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Biomarkers accurately distinguish mesothelioma from non-cancerous tissue

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Scientists have identified four biomarkers that may help resolve the difficult differential diagnosis between malignant pleural mesothelioma (MPM) and non-cancerous pleural tissue with reactive mesothelial proliferations (RMPs). This is a frequent differential diagnostic problem in pleural biopsy samples taken from patients with clinical suspicion of MPM. The ability to make more accurate diagnoses earlier may facilitate improved patient outcomes. This new study appears in the *Journal of Molecular Diagnostics*.

"Our goal was to identify microRNAs (miRNAs) that can aid in the differential diagnosis of MPM from RMPs," says lead investigator Eric Santoni-Rugiu, MD, PhD, of the Laboratory of Molecular Pathology at the Department of Pathology of Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. miRNAs, which are small, non-coding RNA strands composed of approximately 22 nucleotides, have been shown to be potential diagnostic, prognostic, and predictive markers in other cancers.

After screening 742 miRNAs, the investigators identified miR-126, miR-143, miR-145, and miR-652 as the best candidates to diagnose MPM. Using results from these four miRNAs, tissue samples from patients with known outcomes could be classified as MPM or non-cancerous with an accuracy of 0.94, sensitivity of 0.95, and specificity of 0.93. Further, an association between miRNA levels and patient survival could be made.

"The International Mesothelioma Interest Group (IMIG) recommends that a diagnostic marker of MPM have sensitivity/specificity of >0.80, and these criteria are fulfilled by our miRNA classifier," comments Dr. Santoni-Rugiu. The authors suggest that diagnostic accuracy can be further improved by adding immunohistochemical testing of miRNA targets in biopsy tissue to their miRNA assay. This combined assay could enable analysis of samples with low tumor cell count.

MPM, which is linked to long-term asbestos exposure, is an aggressive cancer originating from the mesothelial cells that line the membrane surrounding each lung, known as the pleura. Distinguishing MPM from noncancerous abnormalities, such as reactive mesothelial hyperplasia or fibrous pleurisy (organizing pleuritis), can be challenging as there are no generally accepted diagnostic biomarkers for differentiating these two conditions. As a result, patients often present with the disease when they are already at an advanced stage, and less than 20% of patients can be successfully treated surgically.

The current study, however, suggests that miRNAs may provide new opportunities for improving the accuracy of the differential diagnosis between MPM and noncancerous pleural conditions. If further validated, the combination of ISH for miRNAs with immunohistocemical testing of miRNA targets may therefore have the potential to aid in the diagnosis, and thus outcome, of MPM.

Details of the study

To identify and assess microRNAs as possible diagnostic biomarkers of MPM, the expression of 742 miRNAs in FFPE preoperative diagnostic biopsies, surgically resected MPM specimens previously treated with chemotherapy, and corresponding non-neoplastic pleura (NNP) from five patients were screened using an RT-qPCR-based platform. Four miRNAs (miR-126, miR-143, miR-145, and miR-652) were

significantly down-regulated (≥2 fold) in resected MPM and/or chemotherapy-naïve diagnostic tumor biopsies.

Validation of the obtained miRNA-expression profile was performed on surgically removed tissue samples from 40 MPM patients and 14 patient-matched NNP samples as well as 12 preoperative diagnostic biopsies and five non-neoplastic reactive-mesothelial proliferation due to pneumothorax. By performing binary logistic regression on the RT-qPCR data for the four miRNAs, the classifier differentiated MPM from NNP with high sensitivity and specificity. The classifier's optimal logit(P) value of 0.62 separated NNP and MPM samples with high sensitivity, specificity, and accuracy (all ≥0.93).

For immunohistochemistry, FFPE tissue sections underwent staining using antibodies to the known miR-126 targets LAT1 and Crk-II, were evaluated by light microscopy, and scored by a semiquantitative H score. Although no significant differences were found between MPM and NNP samples for Crk-II, the MPM samples had a median H score of 2 for LAT1 immunostaining, which was significantly higher than the 0.5 median score for the NNP samples (P

More information: "Diagnostic potential of miR-126, miR-143, miR-145, and miR-652 in malignant pleural mesothelioma," by Morten Andersen, Morten Grauslund, Jesper Ravn, Jens Benn Sørensen, Claus Bøgelund Andersen and Eric Santoni-Rugiu, DOI: dx.doi.org/10.1016/j.jmoldx.2014.03.002. Published online ahead of the *Journal of Molecular Diagnostics*, Volume 16, Issue 4 (July 2014)