a transcriptional activation of the cyclin D1 gene. Cyclin D1 is a key regulator of the cell cycle and thus its overexpression leads to a proliferation advantage of the cells, which is important in the MCL pathogenesis. Moreover, proliferation activity is an important and the first biological prognostic factor for the MCL prognosis prediction.

We developed an optimal approach to analyze quantitatively the cyclin D1 expression level in lymphoma specimens using real-time PCR. We detected the cyclin D1 overexpression in 97% MCL specimens. The developed method supported the MCL differential diagnosis with a high reliability, including a differential diagnosis of extranodal lymphomas. Moreover, the cyclin D1 mRNA expression level measurement also provided an approach to study a key molecule in the MCL pathogenesis at the molecular level.

We demonstrated a direct relation between t(11;14), a cyclin D1 mRNA overexpression and a pathologic cyclin D1 protein synthesis in the MCL cells. The cyclin D1 mRNA level also correlated with the mRNA level of proliferation markers implying a quantitative cell cycle regulation by a controlled cyclin D1 level, which controls the proliferation degree, and indicating the MCL pathogenesis as: t(11;14) → cyclin D1 mRNA overexpression → abnormal cyclin D1 protein synthesis → upregulation of the G1 to S phase transition→ increased proliferation.

Moreover, the methodology provided a molecular target for the disease course monitoring in bone marrow (BM). In 97% of BM aspirates the cyclin D1 level corresponded to the MCL BM infiltration. Correlating the data with the disease clinical status we revealed that the cyclin D1 decrease and increase accompanied the disease remission and relapse, respectively. We showed that monitoring of the cyclin D1 expression level as a tumor marker in BM provided important information about the disease course and therapy response at the molecular level and it allowed the disease dynamics monitoring, including minimal residual disease.

We also developed a technique to precisely and objectively measure the expression level of proliferation markers, which has so far been possible to analyze solely at the semi-quantitative level using immunohistochemistry, inadequately for clinical trials. We showed the reliability, reproducibility and objectification for real-time PCR evaluation of the expression level of prognostically important proliferation markers. We observed a heterogeneous proliferation activity in lymphoma specimens, which may be related to a variable disease prognosis. The developed technology accomplishes the clinical trials requirements and it opens the possibility to routinely analyze the prognostic factors at the quantitative level as recommended by "Lymphoma/Leukemia Molecular Profiling Project".