Reactive arthritis is fueled by amyloid protein during salmonella infection

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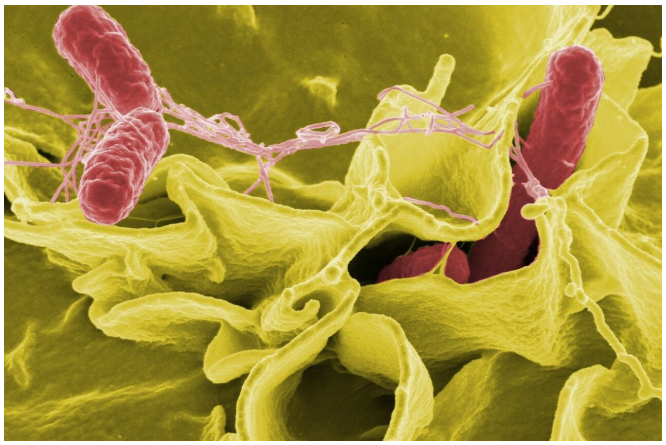

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Like the infrastructure of an apartment building, a fibrous protein known as curli amyloid that is produced by bacteria provides the supportive framework for biofilms—thick extracellular substances made by bacteria that enable multiple bacterial cells to assemble, survive, and thrive together. Curli amyloid, however, is also a key factor in diarrheal illness brought about by bacterial infection, and its harmful effects may extend well beyond the gastrointestinal tract.

In particular, infections with *Salmonella* bacteria, which produce curli amyloid, are implicated in an insidious, painful inflammatory condition known as reactive arthritis (ReA), which affects about five percent of people who have been infected with bacteria that cause gastrointestinal illness. There are no treatments for ReA, and very little is known about how or why it develops.

Now in new work, researchers at the Lewis Katz School of Medicine at Temple University (LKSOM) show that in mice infected with *Salmonella enterica Typhimurium* - a common cause of food-borne diarrheal illness—curli provokes the generation of autoantibodies and joint inflammation. The most damaging of these effects were linked to systemic exposure to curli, revealing a hidden harm inflicted by bacterial components that escape the intestinal tract.

The study was published online July 9th in the journal *PLOS Pathogens*.

"We found specifically that if curli stays in the intestines, its negative inflammatory effects are limited," explained Cagla Tukel, Ph.D., Associate Professor in the Department of Microbiology and Immunology at LKSOM and senior author on the new study. "But in susceptible individuals, if curli escapes the intestinal tract and enters the circulation, an autoimmune reaction ensues."

The research was carried out in collaboration with Dr. Aaron P. White and other scientists at the Vaccine and Infectious Disease Organization-International Vaccine Centre, University of Saskatchewan, Canada.

Dr. Tukel and Dr. White's laboratories developed a mouse model in which animals were orally infected with wild-type *S. Typhimurium*, meant to mimic food- or water-borne transmission in humans. The infectious inoculum consisted of *S. Typhimurium* cells capable of producing curli, though no curli was present in the inoculum itself, enabling the researchers to examine curli production and its impact on autoimmunity in vivo. For comparison, some mice were infected with a mutated strain of *S. Typhimurium* incapable of curli production.

Within a week of infection with wild-type *S. Typhimurium*, bacterial clusters were evident in the cecum and colon of mice, and the bacteria were producing curli. Oral infection further led to the generation of autoantibodies against curli/DNA complexes, which are critical to biofilm formation. Autoantibody production was attributed to the systemic reach of curli.

Evaluation of knee joints and serum from mice with wild-type *S. Typhimurium* confirmed the systemic presence of curli-induced autoantibodies and joint inflammation. Moreover, chronic synovial inflammation, affecting the fluid surrounding joints, and bone resorption (bone break down), which are hallmarks of ReA, were observed.

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"Our findings indicate that curli is a major component of *Salmonella* that drives autoimmune reactions," Dr. Tukel said. "In mice, these reactions were triggered within six weeks of infection, demonstrating that the expression of a bacterial component in the intestine can lead to subsequent autoimmune responses."

A protein known as HLAB27, the production of which is associated with a specific genetic variation, is a risk factor for the development of ReA. "The presence of pathogenic curli in the microbiota may precipitate or exacerbate autoimmunity in individuals with HLAB27," Dr. Tukel noted.

Dr. Tukel and her team plan next to determine whether the new findings translate to humans, and whether curli proteins from other pathogenic bacteria, like *E. coli*, are capable of generating similar autoimmune reactions. Her group is also investigating whether curli plays a role in exaggerating other autoimmune diseases, such as systemic lupus erythamatosus (SLE), where genetic risk factors are involved.

An additional area of study for Dr. Tukel's team concerns a suspected relationship between disease-causing bacterial curli and amyloid disorders, such as Parkinson's and Alzheimer's disease. "Recent research in Parkinson's disease mouse models suggests that curli amyloid fuels neurodegeneration," Dr. Tukel said. "The ability of enteric bacterial curli to escape the intestine and reach the systemic circulation raises questions about a potential role in neurodegenerative processes."

More information: Amanda L. Miller et al, In vivo synthesis of bacterial amyloid curli contributes to joint inflammation during S. Typhimurium infection, *PLOS Pathogens* (2020). DOI: