Prion-like propagation of protein aggregates is thought to be an essential feature in many neurodegenerative diseases, but the mechanisms underlying transcellular transfer of protein aggregates remain unclear. Stopschinski et al. now demonstrate that the cellular uptake of tau, Aβ, and α-synuclein aggregates mediated by heparan sulfate proteoglycans (HSPGs) varies with distinct glycosaminoglycan chain length and sulfation patterns. The results help us to understand how different protein aggregates propagate, leading to distinct neurodegenerative pathologies.

Prion diseases are a group of fatal transmissible neurodegenerative diseases characterized by the accumulation of an abnormal form of prion protein (PrPSc) in the central nervous system (CNS). Prion diseases are transmissible interindividually, crossing even species barriers, and propagate intraindividually. The transmission is mediated by transfer of PrPSc, which functions as a template for the conversion of normal cellular forms of prion protein (PrPC) to PrPSc.

Similar to prion diseases, many neurodegenerative diseases are also characterized by the accumulation of abnormal proteins in the CNS including β-amyloid protein (Aβ) and tau in Alzheimer’s disease (AD), tau in non-AD tauopathies, α-synuclein in Lewy body diseases such as Parkinson’s disease and dementia with Lewy bodies, and transactive response DNA–nuclein aggregates mediated by heparan sulfate proteoglycans (GAGs) compositions, it is unclear which properties of GAGs are necessary for cell–cell transfer of protein aggregates, multiple mechanisms have been proposed: 1) extracellular vesicles like exosomes and ectosomes reaching the cytoplasm of recipient cells by fusion, 2) free protein aggregates exocytosed from donor cells taken up by recipient cells with receptor- or nonreceptor-mediated endocytosis/macropinocytosis, and 3) transfer through nanotubes, although it remains unclear which is the main mechanism for transcellular transfer of certain protein aggregates in certain areas of the CNS.

Diamond and colleagues have focused on heparan sulfate proteoglycans (HSPGs) on the cell surface as receptors for uptake of protein aggregates such as Aβ, tau, and α-synuclein. They previously observed that cellular uptake and consequent intracellular seeding of tau and α-synuclein fibrils require HSPGs, similar to results from another study. Inhibition of the interaction with HSPGs blocked transcellular aggregate propagation, indicating that the interaction between HSPG and protein aggregates may be an essential step for propagation of neurodegeneration induced by protein aggregates. However, as the properties of HSPGs vary with different glycosaminoglycan (GAG) compositions, it is unclear which properties of GAGs are specifically required for binding of different protein aggregates to mediate uptake and intracellular seeding.

Now, Diamond and colleagues report the specificity for interactions of the aggregates with HSPGs. They determined the size and sulfation requirements of aggregate binding to GAGs by measuring direct binding to modified heparins in carbohydrate microarrays and by using competition studies with heparin derivatives in cell-based assays. Specifically, they observed that the binding of tau aggregates required a minimal length and precise sulfation of HSPGs. The authors declare that they have no conflicts of interest with the contents of this article.

1 To whom correspondence should be addressed: Dept. of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Sciences, Takara-machi, Kanazawa 920-8640, Japan. Phone: 81-76-265-2290; Fax: 81-76-234-4253; E-mail: m-yamada@med.kanazawa-u.ac.jp.

2 The abbreviations used are: CNS, central nervous system; Aβ, amyloid β-protein; AD, Alzheimer’s disease; GAGs, glycosaminoglycans; HSPG, heparan sulfate proteoglycan; PrPSc, normal cellular form of prion protein; PrPSc, abnormal form (scrapie type) of prion protein; TDP-43, transactive response DNA–binding protein 43 kDa.

This work was supported by Grants-in-Aid for Scientific Research (Kakenhi) from the Japan Society for the Promotion of Science (JSPS) under Grants JP15K15336 (to M.Y. and T.H.), JP17H04194 (to M.Y. and T.H.), and JP17K09752 (to T.H. and M.Y.), Grants-in-Aid for Research and Development Grants for Dementia from the Japan Agency for Medical Research and Development (AMED) under Grants JP16dk0207021h0001 and JP17dk0207021h0002 (to M.Y. and T.H.), and Grants-in-Aid for the Research Committee of Prion Disease and Slow Virus Infection from the Ministry of Health, Labour and Welfare, Japan, under Grants JP16H029-nanchitolonan-036 (to M.Y. and T.H.).
EDITOR’S PICK HIGHLIGHT: How sulfation codes neurodegeneration

Figure 1. Cell uptake of protein aggregates, such as β-amyloid protein, tau, and α-synuclein via heparan sulfate proteoglycans (HSPGs) on the cell surface. N- and 6-O-sulfation of heparan sulfate is essential for binding of tau aggregates to HSPGs, followed by internalization and intracellular seeding for tau fibrillization (A), whereas N- (B) and 6-O-desulfation (C) inhibits binding of tau aggregates. Aggregated proteins bind longer lengths of glycosaminoglycan chains with greater avidity.

