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Lymphoma drug shrinks dog tumors, could lead to human treatment

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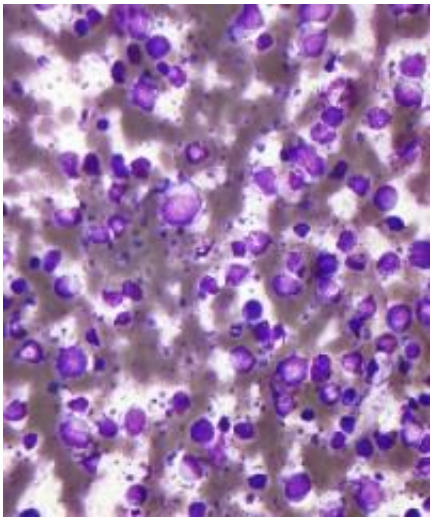

Large B cell lymphoma

There are many kinds of cancers of the immune system, but one, Activated B-Cell Diffuse Large B-Cell Lymphoma, or ABC-DLBCL, is particularly common and pernicious. Researchers at the University of Pennsylvania's School of Veterinary Medicine have shown for the first time that dogs that develop this disease spontaneously share the same aberrant activation of a critical intracellular pathway with humans. They also found that a drug designed to disrupt this pathway helps to kill tumor cells in the dogs' cancerous lymph nodes.

The research was conducted by Nicola Mason, assistant professor of

medicine at Penn Veterinary, along with Michael J. May, associate professor of pharmacology; postdoctoral fellow Anita Gaurnier-Hausser; and veterinary clinical pathologist Reema Patel.

Their work was published in the journal Clinical Cancer Research.

B-cells are the part of the immune system that produce antibodies and protect the body against invading microorganisms or allergens. In ABC-DLBCL, the intracellular signaling pathway involved in B-cell activation and proliferation is, as the name of the disease suggests, constantly activated.

“This signaling pathway, called NF-kappaB, is critical in immune function; following an encounter with antigen, lymphocytes need to be activated and proliferate so that there are sufficient numbers to deal with the invading organism,” Mason said. “But in humans with ABC-DLBCL, and also in dogs with spontaneous DLBCL, this pathway is constitutively active and drives lymphocytes to proliferate continuously.“

Moreover, these malignant B-cells are resistant to apoptosis, or cell death. Their unchecked growth is the basis of the lymph node tumors that are a hallmark of the disease.

For many years, researchers have been investigating ways of interrupting the malfunctioning pathway that forms the tumors and provides resistance to chemotherapy-induced cell death. In order to test whether a canine model for inhibitors would have relevance to cancer treatment in humans, the Penn team first showed that the same aberrant activation of the NF-kappaB pathway exists in dogs.

They then went on to demonstrate that inhibition of this pathway using a drug known as NEMO Binding Domain, or NBD, peptide led to increased cell death of malignant lymphocytes in a laboratory setting.

The next step was to determine whether this peptide could similarly inhibit NF-kappaB activity when used directly in the dogs with the disease.

Treatment of DLBCL in dogs is similar to humans; the cancer usually responds well to chemotherapy, but patients frequently relapse with drug-resistant disease. The five-year survival prognosis for humans is about 50 percent, but in dogs the survival rate is much worse, with more 85 percent of dogs relapsing within the first year and the majority succumbing to their disease during the first or second round of chemotherapy.

Having determined the presence of aberrant pathway activity in the dogs with spontaneous DLBCL and that inhibition of this pathway can lead to increased cell death, the researchers performed a small pilot trial to determine the efficacy of the NBD peptide in dogs that had relapsed with drug resistant lymphoma.

The results were encouraging.

“We injected one malignant lymph node with the NBD peptide and followed up with chemotherapy. One week after a single dose of peptide, the lymph node we injected was a lot smaller than the other cancerous lymph nodes,” Mason said. “This suggests that the peptide either acts alone or synergistically with the chemotherapy drugs to kill the tumor cells.”

Testing the peptide in a live animal model, rather than in tumor cells taken from cell lines in a Petri dish, accelerates the prospects of this research leading to clinical treatments for both dogs and humans.

“The identification of a comparable molecular pathogenesis of ABC-DLBCL between dogs and humans, coupled with our ability to

investigate the therapeutic benefit of targeting this aberrant NF-kappaB pathway in a clinically relevant, large animal model is a perfect example of the 'bench to bedside' paradigm of translational medicine," Mason said. "It's been over 10 years since this pathway was recognized in ABC-DLBCL in humans; however, this is the first indication that specific inhibition of this pathway may have a beneficial effect in human and canine patients with this disease."

Mason and her colleagues are now testing whether the peptide is systemically effective when introduced intravenously, rather than directly injected into a single tumor. The drug has shown to have minimal side effects on the immune systems of small animals, and a successful and safe trial in dogs could not only pave the way to a novel approach to the treatment of this disease in pet dogs but also could lead to clinical trials in humans with this type of lymphoma.

Provided by University of Pennsylvania