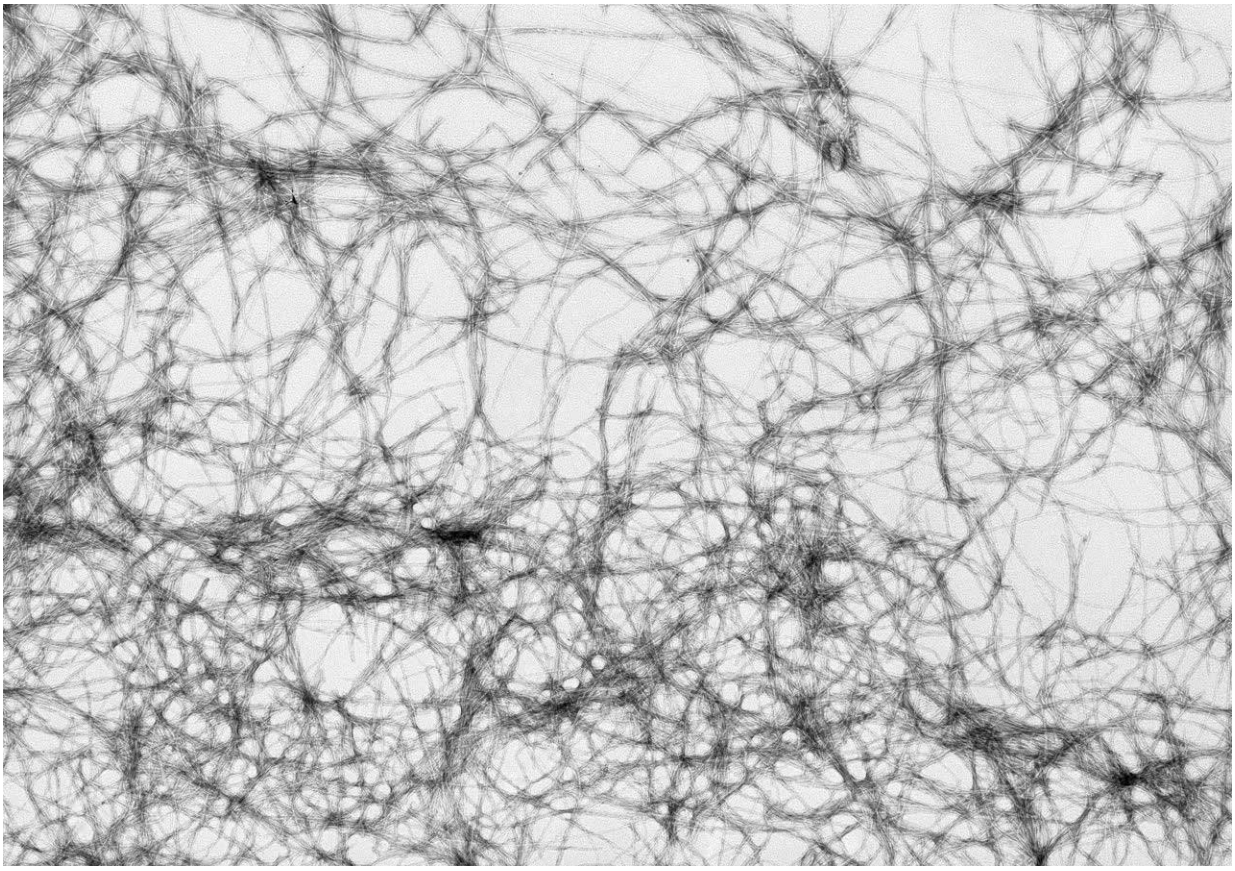
Researchers find protein that could help fight antibiotic resistance

November 1 2017, by Morgan Sherburne



Shown are amyloid fibers made from a peptide derived from the E. coli CsgA protein. Credit: The Chapman Lab

Artificial hip implants, knee implants and catheters are susceptible to infections: bacteria that flow through the blood system can collect on

these foreign surfaces and hunker down to proliferate.

Now, University of Michigan researchers, in collaboration with The Scripps Research Institute, have found that a protein produced within the human body could fight against this problem.

When bacteria collect on a surface, they form a protective layer called a "biofilm." These biofilms are held together by a scaffolding composed of a protein called "amyloid" that the bacteria itself produces. The bacterial amyloid is similar to the structure that snarls neurons in the brains of people with Alzheimer's disease, disrupting the person's ability to form and recall memories.

In the case of bacteria on a prosthetic, biofilms protect the colony of bacteria from its environment, including from antibiotics a doctor might prescribe to attack the infection. In a new study, the researchers found that a protein produced by humans called transthyretin, or TTR, can suppress the formation of amyloid and biofilm in E. coli, a common bacterial strain found in humans.

The team, which includes Matthew Chapman, U-M professor of molecular, cellular and developmental biology; Joel Buxbaum, professor of molecular medicine with TSRI; and lead author Neha Jain, a postdoctoral fellow in the Chapman lab, published their results in the *Proceedings of the National Academy of Science*.

