Inspired by nature: Synthetic nightshade molecule effective against leukemia cells

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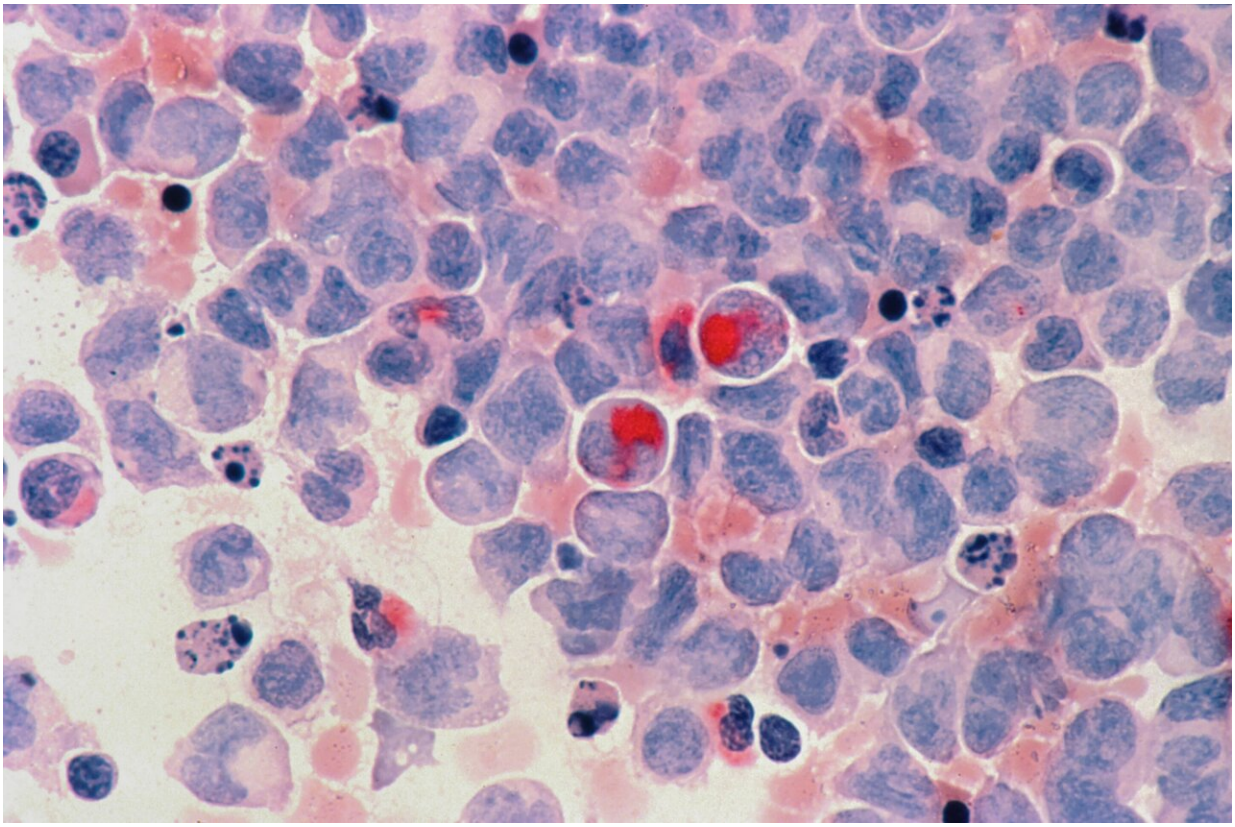

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Nightshade plants produce a diverse array of compounds with therapeutic potential. Researchers at CeMM have now identified an artificial variant inspired by the Withanolides group that acts highly

specifically against leukemia cells.

Using state-of-the-art chemical and genetic high-throughput analyses, the team led by Georg Winter not only confirmed its effectiveness but also elucidated its mechanism of action: the molecule disrupts the cholesterol metabolism of tumor cells. The study's findings were published in the journal *Nature Chemical Biology*.

While some nightshade plants, such as potatoes, tomatoes, or eggplants, offer culinary delights, others contain potent toxins like belladonna, angel's trumpet, or deadly nightshade.

Yet, it is precisely these toxic representatives that are of interest to medicine: in addition to alkaloids, they produce a wide range of steroids, a class of lipids that can influence human metabolism in various ways. Among these steroids are the Withanolides, which have been associated with anti-inflammatory, antioxidant, and cancer-preventive properties.

Therefore, the research group led by Georg Winter, Principal Investigator at CeMM, in collaboration with the research group of Prof. Herbert Waldmann at the Max Planck Institute for Molecular Physiology, meticulously examined a large collection of artificial variants of Withanolides for their effect on leukemia cells—specifically, cells from chronic myeloid leukemia and T-cell leukemia.

This led to the discovery of a variant that selectively kills these tumor cells while minimally affecting non-malignant blood cells—a crucial criterion for consideration as a drug candidate for clinical use. They named the identified substance Orpinolide.

First author Marko Cigler (l) and last author Georg Winter (r) at CeMM Time Capsule Anna Yuwen/CeMM. Credit: Anna Yuwen/CeMM

Cholesterol transport as leukemia's Achilles' heel

Subsequently, through state-of-the-art high-throughput methods like quantitative proteomics and transcriptomics, researchers found that Orpinolide disrupts cholesterol transport in tumor cells.

Cholesterol is a vital component of cell membranes and chemically belongs to the group of sterols. By systematically inactivating all genes using the CRISPR/Cas9 gene-editing tool and analyzing changes in the thermostability of the entire proteome, the precise molecular binding site of Orpinolide was identified: the cholesterol transporter OSBP.

"This study highlights sterol transport as an Achilles' heel in leukemia, one that we can block with chemical agents," says study lead Georg Winter. Elucidating the mechanism of action of Orpinolide could thus serve as a starting point for developing new drugs against this form of blood cancer.

"Natural substances remain an important source of inspiration for new drugs. Our ability to comprehensively understand them should open numerous possibilities for future innovations in drug research," adds lead author Marko Cigler.

More information: Marko Cigler et al, Orpinolide disrupts a leukemic dependency on cholesterol transport by inhibiting OSBP, *Nature Chemical Biology* (2024). DOI: 10.1038/s41589-024-01614-4

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