Rare byproduct of marine bacteria kills cancer cells by snipping their DNA

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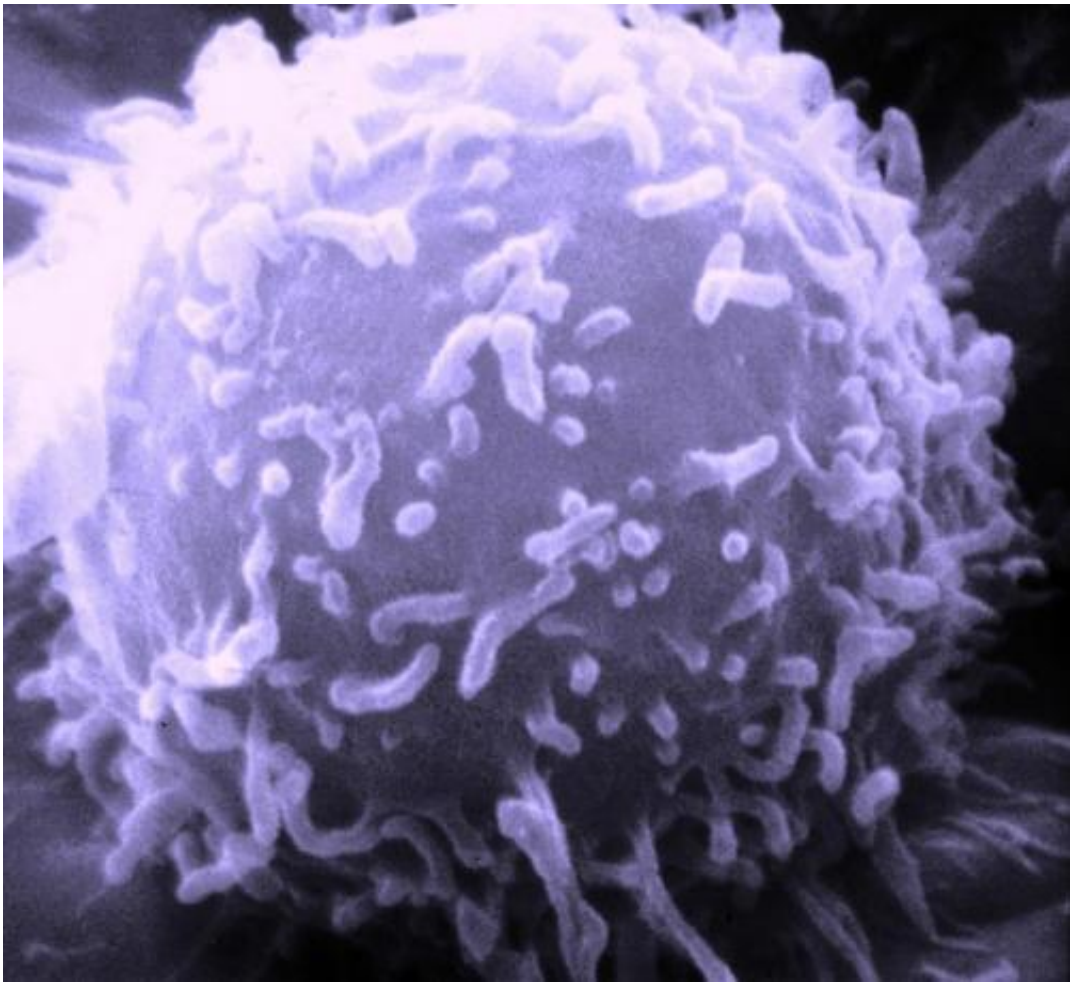

Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

(Phys.org) —Yale University researchers have determined how a scarce molecule produced by marine bacteria can kill cancer cells, paving the way for the development of new, low-dose chemotherapies.

The molecule, lomaiviticin A, was previously shown to be lethal to cultured human cancer cells, but the mechanism of its operation remained unsolved for well over a decade. In a series of experiments, Yale scientists Seth Herzon, Peter Glazer, and colleagues show that the molecule nicks, cleaves, and ultimately destroys cancer cells' DNA, preventing replication.

"DNA is one of the primary targets of anticancer agents, and cleavage of both DNA chains is the most potent form of DNA damage," said Herzon, professor of chemistry. "But few anticancer agents are able to directly cleave DNA. The discovery that lomaiviticin A is capable of this suggests it could be very useful as a novel chemotherapy, possibly at low doses."

Results were published May 11 in the journal *Nature Chemistry*.

Herzon's team tested and distinguished the effects of lomaiviticin A—which is produced by a marine bacterium associated with sea squirts—and two closely related molecules, lomaiviticin C and kinamycin C, which are also produced by bacteria.

All three molecules contain at least one diazofluorene, a particular arrangement of atoms known as a functional group. Lomaiviticin A contains two diazofluorenes, while lomaiviticin C and kinamycin C contain just one. The scientists evaluated and contrasted their effects on cancer cells' growth and DNA.

They found that the two diazofluorenes of lomaiviticin A are intimately involved in DNA cleavage, and that the loss of one diazofluorene

profoundly diminishes the ability of the molecules to kill cells, Herzon said. Lomaiviticin C or kinamycin C – which have only one diazofluorene – are unable to cleave DNA, and are much less toxic to the cells.

"Our data support a model for DNA cleavage involving breakage of both strands of DNA by a single molecule of lomaiviticin," he said. "The best way to think about this is as if lomaiviticin A were a garden shear and the two strands of DNA were the vines you are trimming. As you would grasp the vines and cut two of them to the same length, lomaiviticin A interacts with DNA and then snips the strands at the same site."

Herzon says that researchers still do not know much about the nature of the interaction of lomaiviticin A with DNA, or the specific sequence of events that leads to DNA breaks.

What is clear, Herzon said, is that "lomaiviticin A possesses powerful DNA–damaging properties."

He added: "I have spent the last six years thinking about these molecules, and could not have predicted this activity, or the remarkable differences between lomaiviticins A and C. This work highlights the immense power of interdisciplinary studies in synthetic chemistry and molecular biology to address problems that cannot be solved by either field alone."

The paper is titled "The cytotoxicity of (—)-lomaiviticin A arises from induction of double-strand breaks in DNA."

More information: "The Cytotoxicity of (–)-Lomaiviticin A Arises From Induction of Double-strand Breaks in DNA." Laureen C. Colis, Christina M. Woo, Denise C. Hegan, Zhenwu Li, Peter M. Glazer and Seth B. Herzon *Nat. Chem.* 2014, 6, Advance Online Publiction, DOI: 10.1038/nchem.1944

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