Human transthyretin protein can adopt an aggregated or amyloid form under certain conditions. Credit: The Chapman Lab

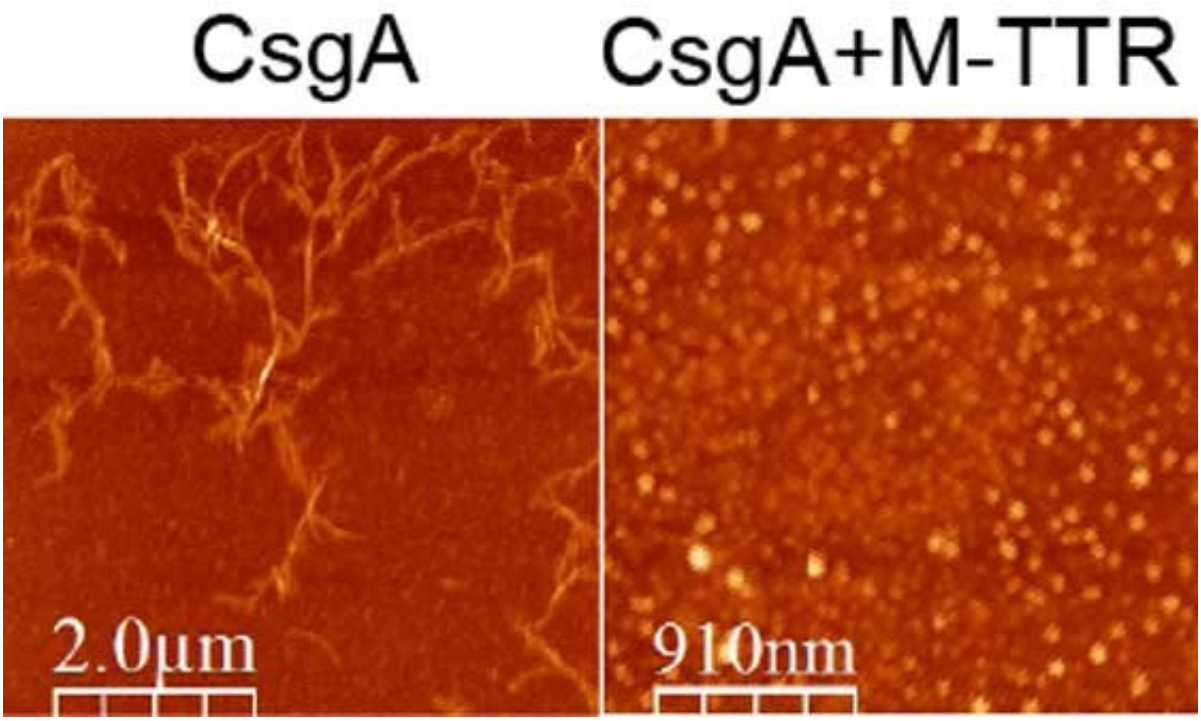
"One of the most important health implications for biofilms is on catheters. On any sort of device that you try to put in a human, a biofilm will form," said Chapman, U-M professor of molecular, cellular and developmental biology. "This is a huge, huge problem because being catheterized for just a few days, bacteria can form biofilms on the device, which can lead to serious infections."

The team studied how TTR interacted with a strain of E. coli found in urinary tract infections. In UTIs, the bacterial strain settles into the bladder, forming biofilm communities. Bacteria in a biofilm encase themselves in a coat of amyloid fibers that help to protect them from stressors in the environment. E. coli amyloids are composed of a protein called CsgA.

When the researchers mixed purified TTR and CsgA, CsgA could not make protective amyloids. Taking down a bacteria's key defense against its environment could allow the body to fight the infection more effectively.

"It's easier to break individual sticks rather than a bundle. Similarly, bacterial infections can be dealt more effectively if bacteria are not held together in biofilms," Jain said. "We found that TTR can prevent biofilm formation in a uropathogenic E. coli strain as well as other bacterial strains."

Buxbaum, who has long studied TTR, pointed out that under some conditions TTR can form amyloid fibers itself, and it could be this ability that gives TTR the structural characteristics to interrupt amyloid formation by other proteins, such as CsgA.



Fighting fire with fire: However, the variant of TTR that can form polymers, called M-TTR, can prevent other proteins from adopting the amyloid fold. Shown on the here are amyloid fibers derived from bacterial curli proteins, and the same proteins mixed with M-TTR. M-TTR prevents amyloid fiber aggregation of the bacterial curli proteins. Credit: The Chapman Lab

About one in 100 people who receive hip or knee replacements experience an infection, according to the American Academy of Orthopaedic Surgeons. A 2001 study found that 95 percent of urinary tract infections in critically ill patients were traced back to their catheters, while 87 percent of bloodstream infections came from an indwelling vascular catheter and 86 percent of pneumonia cases were associated with a mechanical ventilator.

"It's possible that products derived or based on these protein interactions could reduce this problem in medicine, that biofilms form on a lot of artificial surfaces implanted within the body," Buxbaum said. "The

notion is we could impregnate these surfaces with this protein so that they may not form these biofilms and make it easier to treat these infections with antibiotics."

Chapman and Buxbaum say implementing this will require more research, but the move could help prevent infections on implants as well as antibiotic resistance.

"If you could target that resistance, the host may be able to clear the infection," Chapman said. "You could also potentially prescribe lower doses of antibiotics or shorten the duration of antibiotic usage, which would all be good things."

More information: Neha Jain et al. Inhibition of curli assembly andEscherichia colibiofilm formation by the human systemic amyloid precursor transthyretin, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1708805114

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