News Release

Title

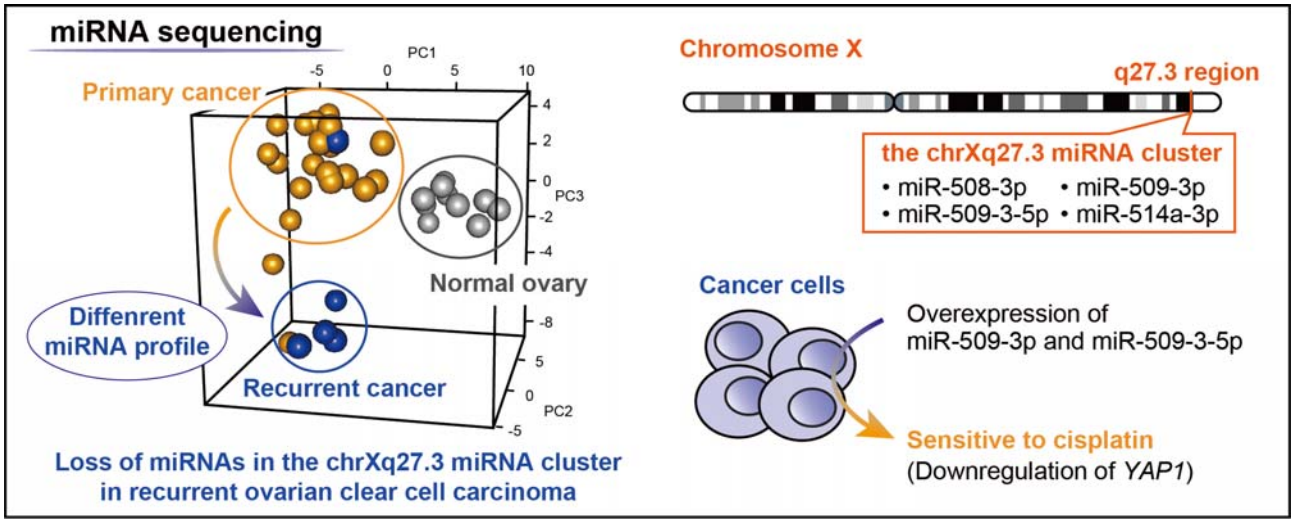
Expression of the chrXq27.3 miRNA cluster in recurrent ovarian clear cell carcinoma and its impact on cisplatin resistance.

Key Points

- Clinically, recurrent cancers exhibit greater chemoresistance compared with corresponding primary cancers.
- The expression of the chrXq27.3 miRNA cluster was remarkably decreased in advanced/recurrent OCCC.
- These miRNAs were involved in the phenotype of cisplatin resistance, suggesting that they can be potential therapeutic targets.

Summary

Dr. Kosuke Yoshida, Dr. Akira Yokoi, and Prof. Hiroaki Kajiyama (Department of Obstetrics and Gynecology, Nagoya University Graduate School of Medicine) showed that a miRNA cluster was involved in platinum resistance in recurrent ovarian clear cell carcinoma. Comprehensive miRNA sequencing revealed that the expression of the chrXq27.3 miRNA cluster (miR-508-3p, miR-509-3p, miR-509-3-5p, and miR-514a-3p) was remarkably decreased in advanced/recurrent ovarian clear cell carcinoma. Moreover, they found that, in ovarian cancer cell lines, overexpression of miR-509-3p and miR-509-3-5p reversed cisplatin resistance. These findings suggest that alteration of the chrXq27.3 miRNA cluster could play a critical role in chemoresistance and miRNAs in the cluster and their target genes can be potential therapeutic targets. This study was published in *Oncogene* on Jan 8, 2020.



Research Background

Epithelial ovarian cancer (EOC) remains one of the leading causes of cancer death among females worldwide. Ovarian clear cell carcinoma (OCCC) is a histological subtype of EOC and exhibits dismal prognosis due to chemoresistance. Standard treatment for EOC is cytoreductive surgery combined with platinum-containing chemotherapy, but some patients eventually develop platinum-resistant disease. Few effective therapeutic options exist for patients with platinum-resistant EOC, and therefore, it is important to know the molecular characteristics of recurrent EOC.

MicroRNAs (miRNAs), small noncoding RNA molecules consisting of approximately 22 nucleotides, regulate gene expression post-transcriptionally and play multiple roles in various processes including cancer progression and drug resistance. MiRNA clusters contain a set of two or more miRNA-encoding genes, and members of a miRNA cluster are considered to be under the control of a common regulatory unit and co-expressed. However, the function of the chrXq27.3 miRNA cluster in recurrent OCCC remains unknown.

Research Results

Comprehensive miRNA sequencings were performed by using recurrent and primary OCCC samples. The heatmap analysis showed that miRNA profiles of recurrent OCCC was different from those of primary OCCC. Comparing paired recurrent and primary tumors, ten miRNAs were remarkably decreased in the recurrent OCCC, and interestingly, the seven of them are located in the chrXq27.3 region on the genome. Especially, miR-508-3p, miR-509-3p, miR-509-3-5p, and miR-514a-3p were significantly downregulating in recurrent tumors than primary tumors. In addition, they investigated the miRNA profiles of advanced OCCC and revealed that the four miRNAs were also downregulated in omental metastasis of OCCC.

Then, they evaluated the function of the miRNAs. Overexpression of miR-509-3p and miR-509-3-5p increased cisplatin sensitivity and cisplatin-induced apoptosis. They identified that YAP1 was one of the target genes of the miRNAs, and silencing of YAP1 also increased cisplatin sensitivity. Moreover, YAP1 expression was inversely correlated with the chrXq27.3 miRNA cluster expression in clinical samples.

Research Summary and Future Perspective

This study showed that several miRNAs in the chrXq27.3 miRNA cluster were remarkably downregulated in recurrent and metastatic OCCC, and downregulation of miR-509-3p and miR-509-3-5p were involved in cisplatin resistance. The chrXq27.3 miRNA cluster may have further important roles in cancer progression, making it a potential therapeutic target in OCCC.

Publication

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