OVEREXPRESSION OF MICRORNA-16-2 CONTRIBUTES TO THE ABNORMAL ERYTHROPOIESIS IN POLYCYTHEMIA VERA.


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SUMMARY:

MicroRNAs are a class of short noncoding RNAs that regulate gene expression at the post-transcriptional level through binding to the 3’ UTR of target mRNAs. Growing evidences show that these molecules are involved in many biological processes such as cell proliferation, differentiation and apoptosis, and that the deregulated expression of microRNAs constitutes a common event in many different neoplasms. In this work, a significantly increased miR-16 expression has been observed during erythroid differentiation of CD34+ cells derived from polycythemia vera (PV) patients compared to healthy donors, suggesting a possible role of this miRNA in driving the abnormal erythropoiesis in PV. Indeed, this alteration appears to be distinctive of PV, since it has not been observed in other myeloproliferative neoplasms, secondary erythrocytosis and myelodysplastic syndromes. It has been shown that miR-16 overexpression is a consequence of the deregulated activation of pre-miR-16-2 gene on chr3 rather than pre-miR-16-1 on chr13, and that miR-16 expression correlates with levels of the host gene SMC4, of which pre-miR-16-2 is intronic. In addition miR-16 expression seems to be independent of JAK/STAT pathway hyperactivation, the main molecular feature in this disease. To address a functional role of this alteration in the pathogenesis of PV, the expression of miR-16 has been forced in normal CD34+ cells; this induced expression caused an overall increased erythroid expansion in cells overexpressing miR-16 compared to controls, both in liquid culture and in clonogenic assays. On the contrary, miR-16 knockdown by siRNAs (small antagonists) leads to a decreased of both erythropoietin-dependent and erythropoietin-independent erythroid colonies formation in semisolid cultures obtained from PV CD34+ cells. Furthermore, the effects of miR-16 depletion through antagoniRs administration in erythropoietin-treated mice, a reliable model of abnormally stimulated erythropoiesis, have been evaluated. miR-16 knockout largely impaired the physiological response to erythropoietin administration compared to placebo treated mice, preventing the development of erythrocytosis. Overall these data favor a role of miR-16 in physiological erythropoiesis and support the hypothesis that its overexpression may constitute a molecular event contributing to PV pathogenesis, shedding new lights on the molecular basis of this disorder.