Inhibition of Rapamycin induced AKT activation elicits differential anti-tumor response in head and neck cancers

Padhma Radhakrishnan[1], Ulaganathan Baraneedharan[1], Muthu Dhandapani[1], Allen Thyakumar[1], Dency Pinto[1], Arun Prasath[1], Ayyappan Velu[1], Kamal A[1], Nilesh Brijwani[1], Rohini Nair[1], Basavaraja R[1], Misti Jain[1], Saravanan Thiyagarajan[1], Biswanath Majumder[1], Mallik Sundaram[1], Prasad Narayanan[2], Vikram D. Kekatpure[2], Pradip K. Majumder[1].

[1]Mitra Biotech, Bangalore, India; [2]Mazumder Shaw Cancer Center, Bangalore, India

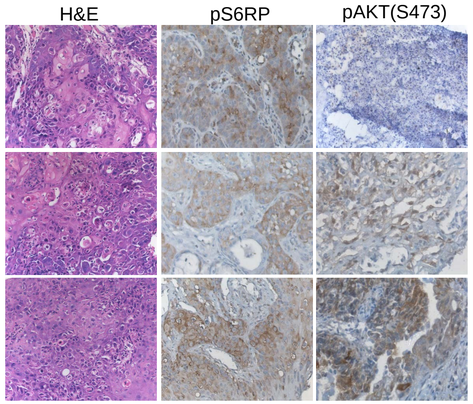
Abstract

The PI3K/AKT/mTOR pathway is an important signaling axis that is perturbed in majority of cancers. Biomarkers such as pS6RP, GLUT1 and tumor FDG uptake are being evaluated in patient stratification for mTOR pathway inhibitors. In the absence of a clear understanding of the underlying mechanisms in tumor signaling, the biomarker strategy for patient stratification is of limited use. Here, we show that no discernible correlation exists between FDG uptake and the corresponding Ki67, GLUT1, pS6RP expression in tumor biopsies from Head and Neck Cancer (HNC) patients. Correlation between GLUT1 and pS6RP levels in tumors was observed but elevated pS6RP was noticed even in the absence of concomitant AKT activation, suggesting other downstream molecules of PI3K/AKT and/or other pathways upstream of mTOR, are active in these tumors. Using an *ex-vivo* platform, we identified putative responders to Rapamycin, an mTOR inhibitor in these tumors. However, Rapamycin did not induce anti-tumor effect in the majority of tumors with activated mTOR, potentially attributable to the observation that Rapamycin induces feedback activation of AKT. Accordingly, treatment of these tumors with an AKT inhibitor and Rapamycin uniformly resulted in abrogation of mTOR inhibition induced AKT activation in all tumors but failed to induce anti-tumor response in a subset. Phosphoproteomic profiling of tumors resistant to dual AKT/mTOR inhibitors revealed differential activation of multiple pathways involved in proliferation and survival. Collectively, our data suggest that in addition to biomarker based segregation, functional assessment of patient tumor prior to treatment with mTOR/AKT inhibitors might be useful for patient stratification.

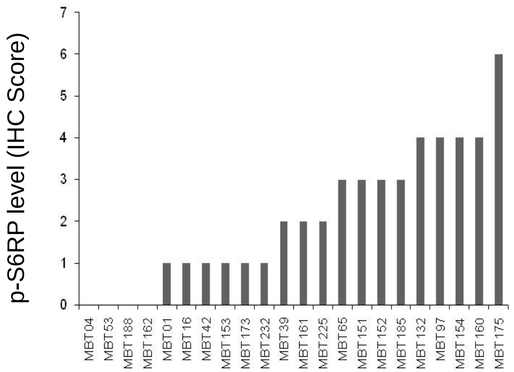
Objectives

- To understand the correlation between FDG-PET, tumor proliferation and the activation of mTOR pathway
- Identifying tumors which are dependent on mTOR and mTOR/AKT axis using a functional assays based platform technology
- Mechanism of tumors which are not sensitive to Rapamycin and AKT inhibitor

