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Neurodegenerative diseases (NDs) are a global epidemic with profound health, social, and economic implications and remain incurable. NDs are increasingly recognized as proteinopathies resulting from abnormal aggregation of proteins such as amyloids, which contribute to neuronal damage and disease propagation.¹ NDs are characterized by chronic central and peripheral, particularly gastrointestinal, inflammation,^{2,3} which contributes to disease progression. The gut microbiota is increasingly recognized as playing an important role in NDs. Indeed, some bacteria can secrete “amyloid” protein, such as curli fibrils, which form biofilms that protect bacteria from stress and host immune responses.^{4–6} These bacterial curli can interact with host amyloids, such as α -synuclein, to promote inflammation and disease progression, as described in models of Parkinson’s disease (PD).^{7,8} However, the mechanisms underlying interactions between bacterial curli and the enteric nervous system, a key regulator of gut function, and immune cells remain largely unknown.

In the elegant study published in this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Verstraelen et al⁹ identify a curli-mediated pathogenic pro-inflammatory cascade in the gut driven by enteric glial cells (EGCs), a major component of the enteric nervous system.¹⁰ Following an unbiased transcriptomic analysis of myenteric networks from adult mice exposed to curli, the authors identified SAA3, a high-density apolipoprotein involved in local and systemic inflammation,¹¹ as significantly upregulated in EGCs relative to enteric neurons. This curli-induced upregulation of SAA3 was also associated with an increase in cytokine expression by EGCs. The authors further demonstrated the ability of curli fibrils to induce EGCs damage characterized by increased DNA double-strand breaks, reminiscent of hippocampal neurons alteration by amyloid- β ($A\beta$) in Alzheimer’s disease (AD).¹² The cytokine profile and changes in EGCs were also observed after injection of curli fibrils into mice colon. Next, the authors established the role of SAA3 as a mediator of curli-induced EGCs dysfunction and inflammatory response by using in vitro genetic deletion methods of SAA3. The authors corroborated their findings by showing an upregulation of SAA3 in the colon of mice after intraperitoneal injection of curli fibrils, inoculation with a curli-producing bacterial strain and after DSS-induced colitis. Finally, the authors identified the JNK pathway as a downstream mediator of the curli/SAA3 pathogenic cascade by pharmacological inhibition.

In summary, Verstraelen et al identify EGCs as a centerpiece of curli-induced intestinal inflammation. This work further supports the role of EGCs as a key player in the innate or adaptive immune response in the gut.¹³ However, this study does not address the direct contribution of intestinal epithelial and immune cells, which are known to be

targeted by curli,¹⁴ to the observed inflammatory response. Furthermore, because EGCs are master regulators of gut functions,¹⁰ it would be of great interest to determine in future studies whether curli-induced damage to EGCs contributes to enteric neuronal and gut dysfunctions (motility, epithelial barrier, immune response) reported in amyloid diseases such as AD¹⁵ or PD.¹⁶ Furthermore, since gut dysfunctions occur early in the course of NDs,^{17,18} pharmacological prevention of curli-induced EGC alterations (using JNK inhibitors) could not only prevent gut dysfunctions but also slow disease progression by modulating both peripheral and central inflammation. Indeed, JNK pathway is activated in astrocytes of the central nervous system upon exposure to $A\beta$ or α -synuclein, subsequently inducing astrogliosis and cell death.^{19–21}

The work by Verstraelen et al is akin to previous study showing that gut microbiota promotes intestinal and systemic inflammation with consequently an aggregation of $A\beta$ and neuroinflammation.²² Whether EGC-mediated inflammation enhances an aggregation of host amyloids such as α -synuclein or $A\beta$ remains to be established. Moreover, a putative involvement of SAA3 pathways in gut inflammation observed in patients with PD²³ or AD³ remains to be demonstrated. An intriguing finding of the study was that colitis activated SAA3 pathways, raising the possibility that bacterial curli could also contribute to inflammatory bowel disease or infectious diseases. Interestingly, inflammatory bowel diseases were shown to be a risk factor for both PD and AD.^{24,25} As highlighted in this study, bacterial-derived amyloids are major driver of intestinal inflammation and could represent genuine preventive or curative targets in amyloids diseases. Among therapeutic interventions, nutritional approaches could have a central place. A recent study has indeed shown that fiber restricted diet enhanced intestinal barrier damages induced by curli-producing bacteria leading to increased gut and motor dysfunctions in an animal model of PD.⁸ Hence, nutritional approaches reinforcing intestinal barrier functions, in particular those leading to a modulation of EGC functions, might be of therapeutic interest in amyloids diseases. Therefore, further studies are warranted to better understand EGC functions along the gut-brain axis in health and diseases.

