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Epigenetic regulation of nuclear inositide signalling in high-risk MDS patients

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Inositide signalling pathways are involved in cell growth, differentiation and apoptosis and play a role in the progression of myelodysplastic syndromes (MDS) towards acute myeloid leukemia (AML). The combination of the DNA methyltransferase inhibitor azacitidine (AZA) and the HDAC inhibitor valproic acid (VPA) has been demonstrated to be active and associated with a high response rate in patients with high-risk MDS and unfavourable prognosis. In the last few years, our group demonstrated not only that phosphoinositide-phospholipase C beta1 (PI-PLCbeta1) promoter gene is hyper-methylated in higher-risk MDS, but also that it is affected by epigenetic therapy. Indeed, AZA, alone or in combination with VPA, was able to induce PI-PLCbeta1 demethylation and expression. In this study we further investigated the role of lipid signalling pathways during epigenetic therapy, focusing on the functional effect of AZA and VPA on PI-PLCbeta1 promoter in high-risk MDS patients. The study included 20 high-risk MDS patients (IPSS risk: intermediate-2 or high): 8 of them were treated with AZA alone (75 mg/m^2/day SC for 7 days/28 days), whereas 6 of them received the combination of AZA with VPA (600-1500 mg/ daily orally) and the remaining 6 were treated only with best supportive care. For each patient we analyzed the effect of epigenetic therapy in correlation to PI-PLCbeta1 signalling, by analyzing the binding affinity of transcription factors correlated to hematopoietic stem cell differentiation and proliferation. 8/20 (40%) of our MDS patients showed a favourable hematologic response to the epigenetic therapy and an increase in PI-PLCbeta1 expression, as compared with the pre-treatment period, thus confirming the involvement of this molecule in response to demethylating agents. Moreover, MDS patients responding to the epigenetic treatment seem to involve the recruitment of specific transcription factors to PI-PLCbeta1 promoter during the regulation of methylation processes. Taken together, our data are therefore consistent with the hypothesis of a correlation between the epigenetic treatment and PI-PLCbeta1 signalling, thus hinting at a role for PI-PLCbeta1 in monitoring the efficacy of epigenetic therapy and possibly paving the way for the development of innovative therapeutic strategies in high-risk MDS.

Keywords: Nucleus, Epigenetics, PI-PLCbeta1, Signal Transduction, Topography, Hematopoietic System