K9 osteosarcoma samples identify drivers of metastasis in pediatric bone cancer

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Human osteosarcoma samples are hard to come by, making the disease difficult to study. However, K9 bone cancer is genetically indistinguishable from the human form of the disease, and over 10,000 canine patients develop the disease every year. Research from the University of Colorado Cancer Center and the Colorado State University Flint Animal Cancer Center presented at the AACR Annual Meeting 2013 used easily available K9 osteosarcoma samples to discover a novel protein that governs metastasis and chemoresistance in pediatric osteosarcoma.

"We have a pediatric osteosarcoma survival rate of 75 percent. But if the disease has already metastasized at the time of diagnosis, the survival rate is only 20 percent. This study takes an important step toward stopping this metastasis and treating the most dangerous form of the disease," says Dawn Duval, PhD, investigator at the CU Cancer Center and assistant professor of molecular oncology at Colorado State University.

Duval and colleagues assessed the gene expression signatures of K9 osteosarcoma samples, comparing cancers that had shown especially long and especially short periods of disease-free progression after the common treatment of amputation and chemotherapy – the theory being that differences in these genetic profiles would mark the difference between metastasic and non-metastatic cancers. The gene most different between more and less aggressive K9 osteosarcomas was the gene that makes IGF2 mRNA binding protein (called IGF2BP1) – a molecule

necessary during fetal development that should go quiet after birth, but whose expression had been restarted in these aggressive cancers.

"Right away, both the over-expression of this protein and its known function made it a strong candidate driver for osteosarcoma metastasis, but we wanted to validate its function in human samples and in mouse models," Duval says.

To do so, the group analyzed IGF2BP1 expression in five available human osteosarcoma cell lines, finding an average 14-fold increase in expression compared to samples of healthy bone. Specifically, the group found that mRNA and protein expression linked to the influence of IGF2BP1 was highest in the most metastatic of these five human cell lines.

When Duval knocked down the expression of IGF2BP1, she found a three-fold decrease in the proliferation of these cells and increased sensitivity to chemotherapy with doxorubicin. The same technique produced similar results in mouse models of the disease – without IGF2BP1, mouse models developed fewer, smaller tumors.

"It's an exciting finding and one with important clinical potential," Duval says.

Though further work is needed to validate IGF2BP1 as a marker and target for controlling the metastasis of pediatric bone cancer, and to identify clinically appropriate ways of targeting the molecule or its gene expression pathway, Duval is optimistic that this first step will result in improved care for the pediatric osteosarcoma patients who remain at the highest risk.

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