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References

- Iadanza MG, Jackson MP, Hewitt EW, et al. A new era for understanding amyloid structures and disease. *Nat Rev Mol Cell Biol* 2018;19:755–773.
- Goyal D, Ali SA, Singh RK. Emerging role of gut microbiota in modulation of neuroinflammation and neurodegeneration with emphasis on Alzheimer's disease. *Prog Neuro-psychopharmacol Biol Psychiatry* 2021;106:110112.
- Heston MB, Hanslik KL, Zarbock KR, et al. Gut inflammation associated with age and Alzheimer's disease pathology: a human cohort study. *Sci Rep* 2023;13:18924.
- Sonderby TV, Najarzadeh Z, Otzen DE. Functional bacterial amyloids: understanding fibrillation, regulating biofilm fibril formation and organizing surface assemblies. *Molecules* 2022;27:4080.
- Yan Z, Yin M, Chen J, Li X. Assembly and substrate recognition of curli biogenesis system. *Nat Commun* 2020;11:241.
- Miller AL, Bessho S, Grando K, Tukul C. Microbiome or infections: amyloid-containing biofilms as a trigger for complex human diseases. *Front Immunol* 2021;12:638867.
- Chen SG, Stribinskis V, Rane MJ, et al. Exposure to the functional bacterial amyloid protein curli enhances alpha-synuclein aggregation in aged Fischer 344 rats and *Caenorhabditis elegans*. *Sci Rep* 2016;6:34477.
- Schmit KJ, Garcia P, Sciortino A, et al. Fiber deprivation and microbiome-borne curli shift gut bacterial populations and accelerate disease in a mouse model of Parkinson's disease. *Cell Rep* 2023;42:113071.
- Verstraelen P, Van Remoortel S, De Loose N, et al. Serum Amyloid A3 Fuels a Feed-Forward Inflammatory Response to the Bacterial Amyloid Curli in the Enteric Nervous System. *Cell Mol Gastroenterol Hepatol* 2024;18:89–104.
- Seguella L, Gulbransen BD. Enteric glial biology, inter-cellular signalling and roles in gastrointestinal disease. *Nat Rev Gastroenterol Hepatol* 2021;18:571–587.
- Sack GH Jr. Serum amyloid A - a review. *Mol Med* 2018;24:46.
- Suberbielle E, Sanchez PE, Kravitz AV, et al. Physiologic brain activity causes DNA double-strand breaks in neurons, with exacerbation by amyloid-beta. *Nat Neurosci* 2013;16:613–621.
- Progatzky F, Pachnis V. The role of enteric glia in intestinal immunity. *Curr Opin Immunol* 2022;77:102183.
- Rochon M, Romling U. Flagellin in combination with curli fimbriae elicits an immune response in the gastrointestinal epithelial cell line HT-29. *Microbes Infect* 2006;8:2027–2033.
- Nakase T, Tatewaki Y, Thyreau B, et al. Impact of constipation on progression of Alzheimer's disease: a retrospective study. *CNS Neurosci Ther* 2022;28:1964–1973.
- Warnecke T, Schafer KH, Claus I, et al. Gastrointestinal involvement in Parkinson's disease: pathophysiology, diagnosis, and management. *NPJ Parkinsons Dis* 2022;8:31.
- Nedelec T, Couvy-Duchesne B, Monnet F, et al. Identifying health conditions associated with Alzheimer's disease up to 15 years before diagnosis: an agnostic study of French and British health records. *Lancet Digit Health* 2022;4:e169–e178.
- Konings B, Villatoro L, Van den Eyde J, et al. Gastrointestinal syndromes preceding a diagnosis of Parkinson's disease: testing Braak's hypothesis using a nationwide database for comparison with Alzheimer's disease and cerebrovascular diseases. *Gut* 2023;72:2103–2111.
- Saha P, Guha S, Biswas SC. P38K and JNK pathways are induced by amyloid-beta in astrocyte: implication of MAPK pathways in astrogliosis in Alzheimer's disease. *Mol Cell Neurosci* 2020;108:103551.
- Solas M, Vela S, Smerdou C, et al. JNK Activation in Alzheimer's disease is driven by amyloid beta and is associated with tau pathology. *ACS Chem Neurosci* 2023;14:1524–1534.
- Rannikko EH, Weber SS, Kahle PJ. Exogenous alpha-synuclein induces toll-like receptor 4 dependent inflammatory responses in astrocytes. *BMC Neurosci* 2015;16:57.
- Leblhuber F, Ehrlich D, Steiner K, et al. The immunopathogenesis of Alzheimer's disease is related to the composition of gut microbiota. *Nutrients* 2021;13:361.
- Devos D, Lebouvier T, Lardeux B, et al. Colonic inflammation in Parkinson's disease. *Neurobiol Dis* 2013;50:42–48.
- Li HX, Zhang C, Zhang K, et al. Inflammatory bowel disease and risk of Parkinson's disease: evidence from a meta-analysis of 14 studies involving more than 13.4 million individuals. *Front Med (Lausanne)* 2023;10:1137366.
- Aggarwal M, Alkhayat M, Abou Saleh M, et al. Alzheimer disease occurs more frequently in patients with inflammatory bowel disease: insight from a nationwide study. *J Clin Gastroenterol* 2023;57:501–507.

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Conflicts of interest

The authors disclose no conflicts.



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