Diagnosis of precancerous high-grade cervical lesions and cervical cancer with a panel of circulating cell-free microRNAs in a liquid biopsy approach

Annika Tamenang[1]
Vanessa Vohl[1], Jolanthe Kropidlowski[1], Anna Jaeger[2], Eik Vettorazzi[3], Katharina Prieske[2], Yvonne Goy[4], Katharina Hintelmann[4], Cordula Petersen[4], Linn Wölber[2], Barbara Schmalfeldt[2], Klaus Pantel[1], Katharina Effenberger[1] and Harriet Wikman[1]
[1] Institute of Tumor Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[2] Department or Gynecology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[3] Institute of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[4] Department of Radiotherapy and Radiation Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background & objectives

Cervical cancer, preventable by vaccination against its causative infectious agent human papillomavirus, is still the fourth most common malign neoplasia in women worldwide. Due to the long latency between HPV infection and cervical cancer manifestation it is also available to secondary prevention by early diagnosis, and by therapy of precancerous cervical lesions with a high risk of progressing into invasive carcinoma (high-grade squamous intraepithelial lesions HSIL). Dysregulated microRNAs (miR), central regulators of gene expression, contribute to cervical carcinogenesis. As they are also secreted into the bloodstream as circulating cell-free microRNAs (ccfmiRNA), their detection may allow for early and minimally invasive diagnosis of precancerous lesions in a liquid biopsy approach. In this case-control study, we therefore analyzed the expression of five different ccfmiRNAs, selected based on literature research (miR-21-5p, miR-142-3p, miR-145-5p, miR-205-5p, miR-218-5p).

Methods

38 plasma samples of patients with HSIL (CIN2/CIN3) and ten cancer samples were collected and analyzed using real-time LNA-enhanced, probe-based qPCR (miRCURY, Qiagen). Expression was normalized to the housekeeping miR-23a with the ΔΔCT-method. Subsequently, the diagnostic potential of these biomarkers was assessed individually and as a panel with ROC curve analysis.

Results

miR-21 was significantly upregulated in HSIL and cervical cancer patients compared to healthy controls, whereas miR-205 and miR-218 were significantly downregulated (all $p<0.05$). miR-145 was significantly upregulated in cervical cancer. As individual markers, miR-205 yielded the highest sensitivity and specificity for HSIL with 78.9% and 59.9%, and cervical cancer with 80.0% and 59.4%, respectively. Combination of miR-21, miR-205 and miR-218 yielded the highest sensitivity for HSIL with 78.9% (specificity of 71.0%), while the combination of miR-205 and miR-218 reached the highest specificity of 74.2% (sensitivity 76.3%). For cervical cancer, miR-205 combined with miR-218 increased sensitivity and specificity to 90.0% and 64.5%, respectively.

Conclusion

In conclusion, three significantly dysregulated ccfmiRNAs were able to diagnose HSIL and cervical cancer with high sensitivity and specificity in a diagnostic panel.