варианты, неспособные к агрегации. Показано, что натуральные полифункциональные вещества, поддерживающие селекцию нетоксичных олигомеров, особенно перспективны для терапии.

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Работа не включала эксперименты с участием животных или людей.

КОНФЛИКТ ИНТЕРЕСОВ

Авторы заявляют, что у них нет конфликта интересов.

СПИСОК ЛИТЕРАТУРЫ

Зубова С.Г. 2019. Многоликость аутофагии и ее неоднозначная роль в биологических процессах. Цитология. Т. 61. № 12. С. 941. (*Zubova S.G.* 2019. The diversity of autophagy and its controversial role in biological processes. Tsitologiya. V. 61. № 12. P. 941). https://doi.org/10.1134/S0041377119120095

Agarwal A., Arora L., Rai S.K., Avni A., Mukhopadhyay S. 2022. Spatiotemporal modulations in heterotypic condensates of prion and α-synuclein control phase transitions and amyloid conversion. Nature Commun. V. 13. P. 1. https://doi.org/10.1038/s41467-022-28797-5

Adem K., Shanti A., Srivastava A., Homouz D., Thomas S.A., Khair M., Stefanini C., Chan V., Kim T.Y., Lee S. 2022. Linking Alzheimer's disease and type 2 diabetes: characterization and inhibition of cytotoxic Aβ and IAPP heteroaggregates. Front. Mol. Biosci. V. 9. P. 842582. https://doi.org/10.3389/fmolb.2022.842582

Alam P., Bousset L., Melki R., Otzen D.E. 2019. α-Synuclein oligomers and fibrils: a spectrum of species, a spectrum of toxicities. J. Neurochem. V. 150. P. 522. https://doi.org/10.1111/jnc.14808

Ashrafian H., Zadeh E.H., Khan R.H. 2021. Review on Alzheimer's disease: inhibition of amyloid beta and tau tangle formation. Int. J. Biol. Macromol. V. 167. P. 382. https://doi.org/10.1016/j.ijbiomac.2020.11.192

Baba M., Nakajo S., Tu P.H., Tomita T., Nakaya K., Lee V.M., Trojanowski J.Q., Iwatsubo T. 1998. Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. Am. J. Pathol. V. 152. P. 879.

Badiola N., de Oliveira R.M., Herrera F., Guardia-Laguarta C., Gonçalves S.A., Pera M., Suárez-Calvet M., Clarimon J., Outeiro T.F., Lleó A. 2011. Tau enhances α-synuclein aggregation and toxicity in cellular models of synucleinopathy. PLoS One. V. 6. P. e26609. https://doi.org/10.1371/journal.pone.0026609

Banerjee D., Sanyal S. 2014. Protein folding activity of the ribosome (PFAR) — a target for antiprion compounds. Viruses. V. 6. P. 3907. https://doi.org/10.3390/v6103907

Barbier P., Zejneli O., Martinho M., Lasorsa A., Belle V., Smet-Nocca C., Tsvetkov P.O., Devred F., Landrieu I. 2019. Role of Tau as a microtubule-associated protein: structural and functional aspects. Front. Aging Neurosci. V. 11. P. 204. https://doi.org/10.3389/fnagi.2019.00204

Barbitoff Y.A., Matveenko A.G., Moskalenko S.E., Zemlyanko O.M., Newnam G.P., Patel A., Chernova T.A., Chernoff Y.O., Zhouravleva G.A. 2017. To CURe or not to CURe? Differential effects of the chaperone sorting factor Cur1 on yeast prions are mediated by the chaperone Sis1. Mol. Microbiol. V. 105. P. 242. https://doi.org/10.1111/mmi.13697

Beeg M., Stravalaci M., Romeo M., Carrá A.D., Cagnotto A., Rossi A., Diomede L., Salmona M., Gobbi M. 2016. Clusterin binds to Aβ1-42 oligomers with high affinity and interferes with peptide aggregation by inhibiting primary and secondary nucleation. J. Biol. Chem. V. 291. P. 6958. https://doi.org/10.1074/jbc.M115.689539

Beldona V., Patel A., Patel K., Abraham N., Halvorsen A., Liu A., Mannem N., Renganathan G. 2022. Natural product polyphenol inhibition of amyloid-β aggregation. J. High School Sci. V. 32281. http://jhss.scholasticahq.com

Bennett R.E., DeVos S.L., Dujardin S., Corjuc B., Gor R., Gonzalez J., Roe A.D., Frosch M.P., Pitstick R., Carlson G.A., Hyman B.T. 2017. Enhanced tau aggregation in the presence of amyloid β. Am. J. Pathol. V. 187. P. 1601. https://doi.org/10.1016/j.ajpath.2017.03.011

