The mTOR kinase inhibitor AZD-2014 enhances the antitumor effects of XPO1 antagonist KPT-185 in mantle cell lymphoma

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Aim/Background: Mantle cell lymphoma (MCL) is an aggressive B-cell lymphoma characterized by the aberrant expression of several oncogenic effectors. The nuclear transporter exportin-1 (XPO1) is highly expressed in MCL and is associated with pathogenesis. The frequent activation of mTOR signaling, a central cellular metabolism regulator, is an important therapeutic target in MCL. In this study, we investigated the antitumor effects and molecular / metabolic changes of the combination of XPO1 antagonist KPT-185 with second generation mTOR kinase inhibitor AZD2014 on MCL.

Methods: Four MCL cell lines Z138, JVM2, MINO, and Jeko-1 were utilized. Cell viability was evaluated by MTT, cell counting and PI flow cytometric analysis. We then performed cDNA array, iTRAQ proteomic analysis, immunoblotting and metabolome analysis using CE-MS.

Results: AZD2014 significantly enhanced the KPT-185-induced cell growth inhibition in the tested MCL cell lines. Transcriptomic analysis using cDNA array showed that KPT-185 / AZD-2014 affected expression of 137 genes (fold change > 2) in Jeko-1 cells. IPA analysis implicated the inhibition of STAT3 as one of the mechanistic leads. iTRAQ detected significant upregulation of glycolysis / gluconeogenesis pathways after KPT-185 treatment and KPT-185 / AZD-2014 repressed ribosomal biogenesis (KEGG analysis) with implicated activation of p53 and inhibition of p70 S6K and MYCN (IPA) in at least 2 of the 4 tested cell lines. We further found the downregulation of p-S6K and c-Myc and the upregulation of p27KIP and cleaved caspase-9 by immunoblotting. Of note, CE-MS demonstrated that the increase of lactic acid by KPT-185 was effectively reversed by AZD-2014, and that TCA cycle metabolites citric acid, succinic acid and malic acid were drastically decreased by KPT-185 / AZD-2014 combination.

Conclusions: Our findings indicated that inhibition of mTOR kinase enhances the antitumor effects of the XPO1 antagonist KPT-185 with effective repression of XPO1 blockage-induced glycolysis / gluconeogenesis upregulation. These findings suggest a novel promising combinatorial strategy targeting pro-survival metabolism in MCL.

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