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V-ATPase inhibitors enhance the effect of Tepotinib (c-MET inhibitor) or RMC-6236 (Pan-Ras(ON) inhibitor) in KRAS-mutant NSCLC

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Introduction

KRAS G12C inhibitors (sotorasib or adagrasib) in monotherapy have short-lived response in metastatic KRAS G12C NSCLC patients. Resistance to KRAS G12C inhibitors appear due to the presence of coexisting KRAS mutations, activation mutations of other RAS isoforms, and amplifications or activation mutations upstream or downstream of RTK pathways.

We previously reported that targeting c-Met (tepotinib), upstream growth factor signal transducer of KRAS, decreased cell viability in a broad panel of KRAS G12C and non-G12C NSCLC cell lines. The proliferation inhibition was increased when tepotinib was combined with omeprazole, known to act as a V-ATPase proton pump inhibitor. The aims were to first assess the half maximal inhibitory concentration (IC₅₀) of tepotinib versus RMC-6236 in KRAS G12C and non-G12C-mutant NSCLC cell lines. Secondly, the potential synergism of omeprazole + tepotinib versus omeprazole + RMC-6236. Finally, by western blot analysis, to see the behaviour of MRAS and YAP1 among other proteins as biomarkers of adaptive resistance.

Methods

In vitro studies were conducted in NSCLC cell lines, including NCI-H358, a generated H358 line resistant to sotorasib (H358R), NCI-A549, and NCI-H23. Cell lines were treated with tepotinib (c-Met inhibitor) or RMC-6236 (pan-RAS(ON) inhibitor) alone and in combination with omeprazole pre-treatment. Cell viability assays were performed by MTT, and synergism/antagonism analysis was carried out using Combenefit and Sinergy finder + computational programs. Western blot analysis was performed to characterize total and phosphorylated proteins.

Results

RMC-6236 showed a stronger inhibitory effect in H358 than in H358R and H23 cell lines. Omeprazole increased the cell growth inhibition effect of RMC-6236 and showed synergism in all cell lines. RMC-6236 and omeprazole pre-treatment decreased activation of several tyrosine kinase receptors: MET, EGFR, and LRP6, as well as downstream proteins such as AKT, ERK1/2, and YAP1. RMC-6236 treatment alone enhanced the expression of MRAS and translocated β -catenin to the nucleus, however, when omeprazole pre-treatment was added, the upregulation of MRAS and β -catenin disappeared.

Of interest is the fact that tepotinib + omeprazole pre-treatment decreased the expression of MRAS, the cancer stem cell marker (Hes1), ERK1/2, AKT, STAT3, and YAP1, as well as EGFR, EphA2, and LRP6.

Conclusions

Early evidence of data points out that omeprazole increases the anticancer effect of either tepotinib or RMC-6236 in KRAS G12C-mutant and non-G12C-mutant NSCLC cell lines. Western blot analysis shows several hints that the combination of omeprazole pretreatment + tepotinib or omeprazole + RMC-6236 both combinations can avoid upregulation of MRAS and YAP1 and several receptor tyrosine kinases. To further discern is the leverage of tepotinib in front of RMC-6236.