Bharadwaj P., Solomon T., Sahoo B.R., Ignasiak K., Gaskin S., Rowles J., Verdile G., Howard M.J., Bond C.S., Ramamoorthy A., Martins R.N., Newsholme P. 2020. Amylin and beta amyloid proteins interact to form amorphous heterocomplexes with enhanced toxicity in neuronal cells. Sci. Rep. V. 10. P. 10356. https://doi.org/10.1038/s41598-020-66602-9

Blondel M., Soubigou F., Evrard J., Nguyen P.H., Hasin N., Chédin S., Gillet R., Contesse M.A., Friocourt G., Stahl G., Jones G.W., Voisset C. 2016. Protein folding activity of the ribosome is involved in yeast prion propagation. Sci. Rep. V. 6. P. 32117. https://doi.org/10.1038/srep32117

Botstein D., Fink G.R. 2011. Yeast: an experimental organism for 21st century biology. Genetics. V. 189. P. 695. https://doi.org/10.1534/genetics.111.130765

Braak H., Alafuzoff I., Arzberger T., Kretzschmar H., Del Tredici K. 2006. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol. V. 112. P. 389. https://doi.org/10.1007/s00401-006-0127-z

Bush A.I. 2003. The metallobiology of Alzheimer's disease. Trends Neurosci. V. 26. P. 207. https://doi.org/10.1016/S0166-2236(03)00067-5

Candreva J., Chau E., Rice M.E., Kim J.R. 2020. Interactions between soluble species of β-Amyloid and α-Synuclein promote oligomerization while inhibiting fibrillization. Biochemistry. V. 59. P. 425. https://doi.org/10.1021/acs.biochem.9b00655

Cascella R., Bigi A., Cremades N., Cecchi C. 2022. Effects of oligomer toxicity, fibril toxicity and fibril spreading in synucleinopathies. Cell Mol. Life Sci. V. 79. P. 174. https://doi.org/10.1007/s00018-022-04166-9

Cascella R., Chen S.W., Bigi A., Camino J.D., Xu C.K., Dobson C.M., Chiti F., Cremades N., Cecchi C. 2021. The re-

lease of toxic oligomers from α-synuclein fibrils induces dysfunction in neuronal cells. Nat. Commun. V. 12. P. 1814.
https://doi.org/10.1038/s41467-021-21937-3

Cheng A., Wang Y.F., Shinoda Y., Kawahata I., Yamamoto T., Jia W.B., Yamamoto H., Mizobata T., Kawata Y., Fukunaga K. 2022. Fatty acid-binding protein 7 triggers α-synuclein oligomerization in glial cells and oligodendrocytes associated with oxidative stress. Acta Pharmacol. Sin. V. 43. P. 552.
https://doi.org/10.1038/s41401-021-00675-8

Chernoff Y.O., Grizel A.V., Rubel A.A., Zelinsky A.A., Chandramowlishwaran P., Chernova T.A. 2020. Application of yeast to studying amyloid and prion diseases. Adv. Genet. V. 105. P. 293.
https://doi.org/10.1016/bs.adgen.2020.01.002

Chernova T.A., Chernoff Y.O., Wilkinson K.D. 2019. Yeast models for amyloids and prions: environmental modulation and drug discovery. Molecules. V. 24. P. 3388.
https://doi.org/10.3390/molecules24183388

Choudhary V., Ojha N., Golden A., Prinz W.A. 2015. A conserved family of proteins facilitates nascent lipid droplet budding from the ER. J. Cell Biol. V. 211. P. 261.
https://doi.org/10.1083/jcb.201505067

Cohen S.I.A., Arosio P., Presto J., Kurudenkandy F.R., Biverstal H., Dolfe L., Dunning C., Yang X., Frohm B., Vendruscolo M., Johansson J., Dobson C.M., Fisahn A., Knowles T.P.J., Linse S. 2015. A molecular chaperone breaks the catalytic cycle that generates toxic Aβ-oligomers. Nat. Struct. Mol. Biol. V. 22. P. 207.
https://doi.org/10.1038/nsmb.2971

Colla E., Coune P., Liu Y., Pletnikova O., Troncoso J.C., Iwatsubo T., Schneider B.L., Lee M.K. 2012. Endoplasmic reticulum stress is important for the manifestations of α-synucleinopathy *in vivo*. J. Neurosci. V. 32. P. 3306.
https://doi.org/10.1523/JNEUROSCI.2617-07.2007

