Blocking biofilms: Alzheimer's research sheds light on potential treatments for urinary tract infections

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(PhysOrg.com) -- Research into Alzheimer's disease seems an unlikely approach to yield a better way to fight urinary tract infections (UTIs), but that's what scientists at Washington University School of Medicine in St. Louis and elsewhere recently reported.

One element links the disparate areas of research: amyloids, which are fibrous, sticky protein aggregates. Some infectious bacteria use amyloids to attach to host cells and to build biofilms, which are bacterial communities bound together in a film that helps resist antibiotics and immune attacks. Amyloids also form in the nervous system in Alzheimer's disease, Parkinson's disease and many other neurodegenerative disorders.

To probe amyloids' contributions to neurodegenerative diseases, scientists altered potential UTI-fighting compounds originally selected for their ability to block bacteria's ability to make amyloids and form biofilms. But when they brought the compounds back to UTI research after the neurology studies, they found the changes had also unexpectedly made them more effective UTI treatments.

"Thanks to this research, we have evidence for the first time that we may be able to use a single compound to impair both the bacteria's ability to start infections and their ability to defend themselves in biofilms," says senior author Scott J. Hultgren, Ph.D., the Helen L. Stoever Professor of

Molecular Microbiology at Washington University.

The findings were reported online in Nature Chemical Biology.

The National Institutes of Health has estimated that over 80 percent of microbial infections are caused by bacteria growing in a biofilm, according to Hultgren. Scientists in Hultgren's laboratory have worked for decades to understand the links between biofilms and UTIs.

"UTIs occur mainly in women and cause around $1.6 billion in medical expenses every year in the United States," says co-lead author Jerome S. Pinkner, laboratory manager for Hultgren. "We think it's likely that women who are troubled by recurrent bouts of UTIs are actually being plagued by a single persistent infection that hides in biofilms to elude treatment."

Co-lead author Matthew R. Chapman, Ph.D., now associate professor of molecular, cellular and developmental biology at the University of Michigan, was a postdoctoral fellow in Hultgren's lab in 2002 when he discovered that the same bacterium that causes most UTIs, Escherichia coli, deliberately makes amyloids. The amyloids go into fibers known as curli that are extruded by the bacteria to strengthen the structures of biofilms.

To treat UTIs, Hultgren's lab has been working with Fredrik Almqvist, Ph.D., a chemist at the University of Umea in Sweden, to develop compounds that block bacteria's ability to make curli, disrupting their ability to make biofilms and leaving them more vulnerable to antibiotics or immune system attacks. Almqvist recently suggested altering a group of the most promising curli-blockers to see if they could also block the processes that form amyloids in Alzheimer's disease.

The alterations worked: In laboratory tests, the new compounds

prevented the protein fragment known as amyloid beta from aggregating into amyloid plaques like those found in the brain in Alzheimer's disease. When scientists took the new compounds back to a mouse model of UTIs, though, they received a surprise. The altered compounds were better at reducing the virulence of infections, inhibiting not only curli formation but also the formation of a second type of bacterial fibers, the pili.

"Pili aren't made of amyloids, but they are essential to both biofilms and to the bacteria's ability to initiate an infection," Hultgren says.

Hultgren and colleagues are already developing even more potent infection and amyloid fighters, screening a library of thousands of chemicals similar to the most promising compounds from the study.

Chapman cautions that it's too early to tell which, if any, of the compounds will be helpful in treating neurodegenerative diseases.

"Much neurodegenerative drug development has focused on ways to break up amyloids or prevent them from forming, but because amyloids may also be an important part of normal cellular physiology, we need to identify molecules that will target only the toxic amyloid state," he says.

More information: Cegelski L, Pinkner JS, Hammer ND, Cusumano CK, Hung CS, Chorell E, Aberg V, Walker JN, Seed PC, Almqvist F, Chapman MR, Hultgren SJ. Small-molecule inhibitors target Escherichia coli amyloid biogenesis and biofilm formation. *Nature Chemical Biology*.

Provided by Washington University School of Medicine in St. Louis

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