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Meta-Analysis with Critical Appraisal of miRNA as a Biomarker in Gastroenteropancreatic Neuroendocrine Tumors

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BACKGROUND: A key issue in neuroendocrine neoplasia management is identification, in peripheral blood, of signals or signatures that define the activity of cancer or the local tumor microenvironment. MicroRNAs regulate a diverse array of biological processes including carcinogenesis and have been proposed as biomarker candidates. We reviewed their expression in tissue and blood and evaluated their clinical utility in GEP-NETs.

METHODS: A systematic review of PubMed to identify all studies investigating miRNA in GEP-NETs and their utility as a blood biomarkers was undertaken.

RESULTS: Sixteen articles were identified. These were exemplified by diverse methodologies (global profiling to quantitative PCR) to identify miRNA, divergent normalization protocols (whole set normalization to individualized SNURP genes) and heterogeneous cohorts (treatment, histology, stage etc).

Tumor tissue: Gastric carcinoid (n=1: MiR-222, regulates p27KIP1); pancreas (n=6: MiR-21 [inflammatory marker] and MiR-144 [PI3K/AKT signaling] both up- and down-regulated depending on method/ ethnic group); small intestine (n=3: no consistent signature); colorectal (n=2: no specific signature).

Blood: Gastric carcinoid (n=1: MiR-222); pancreas (n=2: MiR-21); small intestine (n=2: no consistent signature, MiR-21/22 upregulated MiR-150 downregulated, putative proposal as a prognostic in one study). MiR-21/22 are associated with inflammation and markers of epithelial neoplasia. Where studied (n=1), signatures were unaffected by SSA use.

Studies had low power, included heterogeneous cohorts, were not validated and age- and gender-matched controls were not used (except once). Ethnic variability was noted. Significantly different miRNA isolation methods and detection protocols were used which resulted in non-overlapping expression between tumor tissue and blood compartments.

CONCLUSION: Of ~1500 miRNA studied, potential biomarkers for GEP-NETs include MiR-222 (gastric) and MiR-21 (small bowel, perhaps pancreas). Since MiR-21 has a substantial association with inflammation the specificity of this observation requires validation. No studies met the metrics for biomarker efficacy. There is no data to support the clinical utility of specific neuroendocrine miRNAs in GEP NET management.