Unexpected epilepsy model found in sea lions

Temporal lobe epilepsy is the most common form of partial or localization-related epilepsy, accounting for ~60% of all patients with epilepsy. A variety of rodent models of temporal lobe epilepsy are available, but there is a lack of large animal models with brains more similar to those of humans.

Recently, researchers have noticed that sea lions stranded along the central California coast and admitted to the Marine Mammal Center in Sausalito, CA, for rehabilitation showed symptoms suggestive of temporal lobe epilepsy, including tremors, convulsions, memory loss and even death. Domoic acid, a toxin that is produced by algae blooms of the genus *Pseudo-nitzschia*, was found to be the culprit. During seasonal blooms, the algae are consumed by grazing planktivorous fish such as anchovies, and domoic acid becomes concentrated and accumulates in the fish. When these fish are eaten by sea lions, the toxin is absorbed through the gut. Sea lions affected by domoic acid toxicity develop neurological problems

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including seizures that result in their stranding on beaches.

A Stanford University (CA) team examined the brains of 14 sea lions with epilepsy caused by domoic acid that were admitted to the Marine Mammal Center but did not respond to treatment and died. When compared with the brains of nine sea lions that died from other causes, the sea lions with epilepsy showed varying degrees of significant hippocampal neuron loss. In some hippocampal cell layers, they had more than 50% fewer neurons (*J. Comp. Neurol.* 522, 1691–1706; 2014). Interestingly, the

hippocampal neuron loss in the epileptic sea lions was similar in pattern and extent to that reported previously in human patients with temporal lobe epilepsy.

“We found there was a loss of neurons in specific patterns that closely matched what is found in people,” Paul Buckmaster, first author of the study, said in a press release. “And there is synaptic reorganization—a rewiring of surviving neurons. This also matches what is found in humans with temporal lobe epilepsy.”

Furthermore, only the hippocampus on one side of the brain was damaged in each sea lion. “That is what you find in people,” Buckmaster explained. “80% of the time the damage is just on one side.”

The study’s findings suggest that domoic acid toxicity may provide a useful model for temporal lobe epilepsy. Further research in affected sea lions could lead to the development of better treatments for epilepsy in both sea lions and humans.

Kara Rosania

FISHING FOR INSIGHT INTO LEUKEMIA RELAPSE

Single-cell analyses have shown that individual cancer cells can acquire mutations that make them more aggressive and resistant to chemotherapy. Thus, in some cases, even if chemotherapy seems to have been effective, a particularly aggressive cancer cell may survive and then cause a relapse in the future. The specific mutations that drive cancer progression and the mechanisms by which they do so are not well understood, delaying improvements in treating chemotherapy-resistant relapse.

Researchers from Harvard Medical School and Massachusetts General Hospital (both in Boston, MA) led by David Langenau decided to try a new approach to identify the relapse-driving cells in T-cell acute lymphoblastic leukemia (T-ALL), called leukemia-propagating cells (LPCs), using zebrafish. They induced T-ALL in transgenic zebrafish, then isolated individual leukemia cells and transplanted them into other zebrafish repeatedly to evaluate differences among the cells in the number of LPCs they eventually produced. A minority of leukemia cells produced significantly more LPCs after repeated transplant. Upon closer examination of these cells, the researchers found that a substantial subset of them had acquired a mutation that activated the Akt pathway. Activation of the Akt pathway increased the number of LPCs produced, increased the rate of cell growth and conferred resistance to dexamethasone chemotherapy (*Cancer Cell* 25, 366–378; 2014).

“The Akt pathway appears to be a major driver of treatment resistance [and also] increases overall growth of leukemic cells and increases the fraction of cells capable of driving relapse,” Langenau said in a press release.

Having elucidated a mechanism underlying relapse and chemotherapy resistance in T-ALL, Langenau’s group next sought to apply this knowledge to improve treatment. They transplanted either primary Akt-negative leukemia cells or Akt-activated leukemia cells into zebrafish and then treated them with dexamethasone with or without an Akt inhibitor called MK2206. Dexamethasone alone was effective against Akt-negative leukemia but not against Akt-activated leukemia, as predicted. But the addition of MK2206 restored dexamethasone sensitivity in Akt-activated leukemia, resulting in remission.

The work has implications for the treatment of T-ALL in humans. It is likely that Akt-activated cells resistant to dexamethasone are already present in some patients, even those who have not been exposed to chemotherapy. And in patients undergoing chemotherapy, the selective pressure on leukemia cells to activate the Akt pathway is probably very strong. These patients may benefit from combination treatment with dexamethasone and Akt inhibitors such as MK2206. Langenau’s team suggests that preclinical testing of such combination therapy is warranted.

Monica Harrington