DNA imprinting defects associated with childhood osteosarcoma development and progression

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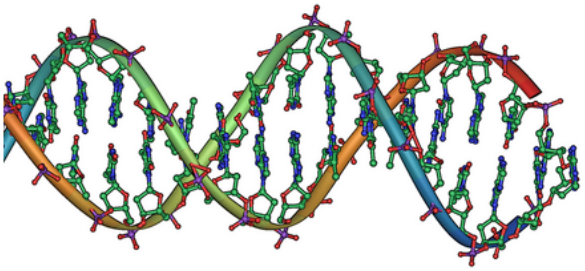

DNA double helix. Credit: public domain

Children diagnosed with osteosarcoma may be impacted by a DNA imprinting defect also found in parents, according to new research from the Masonic Cancer Center, University of Minnesota. DNA imprinting is a phenomenon in which just one of the two inherited genes is active while the other is present but inactive.

The study is published now in the journal *Oncotarget*.

The research was spearheaded by Masonic Cancer Center researcher Subbaya Subramanian, Ph.D., associate professor in the University of Minnesota Medical School's Department of Surgery. The study was also collaboratively supported by David Largaespada, Ph.D., professor in the Department of Pediatric Hematology/Oncology and Clifford Steer, M.D., professor in the Departments of Medicine and Genetics, Cell Biology and Development. Both are members of the Masonic Cancer Center.

Osteosarcoma is a type of bone cancer predominantly affecting children and adolescents. The five year survival rate is about 70 percent, a rate unchanged in over 30 years. Recent research has shown a connection between downregulation of microRNAs and the development and progression of osteosarcoma. In this study, researchers wanted to know if the specific gene and microRNA expression changes associated with osteosarcoma could be due to epigenetic alterations and, specifically, if these alterations are also present in a parent.

Lead author Jingmin Shu, Ph.D., and the team assessed DNA methylation changes as well as reviewed histone modifications in both normal bone tissues and patient samples. Taking an even closer look, researchers also determined the imprinting status of a specific genomic location using the DNA from buccal swab samples from both osteosarcoma patients and their unaffected parents. Simultaneously, they observed pronounced imprinting defects in certain mouse models of osteosarcoma.

What they found

Results of the study show imprinting defects are associated with the pathogenesis of osteosarcoma and these imprinting defects are present in the DNA samples from affected children and their biological parents.

"Through these initial studies, we found the imprinting defects as possible mechanisms altering gene and microRNA expression which are associated with osteosarcoma pathobiology," said Subramanian. "This also allows us to think imprinting defects may be a cause for osteosarcoma to develop predominantly as a pediatric cancer."

They also cautiously noted that a larger cohort study is needed.

Other notable findings include:

- Extent of gene expression and DNA methylation changes may identify the advancement of the disease.
- The imprinting defect researchers found is unique to osteosarcoma.
- Imprinting defects are not the result of pre-existing mutations in the mouse model.

"These findings set the stage for clinical investigation using DNA- and chromatin-modifying drugs, as well as rectifying imprinting defects by genome editing tools in osteosarcoma treatment," said Subramanian. "Further investigation is needed to evaluate novel methods to correct imprinting defects as preventive therapies."

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