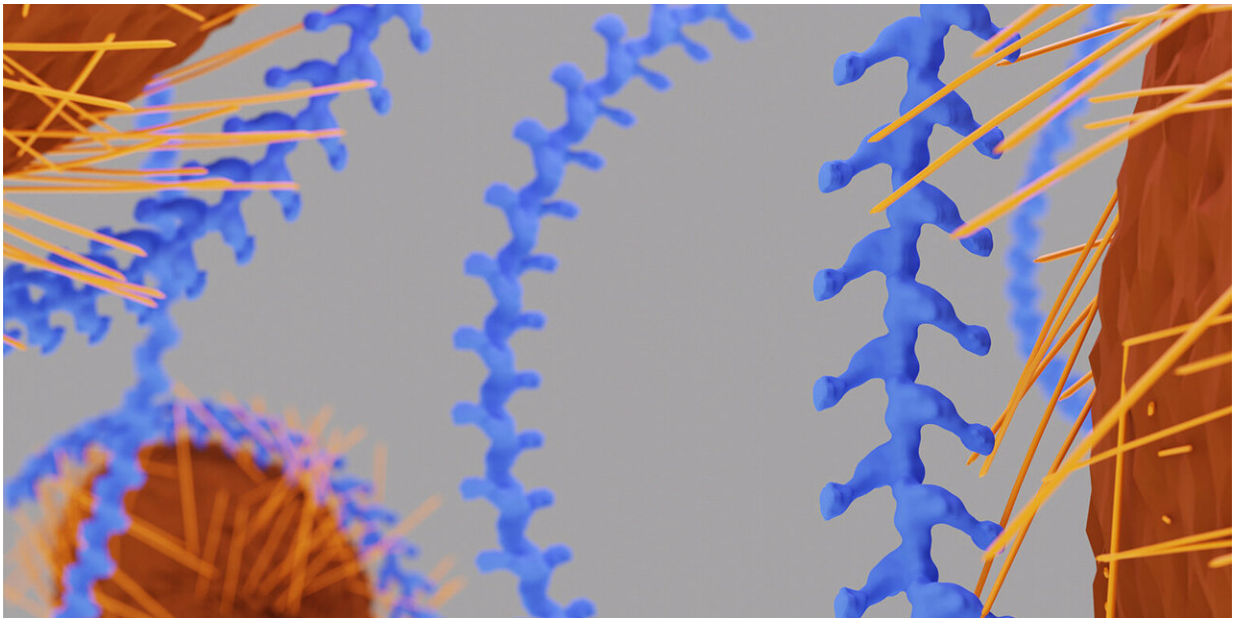


How the body fights off urinary tract infections

July 2 2020



A larger scale shows how the uromodulin filaments (blue) envelop an E. coli cell, thus preventing the pathogen's pili from docking on the cell walls in the urinary tract and causing an infection. The image is a 3D visualisation from electron tomography measurements. Credit: Gregor Weiss / ETH Zurich

Some people are better protected than others against urinary tract infections. This may be because their bodies produce more of a protein called uromodulin. An interdisciplinary research team has now found out exactly how this helper protein brings relief when nature calls and how

this knowledge might benefit the treatment and prevention of these painful inflammations.

Anyone who has ever had cystitis knows that urinary tract infections of this kind are annoying and painful. They can be well treated by antibiotics, but may be fatal if left untreated. These infections are usually caused by what are known as uropathogenic *E. coli* bacteria when they bind to the cells of the bladder, ureter or urethra with their pili, the thread-like appendages that grow out of them like hairs. But protection is at hand in the form of a certain [protein](#), produced naturally in the body, called uromodulin. Around 70 percent of all people carry a uromodulin gene variant in their genome, which means that they produce this protective protein in particularly large quantities. Accordingly, they have a smaller risk of contracting urinary tract infections.

But the exact process by which uromodulin prevents inflammation had never been understood. Now an interdisciplinary team, drawn from three research groups at ETH Zurich together with researchers from the University of Zurich and the Children's Hospital Zurich, has filled this knowledge gap by investigating uromodulin's appearance and how the protein goes about neutralizing uropathogenic *E. coli*. Their findings, which have been published in the journal *Science*, should help to develop new strategies for the treatment of urinary tract infections in the future.

A detailed look at how it works

First, the researchers analyzed how the protein binds to the bacterial pili at the molecular level. "We already knew that a bond is formed and that this presumably plays a part in uromodulin's protective function, but nobody had studied this in greater detail," says Gregor Weiss, a doctoral student in molecular biology at ETH and one of the study's lead authors. Their biochemical investigations have now shown that the bacterial pili recognize certain sugar chains on the surface of the uromodulin and bind

to them extremely readily and strongly.

Next, the team examined uromodulin using cryo-[electron tomography](#), an imaging technique that produces three-dimensional views of the structure of proteins and cells with no need for chemical modification or dehydration. This showed them that uromodulin forms long filaments consisting on average of around 400 individual protein molecules strung together. And that each link of this protein chain contains the characteristic pattern of sugar chains to which bacterial pili like to bind.

Fruitful collaboration

Cryo-electron tomography was also the team's chosen technique for investigating at a larger scale what effect these properties have—this time in the presence of the culprits, the uropathogenic *E. coli* bacteria. They discovered that the uromodulin filaments literally envelop the pathogen, and that a single uromodulin filament can dock with several pili of a bacterium. "This neutralizes the pathogens," Weiss explains: "Once the bacteria are shielded in this way, they can no longer bind to the cells in the urinary tract, which means they can't cause infection." Under an [optical microscope](#), the team also noted the formation of large clumps of hundreds of uromodulin filaments and *E. coli* cells, which are then presumably simply excreted with the urine.

Finally, the researchers checked to see whether all these processes they had observed in the laboratory also occur in patients. They analyzed urine samples from infected patients provided by the Children's Hospital in Zurich and found exactly the same interactions between uromodulin and the pathogens. "Without [interdisciplinary collaboration](#) between different research groups and institutes, it would have been impossible to obtain this set of findings," stresses ETH Professor Martin Pilhofer, who led the electron tomography investigations.

Pointers for treatment and drug development

The research team's work offers pointers for how to treat and prevent urinary tract infections without using antibiotics. Until now, patients have often been given preparations that contain the sugar mannose. To a certain extent, these prevent the E. coli bacteria from attaching themselves to the cells of the urinary tract. "Thanks to our analyzes, we now know that the bacterial pili recognize not only mannose but also other sugars present on uromodulin," says Jessica Stanisich, doctoral student and another lead author of the study. "This might indicate that treatment with combined sugar supplements would be more effective."

The new findings also help in the development of new active substances, adds ETH Professor Rudi Glockshuber. This is because during an [infection](#) the uropathogenic E. coli attach themselves to the same sugar chains on the cell surfaces of the urinary tract as on uromodulin. Pharmaceutical companies are looking to identify new active substances that will prevent precisely these interactions—but this risks also disrupting the protective binding of uromodulin to the bacteria. "It would obviously be a highly undesirable side effect for a drug if that treatment simultaneously interfered with a natural protective function," Glockshuber says. However, the research team's analyzes have now shown that the bonds between bacteria and uromodulin are extremely stable and cannot be broken down by active substances—an important finding in the search for remedies for unpleasant [urinary tract infections](#).

More information: G.L. Weiss et al., "Architecture and function of human uromodulin filaments in urinary tract infections," *Science* (2020). [science.sciencemag.org/cgi/doi/10.1126/science.aaz9866](https://www.science.org/doi/10.1126/science.aaz9866)

Provided by ETH Zurich

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