Antibiotics based on a new principle may defeat MRSA

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(Medical Xpress)—Scientists at Karolinska Institutet in Sweden have presented a new principle for fighting bacterial infections, in other words, a new type of antibiotic, in the *FASEB Journal*. The new antibiotic mechanism is based on selectively blocking the thioredoxin system in the cells, which is crucial to the growth of certain bacteria. Scientists hope to be able to treat such conditions as stomach ulcers, TB and MRSA.

"Much work remains to be done, but we believe that it will be possible to use this mechanism when, for example, broad-spectrum antibiotics have proved to be inadequate", says Professor Arne Holmgren, leader of the study now being published.

The thioredoxin system is present in all cells and is central to the ability to make new DNA (genetic material). It is also important in protecting the cell from a process known as oxidative stress, which arises when excess oxygen radicals and other oxidizing agents are formed. This may occur, for example, during the attack by white blood cells on bacteria, and it can damage or kill the cell. The most important components of the thioredoxin system are the enzymes thioredoxin and thioredoxin reductase, of which the first (very simplified) is required in the process of creating the building bricks of what is to be new DNA, and the second ensures that the thioredoxin remains active.

In addition to the thioredoxin system, mammals and humans, and some bacteria, have a second, similar biochemical process in the cell that is

based on the enzyme glutaredoxin. The thioredoxin system and the glutaredoxin system act as each other's backup. Many bacteria that cause disease, however, such as Helicobacter pylori (which cause stomach ulcers), the TB bacterium Mycobacterium tuberculosis, and the multiresistant staphylococcus bacterium MRSA, have only the thioredoxin system. These bacteria lack the glutaredoxin system. This makes these bacteria very vulnerable to substances that inhibit thioredoxin and thioredoxin reductase.

"Furthermore, the thioredoxin reductases in bacteria are very different in chemical composition and structure from the human enzyme. And it is just these differences, and the fact that certain bacteria lack the glutaredoxin system, that mean that drugs that affect thioredoxin reductase can be used as antibiotics. This is what we have discovered", says Arne Holmgren.

The study now being published describes how the scientists have used a drug candidate known as ebselen, which has previously been tested in the treatment of stroke and inflammation. The scientists discovered that ebselen and similar synthetic substances inhibit, among other things, thioredoxin reductase in bacteria. The scientists saw in laboratory experiments how the ebselen killed certain types of bacteria and not others. They were able to modify the genetic properties of Escherichia coli (E. coli), which is normally not susceptible to ebselen, and in this way investigate the mechanisms behind the antibiotic effect. They showed that the bacteria in which the genes in the DNA molecule that code for the glutaredoxin enzyme or the formation of the tripeptide glutathione, which is another important component of the glutaredoxin system, had been switched off were must more susceptible to ebselen than normal.

Bacteria that are resistant to several different types of antibiotic are a serious and extensive problem all over the world. The method of

attacking bacteria by preventing the construction of their cell wall, which was discovered when penicillin was discovered at the beginning of the 20th century, is still used, in several variations. It has for this reason long been obvious that science must find new ways of combating diseases caused by bacterial infections. The scientists who have written the article believe that the new antibiotic principle they are presenting may be a part of the solution.

"It is particularly interesting that MRSA and the antibiotic-resistant TB are also susceptible to ebselen and new synthetic substances. And it's worth noting that ebselen is an antioxidant, just as vitamin C is. This means that it protects the host against oxidative stress, and in this way we can kill two birds with one stone", says Arne Holmgren.

More information: Jun Lu, Alexios Vlamis-Gardikas, Karuppasamy Kandasamy, Rong Zhao, Tomas N Gustafsson, Lars Engstrand, Sven Hoffner, Lars Engman, Arne Holmgren, Inhibition of bacterial thioredoxin reductase: an antibiotic mechanism targeting bacteria lacking glutathione, *FASEB Journal*, online 17 December 2012, doi:10.1096/fj.12-223305 , Vol. 27 April 2013. www.fasebj.org/content/early/2 … j.12-223305.abstract

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