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Upregulation of miR-29a and genomic DNA hypermethylation in normal karyotype AML showing DNMT3A mutation

Mirto M, Randazzo V, Agueli C, Salemi D, Valenti D, Marfia A, Bica MG, Cannella S, Fabbiano F, La Rosa C, Caradonna F and Santoro A
University of Palermo, Italy

Acute Myeloid Leukaemia (AML) is frequently associated to normal karyotype and *DNMT3A* mutations (R882). Since we previously demonstrated distinctive miRNA expression in some AML groups, we study 384 miRNA in 9 selected *DNMT3A*-mutated NK-AML patients. Comparing these data with our previous results obtained in 31 *DNMT3A*-unmutated AML, we focused on a significant up-regulation of miR-155, miR-29a, miR-196b and miR-25. We investigated expression of these miRNAs in additional 24 *DNMT3A*-mutated AML patients and we confirm the up-regulation of miR-155, miR-29a and miR-196b; in particular, we judged very interesting the over expression of miR-29a since is known to directly target *DNMT3A*, *TET1* and *TDG* mRNAs. Evaluating the expression levels of these targets in 17 AML *DNMT3A*-mutated patients, we revealed a no significant differences in expression of *DNMT3A* and *TDG* but a significant down-regulation of *TET1*.

These data suggest that miR-29a acts as DNA methylation-regulator: in presence of *DNMT3A* activating mutations and *TET1* down-regulation it may probably cause a perturbation of DNA methylation. In fact, analyzing the methylation of the bone marrow genomic DNA from 3 *DNMT3A*-mutated and 3 *DNMT3A*-unmutated cases by Methylation Sensitive Arbitrarily Primed-PCR, we found a genomic hypermethylation of *DNMT3A*-mutated cells compared to the unmutated ones.

How *DNMT3A* mutations contribute to leukemogenesis is not yet well characterized. Uncovering how *DNMT3A* mutations affect DNA methylation and epigenetic regulation of gene expression may have important implications in treatment selection because DNA hypomethylating agents are increasingly used in AML therapies, and response to these drugs may be affected by *DNMT3A* changed function.

Biography

Maria Mirto is completing her master studies in Health Biology at University of Palermo (Italy). She worked and is working with a joint work group dedicated to Epigenetic studies in Acute Myeloid Leukemia consisting of Cellular biology and Genetics Lab of Department STEBICEF (University of Palermo) and Oncohematologic Integrated Diagnostic Lab (United Hospitals "Villa Sofia Cervello" Palermo) – Italy. These teams have several publications in topic. These presented results are part of her degree thesis.

mariamirto87@gmail.com

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