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Gentile Dott.ssa **Valentina Randazzo**,

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Titolo: UPREGOLAZIONE DEL MIR-29A E IPERMETILAZIONE DEL DNA GENOMICO NELLE LAM A CARIOTIPO NORMALE DNMT3A MUTATE

Title: UPREGULATION OF MIR-29A AND GENOMIC DNA HYPERMETHYLATION IN NORMAL KARYOTYPE AML SHOWING DNMT3A MUTATION.

Autori: Randazzo V(1); Agueli C(1); Salemi D(1); Valenti D(1); Mirto M(2); Marfia A(1); Bica MG(1); Cannella S(1); Dragotto P(1); Romano A(1); La Rosa C(2); Caradonna F(2); Fabbiano F (1); Santoro A(1)

Affiliazioni: (1)Laboratorio di Diagnostica Integrata Oncoematologica e Manipolazione Cellulare (Divisione di Ematologia con UTMO) Ospedali Riuniti Villa Sofia-Cervello Palermo, (2)Dipartimento di Scienze e Tecnologie Biologiche Chimiche e Farmaceutiche (Sezione di Biologia Cellulare) Università di Palermo

Testo: DNMT3A, a member of DNA methyltransferases, is mutated in approximately 22% of de novo normal karyotype acute myeloid leukemia (NK-AML) patients leading to adverse overall survival. The highly recurrent mutation in DNMT3A is a “gain of function-like” at codon R882. To indagate about miRNA signature in NK-AML R882-DNMT3A mutated we studied by qRT-PCR the expression of 384 known human miRNA in 9 selected de-novo AML DNMT3A mutated. We compared miRNA expression data with our previous results obtained in 31 AML DNMT3A wild type (WT) and we focused on a strong up-regulation of miR155, miR29a, miR196b and miR25. We consolidated this data in additional 24 new DNMT3A mutated AML and we confirmed the upregulation of miR29a (fold 289,201; p-value 0,000); miR29a has been demonstrated to directly target 3’UTR of DNMT3A resulting in a global hypomethylation but also directly suppress two major DNA demethylases TET1 and TDG.
To understand the pathogenesis of the subgroup of AML DNMT3A mutated and the existing correlation between miR29a and its targets, we evaluated the expression levels of miR29a targets DNMT3A, TET1 and TDG in 43 AML DNMT3A mutated patients and in 43 control group AML DNMT3A WT by qRT-PCR. Results obtained revealed a no significant difference in expression of DNMT3A and of TDG; however we found a significant downregulation of the demethylases TET1 (0,661 fold; p-value 0,039).
These data suggest that miR29a acts as a crucial regulator of DNA methylation and probably in presence of DNMT3A activating mutations and TET1 downregulation may cause a perturbation of methylation pattern. We analyzed the methylation status of the genomic DNA of bone marrow cells

from 6 AML patients (including 3 DNMT3A-mutated and 3 DNMT3A-WT cases) and from 5 healty donors as control by Methylation Sensitive Arbitrarily Primed-PCR that provides a qualitative estimate of genome-wide DNA methylation. Results showed a global hypermethylation of genome in DNMT3A mutated patients compared to DNMT3A WT group and healthy bone marrow. The performed study increasingly suggests that the DNMT3A gain-of-function mutation, the significant upregulation of miR29a and significant downregulation of demethylase TET1 target gene would contribute to the maintenance of the hypermethylation status of the genome in patients with DNMT3A mutation. This issue may have important implications for treatment and response to hypomethylating drugs in patients affected by alterations in DNMT3A.

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Cordialmente

La segreteria editoriale
del 45° Congresso Nazionale SIE
e-mail: support@abstracts.it