Rapamycin treatment of a child with severe PTEN Hamartoma Tumor Syndrome (PHTS) – a case report and in vitro studies

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Background: PTEN Hamartoma Tumor Syndrome (PHTS) is a rare genetic disease associated with mutations in the PTEN gene. A child with PTEN deletion presenting with massive lipomatosis and thymus hyperplasia received an individualized rapamycin treatment.

Aims: We investigated whether rapamycin can improve the patient`s symptoms and tested in vitro whether pharmacological inhibition of AKT, PI3-kinase or mTOR reduced viability of the patient`s lipoma cells. Furthermore, we aimed to elucidate the mechanism of the potential rapamycin resistance in vitro.

Methods: Preadipocyte cultures from resected lipoma tissue of the patient were incubated with inhibitors of the PI3-kinase/AKT/mTOR signaling pathway. Viability and apoptosis were assessed using WST-1 and AnnexinV/PI assay.

Results: Rapamycin treatment led to an attenuation of lipomatosis growth and decreased thymus volume. However, thymus growth accelerated again after 19 months of therapy, suggesting the occurrence of rapamycin resistance. Western blot analysis after rapamycin incubation of lipoma cells revealed attenuated activity of the mTOR complex-1 target p70S6-kinase with subsequent upregulation of AKT, possibly via IRS-1. Rapamycin decreased lipoma cell viability by 43.4±2% and adipocyte differentiation by 72.7±5%, but did not induce apoptosis in vitro. In contrast, inhibitors of the PI3-kinase (LY294002) and AKT (perifosine) induced apoptosis significantly by 65.0±3% and 84.5±1%.

Conclusion: Rapamycin showed only limited treatment success. Our in vitro findings point to PI3-kinase and AKT inhibitors to be of therapeutical value for patients with severe forms of PHTS.