IJAE
Vol. 123, n. 1 (Supplement): 216, 2018
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Argonaute 2 drives miR-145-dependent gene expression program influencing epithelial to mesenchymal transition in breast cancer cells

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To perform their regulatory functions, microRNAs (miRNAs) must assemble with any of the four mammalian Argonaute (Ago) family of proteins, Ago1–4, into an effector complex known as the RNA-induced silencing complex (RISC) [1]. While the mature miRNA guides the RISC complex to its target mRNA, the Ago protein represses mRNA translation [2]. The specific roles of the various Ago members in mediating miRNAs activity, however, haven't been clearly established.

In this study, we investigated the contribution of Ago2, the only human Ago protein endowed with nuclease activity, to the function of tumor-suppressor miR-145-5p in breast cancer (BC). We show that miR-145-5p and Ago2 protein are concomitantly downregulated in BC tissues and that restoration of miR-145-5p expression in BC cells leads to Ago2 protein induction through the loosening of Ago2 mRNA translational repression. Functionally, miR-145-5p exerts its inhibitory activity on cell migration only in presence of Ago2, while, upon Ago2 depletion, we observed increased miR-145/Ago1 complex and enhanced cell motility. Profiling by microarray of miR-145-5p target mRNAs, in BC cells depleted or not of Ago2, revealed that miR-145-5p performs Ago2-dependent and -independent activities. Our results highlight that the Ago2 protein in cancer cells strictly dictates miR-145-5p tumor suppressor activity.

References

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Key words
microRNAs, miR-145-5p, Ago2, breast cancer, cell migration.