event should be considered in benefit-risk calculations for fluoroquinolone use, and further research must explore how these important antibiotics affect collagen.

Reference

Chien-Chang Lee, Meng-tse Gabriel Lee, Yueh-Sheng Chen, Shih-Hao Lee, Yih-Sharng Chen, Shyr-Chyr Chen, Shan-Chwen Chang. (2015). Risk of Aortic Dissection and Aortic Aneurysm in Patients Taking Oral Fluoroquinolone. *JAMA Internal Medicine*, 175(11):1839-1847. DOI: 10.1001/jamainternmed.2015.5389

Professor Shan-Chwen Chang
Department of Internal Medicine, College of Medicine
changsc@ntu.edu.tw

A simple, powerful, and widely applicable 3-microRNA scoring system for prognostication in de novo acute myeloid leukemia patients

Acute myeloid leukemia (AML) is a heterogeneous disease with various pathogenesis, treatment responses and clinical outcomes. Personalized treatment according to individual patient risk could both improve patient survival and reduce treatment side effects.

MicroRNAs are a class of small, non-coding RNAs that are derived from precursor RNAs processed by a protein complex containing Dicer and Drosha. They regulate gene expression post-transcriptionally through either mRNA degradation or translation inhibition. In AML, microRNAs are involved in hematopoietic cell differentiation, proliferation, and survival and can affect treatment responses and outcomes.

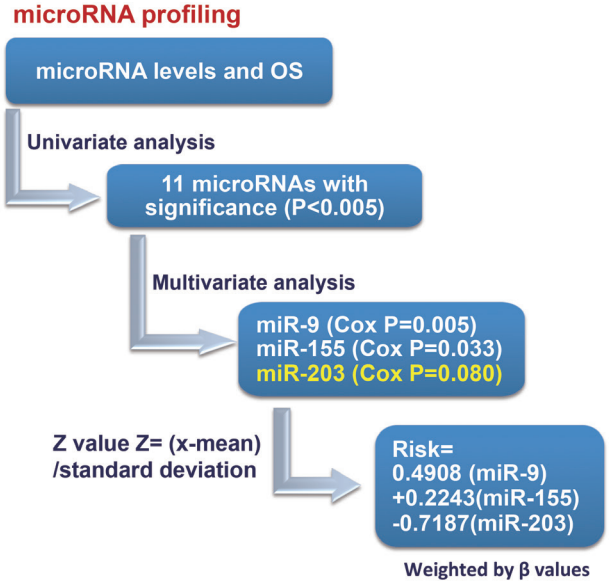


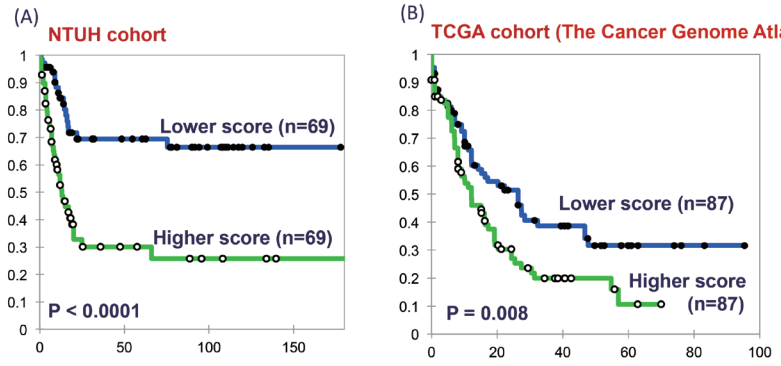
Figure 1. Analysis of miRNA array data, selection of microRNAs whose expressions are associated with survival, and construction of a microRNA scoring system

Using univariate Cox analysis , eleven microRNAs are selected from the microRNA array data whose expressions are significantly associated with overall survival (OS). By multivariate Cox model, expressions of three microRNA are identified as independent prognostic factors. High expression of miR-9 and miR-155 were independently associated with poor OS, while that of miR-203 had a trend of association with favorable OS. By focusing these 3 microRNAs, a risk scoring system is constructed:

Risk = 0.4908 [hsa-miR-9-5p] + 0.2243 [hsa-miR-155-5p] - 0.7187 [hsa-miR-203], where the weights of microRNAs are beta values from multivariate Cox analysis and the expression levels of microRNAs are z-transformed (ie. subtracting the mean and then divided by the standard deviation) across patients so that each microRNA has zero mean and unit standard deviation.

