AB014. OS03.04. Thymic epithelial tumors phenotype relies on MIR-145-5p epigenetic regulation

Teresa Bellissimo[1], Federica Ganci[2], Andrea Sacconi[2], Claudia Tito[1], Enzo Gallo[3], Luciana De Angelis[1], Silvia Masciarelli[1], Daniele Diso[4], Marco Anile[4], Vincenzo Petrozza[5], Felice Giangaspero[6], Edoardo Pescarmona[3], Francesco Facciolo[7], Gabriele Alessandrini[7], Federico Venuta[4], Giovanni Blandino[2], Mirella Marino[3], Francesco Fazi[1]

[1]Department of Anatomical, Histological, Forensic & Orthopaedic Sciences, Section of Histology & Medical Embryology, Sapienza University of Rome, Rome, Italy; [2]Oncogenomic and Epigenetic Unit, [3]Department of Pathology, Regina Elena National Cancer Institute, Rome, Italy; [4]Department of Thoracic Surgery, Azienda Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; [5]Pathology Unit Icot, Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; [6]Department of Radiological, Oncological, and Pathological Science, Sapienza University of Rome, Rome, Italy; [7]Thoracic Surgery, Regina Elena National Cancer Institute, Rome, Italy

Background: Thymic epithelial tumors (TETs) are rare tumors arising from the thymic epithelium, thymoma and thymic carcinoma being the most frequent subtypes. TET show a propensity to recur and to metastasize that is difficult to predict. A relevant advance in TET management could derive from a deeper molecular characterization of these neoplasms. In a previous multicenter study we identified a set of microRNA (miRNAs) differentially expressed in TETs and normal thymic tissues. Among the most significantly deregulated miRNAs we described the down-regulation of miR-145-5p in TET. Here we describe, by gene expression profiling (GEP), the mRNAs diversely regulated in TETs and analyze the correlation between these and the miRNAs previously identified, focusing in particular on miR-145-5p. Moreover we examine the functional role of miR-145-5p in TETs and its epigenetic transcriptional regulation.

Methods: mRNAs expression profiling of a cohort of fresh frozen TETs and normal tissues (peritumoral thymi) from our biobanks was performed by microarray analysis. MiR-145-5p role in TETs was evaluated *in vitro*, modulating its expression in a Thymic Carcinoma (TC1889) cell line. Epigenetic transcriptional regulation of miR-145-5p was examined by treating the TC1889 cell line with the HDAC inhibitor valproic acid (VPA).

Results: Basing on the identification of a 69-gene signature of miR-145-5p putative target mRNAs, whose expression was inversely correlated to that of miR-145-5p, we studied the expression of some of them *in vitro* upon overexpression of miR-145-5p; we observed that this resulted in the down-regulation of the target genes, impacting on TETs cancerous phenotype. We also found that VPA treatment of TC1889 cells led to miR-145-5p up-regulation and concomitant down-regulation of miR-145-5p target genes and exhibited antitumor effects, as indicated by the induction of cell cycle arrest and by the reduction of cell viability, colony forming ability and migration capability. The importance of miR-145-5p up-regulation mediated by VPA is evidenced by the fact that hampering miR-145-5p activity by a LNA inhibitor reduced the impact of VPA treatment on cell viability and colony forming ability of TET cells. Finally, we observed that VPA was also able to enhance the response of TET cells to cisplatin and erlotinib.

Conclusions: Altogether our results suggest that the epigenetic regulation of miR-145-5p expression, as well as the modulation of its functional targets could be relevant players in tumor progression and treatment response in TETs.

Keywords: MicroRNA; gene expression profile; miR-145-5p; epigenetic regulation

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