

Abstract:

Mantle cell lymphoma (MCL) is a subtype of B-non-Hodgkin's lymphoma, characterized by often relapses. Despite an Ibrutinib (a Bruton's kinase inhibitor) implementation into salvage therapy, these patients often relapse with biologically highly aggressive disease and very poor prognosis. An increased activation of alternative metabolic pathways was described as one of ibrutinib-resistance mechanisms. Some of these pathways have also significant proangiogenic activity (e.g. PI3K-AKT-mTOR).

In presented study, we established and standardized a real-time ultrasound and photoacoustic imaging of neovascularization and tissue oxygenation of subcutaneous MCL tumors in mice. Ultrasound and photoacoustic imaging is a fast, non-invasive method for angiogenesis evaluation in subcutaneous tumors with huge preclinical potential. Using MCL mice models, we also demonstrated the importance of CD31/PECAM-1 expression for engraftment, growth and spread of MCL cells *in vivo*. The level of CD31 expression in primary MCL cell (obtained directly from MCL patients) positively correlates with extent of extranodal involvement. CD31 facilitates survival and regulates extranodal spread of mantle cell lymphoma. We found that increased VEGFA expression causes not only increased microvessel density due to higher sprouting angiogenesis stimulation, but also leads to complex changes in biological behavior of MCL cells, which become more aggressive.

On preclinical level, we confirmed a strong positive correlation of angiogenesis extent and biological aggressiveness of MCL. The results confirm, that patients with MCL (including those refractory to ibrutinib) could profit from the implementation of antiangiogenic drugs into salvage therapy regimens.