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Pathways activated in most K9 bone tumors not driving the worst bone tumors

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Many cancers show inappropriate activation of a cell signaling pathway called NOTCH. In the developing body, NOTCH tells brain cells to grow and proliferate. It should be quiet in the adult body, but cancers restart NOTCH to drive their own growth, far and beyond the rate of healthy tissues. A Colorado State University and University of Colorado Cancer Center study expected to find NOTCH signaling elevated in K9 osteosarcoma samples, gathered from patients at the CSU Flint Animal Cancer Center. What they found surprised the researchers: overall, NOTCH signaling was elevated in K9 osteosarcoma, but aspects of Notch signaling were noticeably deactivated in the worst cancers.

"We split the samples into two groups: poor responders who had gone less than 100 days after treatment before the progression of their disease, and strong responders who had made it more than 300 days after their treatment without disease progression. Then we could explore the genetic differences between these two groups," says Dawn Duval, PhD, CU Cancer Center investigator and associate professor of molecular oncology at Colorado State University.

Specifically, Duval and colleagues including first author Deanna Dailey, DVM, looked at the expression of a protein called HES1, which is used as a proxy to test for NOTCH activation. High HES1 means that upstream, NOTCH is firing. Low HES1 means it's not firing or that some other pathway is interfering. They expected to find a linear increase in HES1 as cancers and outcomes got worse – more HES1 would have meant more NOTCH signaling and results in other cancers

imply that the more NOTCH, the worse the outcomes.

"What we found is that the poor responders had lower HES1. That fit nothing we expected," Duval says.

The osteosarcoma samples from dogs with disease progression in the shortest amount of time, also had the lowest levels of HES1.

"We had to go back and try to figure out what was happening, so we measured HES1 levels in normal bone samples and matched bone tumors. For good measure we also looked at several other Notch pathway markers. What we found was that, in general, Notch signaling was activated in the bone tumors, both good and bad, but that HES1 seemed to be disconnected from Notch signaling in the most aggressive tumors."

They validated the finding by examining HES1 protein expression in over 60 tumors and correlating it with cancer progression. This was the real deal: HES1 was down in the most aggressive K9 osteosarcomas.

"I have many hypotheses why. Here are a couple different ones, most of which have been worked out by Deanna," Duval says. "First, it may be that NOTCH is up due to the proliferation that occurs in most cancers, but that something else is driving the worst ones and this pathway interferes with HES1 expression. For example, another signaling pathway called Hedgehog, which can also affect the level of HES1 is deactivated in these aggressive osteosarcomas and so the level of HES1 may be down because Hedgehog was down. Maybe most interestingly, in the development of neurons, you can see an oscillation of HES1 – it has to go up and then down in order for cells to progress through their cycles. Maybe these osteosarcoma cells have overcome this regulatory pattern to progress?"

For now, the finding of low HES1 signaling in the worst K9 osteosarcomas remains a counterintuitive mystery. Dr. Duval's ongoing work hopes to provide answers to this surprising finding.

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