A new synthetic amino acid for an emerging class of drugs

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Credit: Alain Herzog/EPFL

Swiss scientists have developed a new amino acid that can be used to modify the 3-D structure of therapeutic peptides. Insertion of the amino acid into bioactive peptides enhanced their binding affinity up to 40-fold. Peptides with the new amino acid could potentially become a new class of therapeutics.

One of the greatest challenges in modern medicine is developing drugs that are highly effective against a target, but with minimal toxicity and side-effects to the patient. Such properties are directly related to the 3D structure of the drug molecule. Ideally, the drug should have a shape that is perfectly complementary to a disease-causing target, so that it binds it with high specificity. Publishing in *Nature Chemistry*, EPFL scientists

have developed a synthetic amino acid that can impact the 3D structure of bioactive peptides and enhance their potency.

Peptides and proteins as drugs

Many of the drugs we use today are essentially naturally-occurring peptides (small) and proteins (large), both of which are made up with the amino acids found in all living organisms. Despite the enormous variety of peptides and proteins, there are only twenty natural amino acids, each with a different structure and chemical properties. When strung together in a sequence, amino acids create peptides and proteins with different 3D structures and, consequently, different biological functions.

Until recently, the vast majority of amino acid-based drugs were the kinds occurring in nature: hormones such as insulin, antibiotics such as vancomycin, immunosuppressive drugs such as cyclosporine etc. But the mounting burden of diseases means that newer and more effective medications must be developed; for example, bacterial resistance is growing globally, pushing our need for novel antibiotics. One way to address this need is the cutting-edge field of directed evolution, which mimics natural selection in the lab to evolve and develop new peptides and proteins.

A new amino acid for new peptides

The team of Christian Heinis at EPFL has developed a synthetic amino acid whose unique structure can considerably increase the effectiveness of therapeutic peptides and proteins. The synthetic amino acid has a very similar structure to a natural amino acid called cysteine. Cysteine is unique among the twenty natural amino acids because it contains a sulfur group. This allows it to form a bridge with another cysteine, and thereby influence the overall 3D structure – and function – of a peptide or

protein.

The EPFL researchers initially designed five cysteine-like amino acids, all with one crucial change: each one could form two bridges instead of just one. The team achieved this by replacing cysteine's single sulfur group with a branch containing two sulfur groups. After synthesizing the five new amino acids, the team integrated them into the structure of two bioactive peptides, one that inhibits an enzyme implicated in cancer, and one blocking a receptor found in neurons.

Testing only a handful of cyclic peptides with the synthetic amino acid, Heinis' team was able to identify several peptides that showed enhanced activities. The best inhibitor of the neuron receptor was 8-fold improved and the best protease inhibitor had even a 40-fold higher activity.

"This was unexpected", says Christian Heinis. "Usually when you tamper with a natural molecule, you end up making it worse. In this case, we found the exact opposite, which is very exciting."

The emerging class of bicyclic peptides

The team focuses on therapeutics, where they have a strong background in developing "bicyclic" peptides – peptides that contain two rings in their structure. Bicyclic peptides have grown into a new class of therapeutic peptides that can be used on disease target that conventional small molecules or large antibodies cannot reach. Heinis' group has generated bicyclic peptides against a range of disease targets using directed evolution. "In our work with bicyclic peptides, we learned that wide structural diversity in peptide libraries is key for achieving good binding. With this new amino acid, it is possible to produce highly diverse peptide structures."

Heinis aims now to use the new amino acid in directed evolution

experiments. Its structural features and its ability to efficiently make cyclic peptides makes the synthetic amino acid a promising candidate for developing new, effective polycyclic peptides for targeted therapy.

More information: Chen S. Gopalakrishnan R, Schaer T, Marger F, Hovius R, Bertrand D, Pojer F, Heinis C. Dithiol amino acids can structurally shape and enhance the ligand-binding properties of polypeptides. *Nature Chemistry* 31 August 2014. DOI: 10.1038/nchem.2043

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