Abnormalities of microRNAs in myeloproliferative neoplasms

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MicroRNAs (miRNAs) are small non-coding single-strand RNA molecules that regulate the expression of an usually wide number of target genes through binding to their 3’ untranslated region. Due to this pleiotropic action, miRNAs are powerful regulators of many cellular processes in the steady state, during cell differentiation, and are involved in cancer as they can function both as oncogenes and tumor suppressor molecules. There is also strong evidence that miRNAs are involved in the development, maturation and activity of hematopoietic cells by finely tuning differentiation and modulating the cell response to stimuli. miRNA deregulation has been observed in chronic and acute leukemias and in lymphomas, and a role for some miRNAs in leukemogenesis is being increasingly recognized. Deregulation may be due to mutations, defective epigenetic control, multi-factor circuit regulation, and a combination of these. A better understanding of the interplay between miRNAs and coding RNAs will be pivotal also to address the therapeutic impact of miRNA based approaches.

Studies of microRNA abnormalities in the myeloproliferative neoplasms (MPN) are in their beginning and no validated miRNA profiling has been established yet. We studied miRNA expression in granulocytes from patients with primary myelofibrosis (PMF), and found 60 miRNAs with differential expression compared to normal cells. Furthermore, there was a global down-regulation of miRNAs, as typically reported in cancer cells. Only imperfectly some miRNAs allowed to classify PMF granulocytes from PV or essential thrombocythemia (ET), while the difference with controls was more defined. Increased expression of miR-182 and -183 correlated with the JAK2V617F allele burden. No validated target could be identified. By studying mononuclear cells, Bruchova et al. first found a significant down-regulation of miR150 in PV. Then, by studying erythroid maturation in culture, three expression patterns of miRNAs were observed in normal erythropoiesis: progressive downregulation of miR-150, miR-155, miR-221, miR-222; upregulation of miR-451, miR-16 at late stages of erythropoiesis; and biphasic regulation of miR-339, miR-378. An abnormal decrease of miR-150 during the intermediate and late stages of differentiation in PV erythroid progenitors was documented.

We are in the process of detailing miRNA profiling in isolated CD34+ cells from patients with PV, PMF and ET. Eight miRNAs appear to be strongly differentially expressed in CD34+ cells from MPN compared to control cells, six are increased and two decreased. Among these are miRNAs included in a signature associated with common myeloid/erythroid progenitor commitment (e.g., miR-181 family, miR-221, miR-154) in cord blood-derived CD34+ or included in a gene signature in LAM M3. We will also present data showing that miR-16 may be involved in the abnormal expansion of erythropoiesis in patients with PV. We found significantly increased levels of mature miR-16 in purified CD34+ cells and erythroid cells generated in-vitro from PV patients. Forced expression of miRNA-16 in normal CD34+ cells enhanced erythroid progenitor cell proliferation and maturation, while exposure of PV CD34+ cells to pre-miR-16 siRNA caused a reduced
proliferation of erythroid progenitors and prevented the formation of erythropoietin-independent erythroid colonies. Finally, we described a role of miR-16 in in-vivo erythropoiesis since mice injected with a miR16 antagonim showed attenuated erythroid response to exogenous erythropoietin.

In summary, there are still scanty information about miRNA abnormalities in MPN and their role in disease pathogenesis, and no specific molecular abnormality nor a mechanistic explanation for the observed differential expression is available, but evidence continues to accumulate supporting the involvement of miRNAs in MPN.

Selected references