



# Setting the base for new therapeutic strategies against thymic epithelial tumors – miR-145-5p epigenetic regulation

Wolfgang Jungraithmayr<sup>1,2</sup>, Walter Weder<sup>1</sup>

<sup>1</sup>Department of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland; <sup>2</sup>Department of Thoracic Surgery, Brandenburg Medical School, Neuruppin, Germany

Correspondence to: Wolfgang Jungraithmayr, MD, PhD. Department of Thoracic Surgery, Brandenburg Medical School, Neuruppin 16816, Germany. Email: wolfgang.jungraithmayr@mhb-fontane.de.

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The rarity and biological variety of thymic malignancies hampers the performance of randomized clinical trials and thus limits the availability for guidelines in treatment decisions. However, the molecular biology of thymic epithelial tumors (TETs) has been increasingly gained center space in recent years which might result in more precise and individual therapeutic pathways: gene expression profiling and genomic clustering studies showed that types of thymoma, but also thymic carcinoma have different molecular features that may be clinically relevant (1).

MicroRNAs (miRNAs) constitute a class of small (21–24 nucleotides) non-coding RNAs that regulate gene expression at the post-transcriptional level. They are able to modulate gene expression degrading mRNA or impairing translation. Notably, miRNA activity has been correlated to the pathogenesis of cancer (2); they are aberrantly expressed in several tumors, suggesting that they could function as oncogenes or tumor suppressors. The role of miRNAs in the carcinogenesis and tumor progression has been recognized as opportunities for clinical application in the capacity of cancer detection, diagnosis, and prognosis prediction (3).

In the current issue of *Molecular Cancer*, Bellissimo and colleagues unravel important mechanisms in epigenetic regulation of a particular miRNA, namely miR-145-5p, and the modulation of its functional targets might be relevant in tumor progression and treatment response in TETs. Authors showed convincingly on the base of a cohort of fresh frozen TETs and normal tissues of miR-145-5p target mRNAs that their expression was inversely correlated

to that of miR-145-5p. In a differential set of *in vitro* experiments, they showed that indeed target genes were down-regulated thus changing the phenotype of TETs. In order to evaluate the level of epigenetic transcription, authors employed the histone deacetylase inhibitor valproic acid, a compound that exhibits anticancer, anti-inflammatory and neuroprotective effects. Valproic acid (VPA) acts through a distinct pathway that involves direct inhibition of histone deacetylase. It impairs cell proliferation or survival as indicated by decreased incorporation of [3H] thymidine in teratocarcinoma cells (4). The *in vitro* treatment by VPA resulted in (I) miR-145-5p upregulation, at the same time down-regulating of miR-145-5p target genes; (II) exerting anti-tumor effects in the form of induction of cell cycle arrest, reduced cell viability and impaired cell migration capability (5). They also showed that this inhibitor sensitized TET cells to the treatment of cisplatin and erlotinib.

This study does not only open a new therapeutic field by modulating functional targets in TETs, it also brings the debate about the indication when and how to treat TETs by chemotherapy to another level—by showing a higher sensitivity of TET cells to cisplatin and the tyrosine kinase inhibitor erlotinib, this could provide the base for evidence to give this adjuvant treatment in certain types of TETs. This has particular importance in the light of the fact that there is no standard second-line medical therapy option. However, it remains open which TET subtype in particular would profit from such a treatment. In addition, those TETs that have metastasized into adjacent tissue or pleura,

the most affected site of metastases by TETs have a poor prognosis. Epigenetic characterization of this metastatic tissue would be most helpful for a potential treatment response protocol, even in palliative cases.

Any therapeutic measure that results in a subtle characterization of TETs and its subtypes is urgently needed in order to treat these rare tumors, tumors that are oncologically still not completely understood. Considering the scarcity of TETs, this can only be done in a more collaborative work by pooling series of thymic tumor treating centers.

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