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Molecular pathology

NEW DEVELOPMENTS: USING MIRNA GENES TO SUBTYPE RENAL CELL CARCINOMA AND TO CLASSIFY NEUROENDOCRINE TUMOURS OF THE LUNG

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TRIAL SUMMARY: Subtyping renal cell carcinoma via miRNA genes

Di Meo A, Hanna M, Saleeb R, et al. P47 miRNAs as diagnostic biomarkers for renal cell carcinoma subtypes by chromogenic in situ hybridization. Screen 5.11, Canadian Association of Pathologists Annual Meeting, Charlottetown, PEI, June 10-13, 2017.

Conventionally, renal cell carcinoma (RCC) is categorized into subtypes based on histopathologic examination. This traditional practice has its limitations due to the subjectivity of morphologic interpretation, the heterogeneity of tumour constituents, and the fact that tumours with similar histomorphology may not have the same clinical behaviour and may respond differently to therapeutic interventions.

Dr. Di Meo and his team from St Michael's Hospital, University of Toronto, demonstrated that RCC could be subtyped by 5 microRNA (miRNA) genes: miR-221, miR-222, miR-126, miR-200b, and miR-200c. RNA was extracted from formalin-fixed paraffin-embedded (FFPE) tissue. The results were robustly depicted in a very simple and concise 2-step algorithm. These 5 miRNAs can successfully distinguishing between clear-cell RCC, papillary RCC, chromophore RCC and oncocytomas. This more accurate subtyping by miRNA technology can guide clinicians to implement individualized treatment protocols, and better predict patient response to therapy and prognosis.

TRIAL SUMMARY: Classifying lung neuroendocrine tumors via miRNA genes

Ginter PS, Barsoum IB, Yang X, Tyryshkin K, et al. Differential expression of miRNAs in lung neuroendocrine tumours using barcoded small RNA sequencing. Screen 6.13 P44, Canadian Association of Pathologists Annual Meeting, Charlottetown, PEI, June 10-13, 2017.

The 2015 World Health Organization (WHO) classification distinguishes 3 categories of lung neuroendocrine tumour (NET): small cell carcinoma (SCLC), large cell neuroendocrine carcinoma (LCNEC) and carcinoid tumours. Carcinoid tumour is further divided into typical carcinoid (TC) and atypical carcinoid (AC). Clinically, typical and atypical carcinoid are indolent tumours, whereas small cell carcinoma and large cell neuroendocrine carcinoma are aggressive tumours.[1]

The research team of Dr. Barsoum from Queen's University, Kingston, explored the possibility of classifying lung neuroendocrine tumours using miRNA genes. They used FFPE tissue blocks in this study and found that 4 miRNAs genes could differentiate between all 4 types of lung neuroendocrine tumours: miR-378 could differentiate TC from AC, and miR-24 could differentiate SCLC from LCNEC. Furthermore, miR196a and miR-123-2-3p helped differentiate indolent from aggressive lung neuroendocrine tumours. The authors also compared 2 miRNA profiling methodologies: barcoded small RNA sequencing and qrt-PCR. The former method was shown to be more accurate than the latter.

Classifying lung neuroendocrine tumours using miRNA technology can guide clinicians to provide more accurate therapeutic interventions and to better predict patient prognosis.

COMMENTARY: Discovered by Lee et al in 1993, microRNA (miRNA) is a small noncoding RNA molecule that has a role in RNA silencing and posttranscriptional regulation of gene expression.[2] The first association between miRNA and cancer was discovered in 2002, when miR-15 and miR-16 were identified at 13q14.3 region in chronic lymphocytic leukemia.[3] Henceforth, the importance and significance of miRNA has been gradually recognized, and it has played an increasing role in cancer diagnosis. Certain distinct circulating miRNAs have been seen in lung, prostate, hepatocellular cancer and other cancers.[4] They have also been seen in non-neoplastic disease like diabetes mellitus, cardiovascular disease and HIV/AIDS, among others.[4] It is believed that the circulating miRNA will usher in a new era of progress in diagnosing various cancers and predicting prognosis.

These 2 studies by Dr Di Meo and Dr Barsoum and their teams have provided a glimpse into the future of molecular pathology. Currently, subtyping RCC and classifying lung NET mostly relies on morphology and immunohistochemistry. These miRNA studies have provided a new and promising modality for pathologists, especially as they come at a time when results with conventional techniques are equivocal. The genome-based subtyping and classification of tumours will enable clinicians to provide personalized therapy, predict disease response to therapy and more accurately anticipate prognosis.

In the foreseeable future, miRNA profiling is likely to have a wide range of applications in the field of pathology diagnostics, for example in subtyping or classifying different cancers or even non-neoplastic diseases.[5] However, before adopting miRNA markers into routine practice, the results

achieved in these studies need to be validated in large multicentre studies using standardized methodology and bioinformatics analysis.

References:

1. Travis WD, et al. The 2015 World Health Organization classification of lung tumors. Impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol*. 2015;10: 1243–126
2. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell*. 2004; 116 (2): 281–97.
3. Calin GA, et al. Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. *Proc Natl Acad Sci*. 2002; 99(24): 15524-15529
4. Faruq O and Vecchione A. MicroRNA: diagnostic perspective. *Front Med*. 2015; 2 :15
5. Blenkiron C et al. MicroRNA expression profiling of human breast cancer identifies new markers of tumor subtype *Genome Biol*. 2007; 8:R214

IN BRIEF

Already known

- miRNAs are stable, conserved, small noncoding RNA genes.
- miRNA plays a role in gene regulation and is involved basically in all cellular functions, such as cell proliferation, differentiation, etc.
- miRNA has potential as a diagnostic marker in cancer and other diseases.

What these studies showed

- miRNA can be used to subtype renal cell carcinomas and classify lung neuroendocrine tumours.
- miRNA can help pathologists when histopathologic examination is equivocal.
- miRNA markers may help guide clinicians in providing more personalized therapeutic interventions to their patients.

Next steps

- Validate data in large multicentre studies.
- Standardize the methodology of miRNA profiling and bioinformatics analysis.