Novel polymer could improve protein-based drugs

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A new method for attaching a large protective polymer molecule to a protein appears to improve protein drugs significantly.

Bioengineers at Duke University developed the new approach and demonstrated in an animal model that the newly created protein-polymer combinations, known as conjugates, remained in circulation significantly longer than an unprotected protein.

The scientists say they are encouraged that their findings represent a new strategy to improve the efficacy of protein drugs.

Protein-based drugs are an increasingly important new class of drugs, said Ashutosh Chilkoti, Theo Pilkington Professor of Biomedical Engineering at Duke's Pratt School of Engineering. He cited such examples as insulin for the treatment of diabetes and more exotic "magic bullet" antibodies like herceptin that are used to treat certain cancers.

Unmodified proteins that are injected into the blood are quickly recognized by the body and broken down or cleared by the body's defense system, which limits their effectiveness as drugs. To get around this problem, drug makers have been attaching another molecule, a polymer known as polyethyleneglycol (PEG), to the protein in order to protect it. But this approach has its own drawbacks.

"The current method of combining the two molecules often only works with 10 to 20 percent efficiency, so that a lot of the very expensive

starting materials are wasted," said Chilkoti, who had the results of his team's experiments published this week online in the Proceedings of the National Academy of Sciences. "Additionally, the two large molecules are attached by a small chemical link and often these linkages can occur at many different sites on the protein, so the final product is poorly defined."

Chilkoti took a different approach. Instead of combining two large molecules, he grew the polymer out from the protein itself, increasing the efficiency of the protein by more than 70 percent and greatly extending the amount of time it remained active in a living model.

"We also addressed the problem of getting a pure and well-defined product by growing the polymer from a single, unique site on the protein," he said. "Another twist to our work is that instead of using PEG, we used a somewhat different polymer that turns out to be as good and perhaps even better than PEG in extending circulation of the protein in the body."

There are many protein-polymer based medications in use today, such as human growth hormones, drugs to stimulate blood cell formation in cancer patients and anti-viral agents. Chilkoti will be reviewing existing protein-polymer drugs to determine if the new technique can improve their effectiveness.

In their experiments, the researchers used myoglobin, a protein responsible for creating the red pigments that give meat its color. Instead of creating a chemical bond between myoglobin and the polymer, the Duke researchers chose a specific spot on the protein, known as the N-terminus, and then grew the polymer from that specific location. Every protein has an N-terminus, so this method should be broadly useful, Chilkoti said.

After demonstrating they could create a stable compound using the new method, the researchers tested how well it worked by comparing its actions to the conventional compound in mice.

"The conventional compound - myoglobin - had a half-life of three minutes and was totally eliminated by two hours," Chilkoti explained. "By contrast, the new compound had a half-life 40 times greater and remained in circulation for 18 hours. The longer a protein remains in the system and is active, the more it helps the patient."

"The dramatic improvement in how the new compound acted encourages us that this new approach will have broad applications in improving the efficacy of many protein drugs," Chilkoti said.

Another benefit of this approach, according to Chilkoti, is that the polymer should naturally degrade in the body over time and be easily excreted. "Because the compound is biodegradable, we should in principle be able to make even larger protein-polymer combinations with potentially even better pharmacologic properties," he said.

The researchers plan to apply their invention to other protein-based therapies, such as for cancer and diabetes, to determine if they can improve effectiveness of the protein drug while reducing its undesirable toxic effects.

Source: Duke University (news : web)