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Identification of post-transcriptional regulatory networks during myeloblast-to-monocyte differentiation transition

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During hematopoiesis it is clearly emerging that microRNAs are integrated with target genes in regulatory circuitries involved in the decisions regarding the ability to self-renew and to generate a differentiated progeny in hematopoietic cells including myeloid cells (1).

microRNAs are able to modulate genes expression mainly by tuning the rate of proteins' synthesis inhibiting the initiation or later stages of translation. A change in the association of an mRNA with polysomes is indicative of changes in its translation state. For instance, a block in translational initiation would result in reduced ribosome density on the affected mRNA and a shift toward the lower-density fractions of the gradient (2).

Prediction algorithms usually provide hundreds of target genes for each microRNA and the identification of reliable target genes is feasible only through single-gene approaches. To identify microRNA-mRNA networks relevant for the transition from myeloblasts to monocytes, we here evaluated the localization of microRNAs and mRNAs in ribosomal/polysomal cell fractions obtained by sucrose density gradient centrifugation from the myeloblastic cell line HL60 induced or not to differentiate by 1,25-dihydroxyvitamin D3 treatment to induce monocyte/macrophage differentiation. The co-localization of miRNAs and predicted target mRNAs in low-density ribosomal fractions is strongly indicative of their functional interaction.

Intersection between mRNAs shifted across the fractions after treatment with putative target genes of modulated microRNAs showed a series of molecular networks relevant for the monocyte cell fate determination, as for example the post-transcriptional regulation of the Polo-like kinase 1 (PLK1) by miR-22-3p and let-7e-5p.

The disclosing of new molecular players involved in myeloid cell fate determination paves the way for the identification of new potentially interesting molecular targets for the treatment of acute myeloid leukemia cells.

References

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Keywords

MicroRNAs; myeloid differentiation; ribosomal/polysomal fractions; PLK1.

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