lular uptake of tau versus α-synuclein and Aβ aggregates. These data inspire yet more questions concerning the full role of HSPGs in transcellular propagation of protein aggregates in neurodegenerative diseases. For example, the results for binding of α-synuclein aggregates to HSPGs were variable among different experimental approaches, suggesting that interactions between protein aggregates and HSPGs are very complex. Further exploration of other molecular determinants that govern the binding and internalization of each aggregated protein would be interesting. Second, the authors used fibrils of tau, α-synuclein, Aβ, and huntingtin in this study. However, smaller nonfibrillar aggregates, such as soluble oligomers, could be important for cell-to-cell propagation. It was reported for α-synuclein that internalization of amyloid fibrils depends on heparin sulfate, whereas that of smaller non-amyloid oligomers does not (7). Thus, binding of smaller oligomeric forms of tau and other protein aggregates to HSPGs should be investigated. In addition, fibrils formed in vitro from synthetic or recombinant proteins consist of a mixture of different fibrillar structures, such as spiral and straight fibrils (9). Different fibrillar structures of the same protein may represent different “strains” associated with peculiar patterns of neuropathological lesions. These different fibrillar structures of the same protein may require different HSPG structures for cellular uptake, a possibility that should be examined. Finally, it would be fascinating to evaluate compositions of HSPGs on the cell surface of the brain and peripheral tissues that actually could be involved in propagation of protein aggregates in vivo. Neuronal subtypes that express HSPGs with distinct GAG chain length and sulfation patterns specific for protein aggregates would be preferentially affected in neurodegenerative disorders due to high levels of uptake and intracellular aggregation. Such studies help us to understand how different “strains” of the same protein aggregates, as well as different protein aggregates, produce distinct progression patterns of pathologies in neurodegenerative diseases.

Treatment with heparan sulfate mimetics has shown beneficial effects in animal models of prion diseases or neurodegenerative diseases with prion-like propagation of protein aggregates; however, clinical trials have been unsuccessful so far (10). Further understanding of molecular mechanisms underlying HSPG-mediated cellular uptake of protein aggregates is essential for the development of HSPG-targeting therapies to inhibit progression of neurodegenerative diseases.

References
1. Walker, L. C., Schelle, J., and Tucker, M. (2016) The prion-like properties of amyloid-β assemblies: Implications for Alzheimer’s disease. Cold. Spring. Harb. Perspect. Med. 6, a024398 CrossRef Medline
2. Goedert, M., Masuda-Suzukake, M., and Falcon, B. (2017) Like prions: The propagation of aggregated tau and α-synuclein in neurodegeneration. Brain 140, 266–278 CrossRef Medline
3. Mudher, A., Colin, M., Dujardin, S., Medina, M., Dewachter, I., Alavi Naini, S. M., Mandelkow, E. M., Mandelkow, E., Buée, L., Goedert, M., and Brion, J. P. (2017) What is the evidence that tau pathology spreads through prion-like propagation? Acta Neuropathol. Commun. 5, 99 CrossRef Medline
4. Jaunmuktane, Z., Mead, S., Ellis, M., Wadsworth, J. D., Nicoll, A. J., Kenny, J., Launuchby, F., Linhean, J., Richard-Loendt, A., Walker, A. S., Rudge, P., Collinge, J., and Brandner, S. (2015) Evidence for human transmission of amyloid-β pathology and cerebral amyloid angiopathy. Nature 525, 247–250 CrossRef Medline
5. Hamaguchi, T., Taniguchi, Y., Sakai, K., Kitamoto, T., Takao, M., Murayama, S., Iwasaki, Y., Yoshida, M., Shimizu, H., Kakita, A., Takahashi, H., Suzuki, H., Naiki, H., Sanjo, N., Mizusawa, H., and Yamada, M. (2016) Significant association of cadaveric dura mater grafting with subpial Aβ deposition and meningeal amyloid angiopathy. Acta Neuropathol. 132, 313–315 CrossRef Medline
6. Holmes, B. B., DeVos, S. L., Kfouri, N., Li, M., Jacks, R., Yanamandra, K., Ouidia, M. O., Brodsky, F. M., Marasa, J., Bagchi, D. P., Kotzbauer, P. T., Miller, T. M., Papy-Garcia, D., and Diamond, M. I. (2013) Heparan sulfate proteoglycans mediate internalization and propagation of specific proteopathic seeds. Proc. Natl. Acad. Sci. U.S.A. 110, E3138–E3147 CrossRef Medline
7. Ilse, E., Yamakado, H., van Wijk, X. M., Lawrence, R., Esko, J. D., and Masliah, E. (2017) Cellular internalization of α-synuclein aggregates by cell surface heparan sulfate depends on aggregate conformation and cell type. Sci. Rep. 7, 9008 CrossRef Medline
8. Stopchinski, B. E., Holmes, B. B., Miller, G. M., Manon, V. A., Vaquer-Alcica, J., Prueitt, W. L., Hsieh-Wilson, L. C., and Diamond, M. I. (2018) Specific glycosaminoglycan chain length and sulfation patterns are required for cell uptake of tau versus α-synuclein and β-amyloid aggregates. J. Biol. Chem. 293, 10826–10840 CrossRef Medline
9. Watanabe-Nakayama, T., Ono, K., Itami, M., Takahashi, R., Teplow, D. B., and Yamada, M. (2016) High-speed atomic force microscopy reveals structural dynamics of amyloid β1–42 aggregates. Proc. Natl. Acad. Sci. U.S.A. 113, 5835–5840 CrossRef Medline
10. Tsuoi, Y., Doh-ura, K., and Yamada, T. (2009) Continuous intraventricular infusion of pentosan polysulfate: Clinical trial against prion diseases. Neuropathology 29, 632–636 CrossRef Medline