Scientists teach enzyme to make synthetic heparin in more varieties

November 25 2008

Scientists at the University of North Carolina at Chapel Hill have learned to customize a key human enzyme responsible for producing heparin, opening the door to a more effective synthetic anticoagulant as well as treatments for other conditions.

Jian Liu, Ph.D., and colleagues at the UNC Eshelman School of Pharmacy have learned to modify the enzyme heparan sulfate 2-O-sulfotransferase, which produces heparin in the human body in addition to other heparin-like molecules. By modifying 2-O-sulfotransferase, researchers will be able to create customized forms of synthetic heparin with different properties.

"Previously it was nearly impossible to change the nature of the heparin generated by the enzyme," said Liu, associate professor in the school's medicinal chemistry and natural products division. "The degree of difficulty was 10-plus. Now it's more like a two or three, which opens the door to the possibility of improving on the natural product."

Heparin is produced naturally by many creatures, including humans. As a drug, it is a common anticoagulant derived mainly from the intestinal lining of pigs. The manufactured form of the substance is most often used during and after procedures such as kidney dialysis, heart bypass surgery, stent implantation, indwelling catheters, and knee and hip replacements to prevent clots from blocking or restricting the flow of blood. The annual worldwide sales of heparin are estimated at $3 billion.

The drug was in the spotlight earlier this year when more than 80 people died and hundreds of others suffered adverse reactions to it, leading to recalls of the drug in countries around the world. Authorities linked the problems to a contaminant in raw natural heparin made from pigs in China. A synthetic version of the drug that can be produced in controlled conditions is key to preventing a recurrence of that tragedy, Liu said.

"The pig stuff has served us well for 50 years and is very inexpensive, but if we cannot control the supply chain, we cannot ensure the safety of the drug," Liu said. "I am working for the day when synthetic heparin can be brewed in large laboratories at a low cost."

There is also interest in heparin as a treatment for small-cell lung cancer, Liu said. Being able to produce customized versions of the heparin molecule using 2-O-sulfotransferase would allow researchers to emphasize the drug's potential anti-cancer properties. Heparin-like structures have also shown potential as treatments for arthritis, asthma and transplant rejection, among other conditions.

An article describing these findings, "Redirecting the substrate specificity of heparan sulfate 2-O-sulfotransferase by structurally guided mutagenesis," was recently published online in the journal *Proceedings of the National Academy of Sciences*.

Source: University of North Carolina at Chapel Hill