In collaboration with prof. Eric Y. Chuang's team at the Graduate Institute of Biomedical Electronics and Bioinformatics, prof. Hwei-Fang Tien and Wen-Chien Chou and the leukemia research team at the Division of Hematology, Department of Internal Medicine, comprehensively profiled microRNAs in 138 AML patients and found that high expression of hsa-miR-9-5p and hsa-miR-155-5p independently predicted poor prognosis, whereas high hsa-miR-203 tended to indicate a favorable outcome (Figure 1). They constructed a scoring system from the expression of these 3 microRNAs by considering the weight of each. The scores correlated with distinct clinical and biological features and outperformed single microRNA expression in prognostication. The power of this signature was validated by another independent AML cohort from the Cancer Genome Atlas (TCGA). Higher scores were associated with shorter overall survival (Figure 2) independent of other well-known prognostic factors, such as age, white blood cell counts, cytogenetics and molecular mutations. By analyzing mRNA expression profiles, they identified several cancer-related pathways that were highly correlated with the prognostic microRNA signature (Figure 3).

This 3-microRNA scoring system is simple, powerful, and widely applicable for the risk stratification of AML patients. From a practical point of view, these three microRNAs can be analyzed by simple qPCR-based methods for each newly diagnosed AML patient, and the 3-microRNA risk score can be calculated. The procedures are inexpensive and fast and can be performed in a high-throughput manner to help clinicians choose the proper treatment for individual patients.



NTUH: national Taiwan University Hospital; TCGA: The Cancer Genome Atlas

Figure 2. High MicroRNA Score Predicts Poor Overall Survival

The Kaplan Meier curves for overall survival (OS) according to the scores. (A) In NTUH discovery set, patients with lower scores have significant longer OS than those with higher scores (median not reached vs.13.5 months, *P<0.0001*); (B) In TCGA validation cohort, the scoring system still holds true (median 26.4 vs 12.2 months, *P=0.008*).

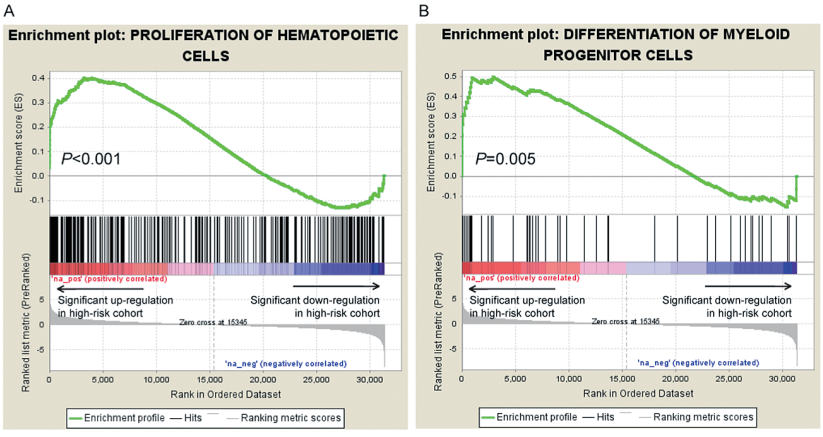


Figure 3. Gene set enrichment analysis (GSEA)

GSEA plots on genes associated with (A) proliferation of hematopoietic cells and (B) differentiation of myeloid progenitor cells. Genes relating to these two functions are highly up-regulated in the patients with high microRNA scores, suggesting significant correlations between these two pathways and the scoring.

Reference

Ming-Kai Chuang, Yu-Chiao Chiu, Wen-Chien Chou, Hsin-An Hou, Eric Yao-Yu Chuang, Hwei-Fang Tien. (2015). A 3-microRNA scoring system for prognostication in de novo acute myeloid leukemia patients. *Leukemia*, 29, 1051-1059. DOI: 10.1038/leu.2014.333

Professor Hwei-Fang Tien
Division of Hematology, Department of Internal Medicine, National Taiwan University Hospital
hftien@ntu.edu.tw

Professor Wen-Chien Chou
Department of Laboratory Medicine
National Taiwan University Hospital
wcchou@ntu.edu.tw