The role of the long non-coding RNA ANRIL in chemosensitivity in osteosarcoma and clinical outcomes

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OSTEOSARCOMA

Osteosarcoma is a primary skeletal malignancy that affects children, adolescents, and young adults. New advances in chemotherapy and surgical resection is the mainstay of therapy. Patients receive an initial 2 cycles of chemotherapy with cisplatin, doxorubicin, and methotrexate. Following, patients undergo resection of their primary tumor and undergo an assessment of necrosis of their primary tumor. Patients complete therapy with 4 more cycles of cisplatin, doxorubicin, and methotrexate.

HYPOTHESIS

Decreased ANRIL expression in an osteosarcoma cell line will lead to increased cisplatin- and doxorubicin-sensitivity and improved clinical outcomes.

RESULTS

The SaOS2 cells were exposed to increasing concentrations of cisplatin or doxorubicin. Cellular sensitivity to these drugs was compared between ANRIL siRNA and scramble control at 24, 48, and 72 hours.

METHODS

In Dr. R. Stephanie Huang’s lab, there has been much work done in understanding the possible role of IncRNA in cancer biology. Utilizing high-throughput large-scale cancer cell lines (approximately 900 cancer cell lines, each with detailed RNA-seq data), we focused on 3 chemotherapies to demonstrate expression.

The IncRNA ANRIL demonstrated a strong association with drug sensitivity to cisplatin, doxorubicin, and methotrexate (IC50 < 5.00 mg/ml). The ANRIL expression is significantly increased in cisplatin-resistant doxorubicin-sensitive cells. The ANRIL expression is decreased in doxorubicin-resistant cisplatin-sensitive cells.

CLINICAL CORRELATION

Knowing that the knockdown of ANRIL leads to increased sensitivity of osteosarcoma cells to cisplatin and doxorubicin, we wanted to know if this increased sensitivity translated to improved clinical outcomes. We utilized two independent clinical datasets: TARGET (Therapeutically Applicable Research to Generate Effective Treatments) and BOOST (Biology of Osteosarcoma Study Team).

CONCLUSIONS

Knocking down the IncRNA ANRIL, thereby decreasing its expression, increases the sensitivity of osteosarcoma cells to cisplatin and doxorubicin. High ANRIL expression is associated with increased death and metastases at diagnosis in a statistically significant manner in a clinical dataset. Therefore, ANRIL may serve as a biomarker in predicting impending chemo-resistance in patients with osteosarcoma.

REFERENCES


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