ACTIVATED MTORC1/2 COMPLEXES AND THEIR BIOLOGICAL IMPORTANCE IN LYMPHOID MALIGNANCIES

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Elevated mammalian target of rapamycin (mTOR) activity is characteristic in several tumors and lymphoid malignancies. The mTOR kinase regulates cell growth, cell cycle progression, survival and cellular metabolism in response to cellular signals and different microenvironmental factors. However, mTOR activity related changes and their relation to protein expression of mTOR complexes in lymphoid malignancies are poorly understood.

We investigated mTOR activity related phospho-proteins and the elements of complexes using different methods (immuncyto- and immunohistochemistry, ELISA, Western-blott, flow cytometry), depending on sample type (fresh/fixed human tissues, isolated cells or cell lines). The results were compared to mTOR inhibitor sensitivity in vitro or correlated with clinical data. The effects of in vitro treatments were analyzed to study the mTOR inhibitor sensitivity of cell lines and in parallel Duolink technique was used to detect mTORC1/C2 complex availability, which was compared to inhibitors sensitivity.

We found high mTOR activity in all acute lymphoid leukemia (ALL) cases and in certain lymphomas (mantle cell, anaplastic large cell, Burkitt, diffuse large B cell [DLBCL], Hodgkin [HL] and cutaneous T cell lymphomas). Detailed characterization of DLBCLs, HLs and ALL cases showed that high mTOR activity – especially mTORC2 expression – is a sign of unfavorable prognosis. mTORC1 activity was significantly higher in ALL patients with poor prognosis. Moreover, high mTOR activity with Rictor overexpression correlated to worse prognosis and shorter survival in DLBCL patients. HL patients usually have favorable prognosis. We detected elevated mTOR activity in 92% of HLs, however, Rictor (an element of mTORC2) was not found in these cases. The examined lymphoma cell lines were characterized by increased mTOR activity; however, the expression pattern of Raptor, Rictor, phospho-S6 and mTOR-Rictor complex was cell line dependent. Moreover, inhibitor sensitivity of these cell lines showed good correlation with the expression of proteins related to mTORC1 and C2.

These results confirm that mTOR activity is increased in certain human lymphomas and ALLs. Accordingly, the prognostic and predictive value of mTOR complexes should be taken into consideration for personalized therapy design with targeted mTOR inhibitors available soon, especially in cases with high expression of mTORC2 related proteins.

Supported by OTKA81624, OTKA 84262