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Effect of combination of azacitidine and valproic acid on PI-PLCbeta1 signaling in high-risk myelodysplastic syndromes

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Nuclear inositides are involved in several processes, including DNA repair, transcription regulation and RNA dynamics in normal and neoplastic conditions. Namely, nuclear phosphoinositide-phospholipase C (PI-PLC) beta1 plays an essential role in cell cycle regulation, mainly targeting cyclin D3. Moreover, PI-PLCbeta1 has been linked to the pathogenesis of myelodysplastic syndromes (MDS), i.e. clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis in one or more of the lineages of the bone marrow. Frequently, MDS result in a slow decrease in blood cell counts, but they may also show a worsening severe cytopenia or, in about 30% of all the cases, evolve into Acute Myeloid Leukemia (AML). Currently, azacitidine (AZA), a DNA methyltransferase inhibitor, is used to prolong survival and delay the MDS evolution into AML, alone or in combination with the histone deacetylase inhibitor valproic acid (VPA).

In this study we analyzed the effect of AZA and VPA on inositide signaling pathways on high-risk MDS patients receiving AZA (75 mg/sqm/die SC for 7 days/28 days) and VPA (600-1.500 mg/die orally). We also studied the effect of AZA and VPA on HL60 cell line, which shows a hyper-methylation of PI-PLCbeta1 promoter and is affected by AZA treatment. Our results demonstrate that VPA enhances the effect of AZA on inositide signaling pathways, increasing the demethylation effect induced by AZA on PI-PLCbeta1 promoter and inducing gene and protein expression of other critical molecules. Taken together, our findings demonstrate for the first time that, at a molecular level, AZA and VPA can modulate key molecules of inositide signaling pathways, thus hinting at a role for these molecules as therapeutic targets for high-risk MDS.

Key words

PI-PLCbeta1, Nucleus, Myelodysplastic Syndromes