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Discovery paves the way for a new generation of chemotherapies

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A new mechanism to inhibit proteasomes, protein complexes that are a target for cancer therapy, is the topic of an article published in the journal *Chemistry & Biology*. The first author of the study is Daniela Trivella, researcher at the Brazilian Biosciences National Laboratory at the Brazilian Center for Research in Energy and Materials (LNBio/CNPEM).

The findings of the study, conducted with FAPESP support in partnership with researchers from the University of California in San Diego, United States, and at the Technische Universität München, in Germany, are paving the way for the development of a new generation of chemotherapy drugs that are more effective and less toxic.

"We have already developed a series of molecules based on the newly identified mechanism. Now we plan to synthesize them in partnership with CNPEM researcher Marjorie Bruder and test their potential. The goal is to optimize the proteasome inhibition effect, make the compound even more selective of tumor cells and eliminate the resistance problems found with drugs that are currently available on the market," Trivella said.

A member of the category of enzymes known as proteases, the proteasome is a protein complex responsible for several essential functions inside cells, such as eliminating harmful or non-functioning proteins and regulating the processes of apoptosis (programmed cell death), cell division and proliferation.

In 2012, the drug carfilzomib, inspired by a natural molecule called epoxomicin, was approved. Also in 2012, U.S. and Brazilian researchers isolated a natural molecule in cyanobacteria from the Caribbean called carmaphycin, whose reactive group (the portion of the molecule that interacts with the proteasome) is the same as that of carfilzomib. The molecule is known as an epoxyketone.

"Epoxyketones are very potent selective inhibitors of the proteasome because they interact with this enzyme in two stages: the first reversible and the second irreversible," Trivella explained.

To optimize its effect and find new reactive groups, researchers from the Scripps Institution of Oceanography at the University of California in San Diego developed a series of synthetic analogs with slight structural modifications.

Trivella tested these compounds during an internship in California in her post-doctoral research when she was still associated with the Chemistry Institute at the University of Campinas (Unicamp).

One of the molecules tested had an enone as a reactive group and had characteristics of carmaphycin and another natural molecule named syringolin, isolated from plant pathogens.

By investigating the reaction mechanisms of the new molecule, named carmaphycin-syringolin enone, the researcher verified that unlike syringolin, and thus like the epoxyketone, the enone interacts with the proteasome in two stages, with the second stage being irreversible.

Additionally, Trivella had observed that in the case of the enone, the second reaction occurs more slowly, increasing the duration of the reversible phase of carmaphycin-syringolin enone inhibition.

"Because the irreversible inactivation of the proteasome has toxic effects, the best window of reversibility observed for the carmaphycin-syringolin enone will potentially reduce the toxicity of this new class of proteasome inhibitors," Trivella said. "The compound would therefore present a balance between selectivity and potency."

Toxicity tests are still underway. In parallel, studies have been conducted with the help of crystallography techniques to discover exactly how the interaction between the enzyme target and the carmaphycin- syringolin enone target occurs.

"We discovered that a chemical reaction called hydroamination occurs, which had never before seen under physiological conditions. This type of reaction is frequently used by synthetic chemists in preparing substances, but normally it requires very specific temperature and pH conditions and the use of catalysts to occur. It has never been reported as a mechanism of enzyme inhibition," Trivella said.

Inspired by this new mechanism for proteasome inhibition, the LNBio group plans to synthesize and test a new series of carmaphycin-syringolin enone analogs to determine their effects on the therapeutic window (preferential death of tumor cells in relation to healthy cells) and assess whether they are also capable of reacting with proteasomes that are resistant to traditional inhibitors.

Another of Trivella's goals is to look for natural compounds in Brazilian biodiversity that could serve as inspiration for the design of other categories of proteasome inhibitors.

More information: *Chemistry & Biology*, www.cell.com/chemistry-biology … 1074-5521(14)00177-X

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