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Differential activation of nuclear inositide-dependent signalling pathways during erythropoiesis and myelopoiesis induced by lenalidomide and azacitidine in myelodysplastic syndromes (MDS)

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Inositide-dependent signalling pathways regulated by phosphoinositide-specific phospholipase C (PI-PLC) beta1 have been demonstrated to play important roles in MDS pathogenesis and in cell differentiation (1). Moreover, the MDS therapy aims at inducing myeloid and/or erythroid differentiation of MDS stem cells. Indeed, azacitidine is a demethylating agent that can induce myeloid differentiation. On the other hand, lenalidomide may restore a normal erythropoiesis. The exact molecular mechanisms underlying the effect of azacitidine and lenalidomide in MDS cells are still unclear, although it is clear that these therapies regulate stem cell proliferation, differentiation and apoptosis (2).

The combination of azacitidine and lenalidomide in MDS therapy is now under consideration, given the capability of both drugs to balance proliferation and differentiation processes (3).

In this study we analyzed the molecular effect of this combination therapy on PI-PLC isoenzymes, not only studying PI-PLCbeta1, but also PI-PLCgamma1, that can be associated with erythropoiesis.

We analyzed 44 patients diagnosed with high-risk MDS who were given azacitidine and lenalidomide. Given the limited number of cells, we quantified the expression of these molecules by Real-Time PCR analyses and immunocytochemical experiments. Moreover, we carried out cell cycle analyses and studied both PI-PLCbeta1 methylation status and the expression of Globin genes.

In our case series, 28/44 patients were evaluable, with an overall response rate of 78.6% (22/28 cases). At a molecular level, a significant increase of PI-PLCbeta1 and/or PI-PLCgamma1 expression was associated with a favourable clinical response to the combination therapy. Responder cases also showed an increase of Beta-globin expression, hinting at a specific contribution of lenalidomide on erythroid activation, whilst the frequent demethylation of PI-PLCbeta1 promoter could be specifically linked to azacitidine.

Taken together, our results show that the combination of azacitidine and lenalidomide can be important for activating PI-PLC isoenzymes, therefore regulating myeloid and erythroid differentiation in MDS cells.

References

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Keywords

Nuclear Inositide Signalling; Erythroid Differentiation; Myeloid Differentiation.

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