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POSTERS

P – 004 MicroRNAs and CDH1 regulation in intestinal-type gastric cancer

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Introduction: Gastric cancer (GC) remains a major source of cancer morbidity and mortality worldwide. The most commonly accepted histologic classification of this disease separates it into two main subtypes: intestinal (IGC) and diffuse (DGC). The cadherin family is a cell adhesion-related protein family largely implicated in carcinogenesis of both histotypes, with the best-known member being E-cadherin. This calcium-dependent transmembrane adhesion protein is encoded by CDH1 tumor suppressor gene. While complete loss of E-cadherin is predominant in DGC, more subtle factors can be involved in its modulation in IGC, in which some level of protein is often retained. Such factors include miRNAs that play a role in gene expression dosage either directly by interacting with the CDH1 transcript, or indirectly by acting on genes that are part of its regulatory network. Aim of the study was to evaluate the levels of specific miRNAs involved in the regulation of CDH1 expression in IGC.

Methods: Fresh-frozen paired normal and cancer tissue samples were obtained from 40 patients diagnosed with IGC. An in silico and literature based approach was performed to determine the miRNAs most likely targeting CDH1 in GC. In case of an indirect effect on CDH1, the direct miRNA targets were noted. Expression analysis was carried out by using a custom-made RT pool containing primers for the miRNAs of interest and the TaqMan microRNA RT Kit. This was followed by qPCR reactions in miRNA custom-made 96-well plates and quantification by the 2-ΔCt method with RNU6 as a

reference. CDH1 expression levels were quantified by two step reverse transcription dPCR with GAPDH as an endogenous control.

Results: The combined in silico and literature-search based approach gave rise to a list of 14 miRNAs possibly involved in the regulation of CDH1 expression in GC (miR-506, miR-217, miR-199a, miR-153, miR-544a, miR-34c, miR-141, miR-429, miR-101, miR-200a, miR-200b, miR-200c, miR-26b, miR-23a). Tumor and normal paired samples from 17 patients have been analyzed so far. At the end of the qPCR reactions, 8 miRNAs could be successfully quantified (miR-141, miR-429, miR-200a, miR-200b, miR-200c, miR-101, miR-26b and miR-23a); among those miR-101 ($p = 0.00236$) and miR-26b ($p = 0.001623$) were found to be significantly lower in tumors compared to normal tissue, while miR-200c showed borderline significance ($p = 0.05373$). With respect to CDH1, it was similarly found to be significantly less in tumor than normal tissue ($p = 0.01$). Meanwhile, no significant correlations were found between miRNAs and CDH1 expression levels.

Conclusion: Based on our preliminary results both miR-26 and miR-101 seem to contribute to IGC carcinogenesis. To further investigate whether they act by perturbing E-cadherin-mediated signaling and cell-cell adhesion we are planning to analyze a bigger case series.