Study design

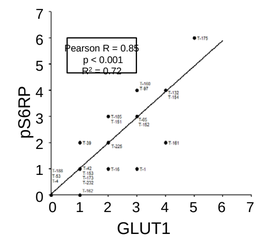


Activation of mTOR pathway in tumors of patients with Head and Neck Cancer is not contingent upon AKT activation

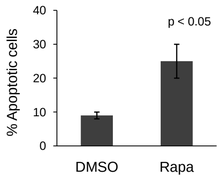


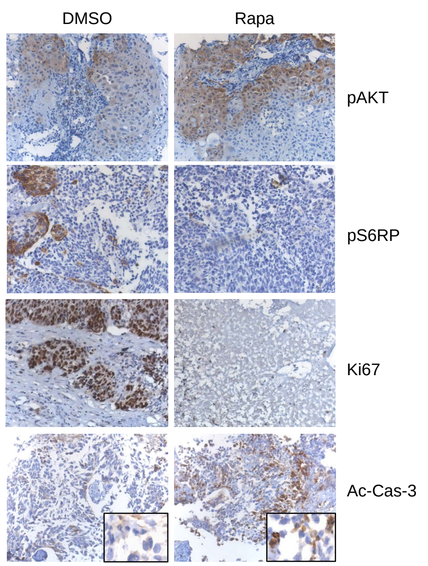
Expression level of pS6RP in all twenty two patients was plotted based on IHC score

Results

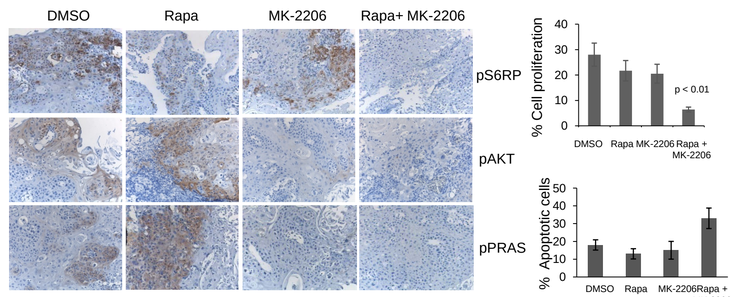


Correlation of GLUT1 and pS6RP levels in all HNC tumors



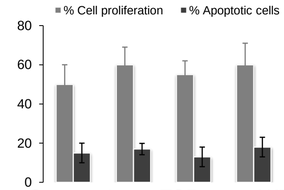


A small subset of tumors with activated mTOR, are sensitive to Rapamycin treatment.

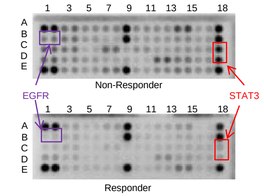


Targeted ablation of Rapamycin mediated up-regulation of AKT signaling is key for anti-tumor effect in a subset of Rapamycin insensitive tumors

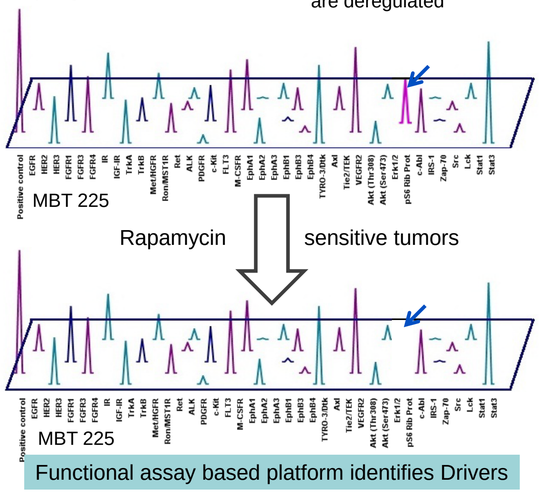
Results



Co-targeting mTOR and AKT does not elicit anti-tumor efficacy in majority of Rapamycin insensitive tumors



Targeted phospho-protein expression profiling suggests multiple pathways are deregulated



Functional assay based platform identifies Drivers

Summary

- No correlation between FDG-PET and tumor cell proliferation and mTOR activation was found in HNSCC. However, a strong correlation was observed between mTOR pathway and GLUT1 up-regulation
- Functional assays based platform technology accurately identifies tumors which are dependent on mTOR pathway