Desplats P., Lee H.J., Bae E.J., Patrick C., Rockenstein E., Crews L., Spencer B., Masliah E., Lee S.J. 2009. Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. Proc. Natl. Acad. Sci. USA. V. 106. P. 13010.
https://doi.org/10.1073/pnas.0903691106

Doody R.S., Gavrilova S.I., Sano M., Thomas R.G., Aisen P.S., Bachurin S.O., Seely L., Hung D., Dimebon I. 2008. Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. Lancet. V. 372. P. 207.
https://doi.org/10.1016/S0140-6736(08)61074-0

Dujardin S., Bégard S., Caillierez R., Lachaud C., Delattre L., Carrier S., Loyens A., Galas M.-C., Bousset L., Melki R., Auregan G., Hantraye P., Brouillet E., Buee L., Colin M. 2014. Ectosomes: a new mechanism for non-exosomal secretion of Tau protein. PLoS One. V. 9. P. e100760.
https://doi.org/10.1371/journal.pone.0100760

Ehrnhoefer D.E., Bieschke J., Boeddrich A., Herbst M., Masino L., Lurz R., Engemann S., Pastore A., Wanker E.E. 2008. EGCG redirects amyloidogenic polypeptides into unstructured, off-pathway oligomers. Nat. Struct. Mol. Biol. V. 15. P. 558.
https://doi.org/10.1038/nsmb.1437

Emmanouilidou E., Melachroinou K., Roumeliotis T., Garbis S.D., Ntzouni M., Margaritis L.H., Stefanis L., Vekrellis K. 2010. Cell-produced alpha-synuclein is secreted in a calcium-dependent manner by exosomes and impacts neuronal survival. J. Neurosci. V. 30. P. 6838.
https://doi.org/10.1523/JNEUROSCI.5699-09.2010

Faria C., Jorge C.D., Borges N., Tenreiro S., Outeiro T.F., Santos H. 2013. Inhibition of formation of α-synuclein inclusions by mannosyl glycerate in a yeast model of Parkinson's disease. Biochim. Biophys. Acta. V. 1830. P. 4065.
https://doi.org/10.1016/j.bbagen.2013.04.015

Fernandes J.T., Tenreiro S., Gameiro A., Chu V., Outeiro T.F., Conde J.P. 2014. Modulation of α-synuclein toxicity in yeast using a novel microfluidic-based gradient generator. Lab. Chip. V. 14. P. 3949.
https://doi.org/10.1039/C4LC00756E

Fernandez-Funez P., Sanchez-Garcia J., de Mena L., Zhang Y., Levites Y., Khare S., Golde T.E., Rincon-Limas D.E. 2016. Holdase activity of secreted Hsp70 masks amyloid-β42 neurotoxicity in *Drosophila*. Proc. Natl. Acad. Sci. USA. V. 113. P. E5212.
https://doi.org/10.1073/pnas.1608045113

Franić D., Zubčić K., Boban M. 2021. Nuclear ubiquitin-proteasome pathways in proteostasis maintenance. Biomolecules. V. 4. P. 54.
https://doi.org/10.3390/biom11010054

Fusco G., Chen S.W., Williamson P.T.F., Cascella R., Perni M., Jarvis J.A., Cecchi C., Vendruscolo M., Chiti F., Cremades N., Ying L., Dobson C.M., De Simone A. 2017. Structural basis of membrane disruption and cellular toxicity by α-synuclein oligomers. Science. V. 358. P. 1440.
https://doi.org/10.1126/science.aan6160

Gauci A.J., Caruana M., Giese A., Scerri C., Vassallo N. 2011. Identification of polyphenolic compounds and black tea extract as potent inhibitors of lipid membrane destabilization by Aβ42 aggregates. J. Alzheimers Dis. V. 27. P. 767.
https://doi.org/10.3233/JAD-2011-111061

Gomes L.M.F., Bataglioli J.C., Storr T. 2020. Metal complexes that bind to the amyloid-β peptide of relevance to Alzheimer's disease. Coordinat. Chem. Rev. V. 412. P. 213255.
https://doi.org/10.1016/j.ccr.2020.213255

Grelle G., Otto A., Lorenz M., Frank R.F., Wanker E.E., Bieschke J. 2011. Black tea theaflavins inhibit formation of toxic amyloid-beta and alpha-synuclein fibrils. Biochemistry. V. 50. P. 10624.
https://doi.org/10.1021/bi2012383

Habchi J., Chia S., Galvagnion C., Michaels T.C.T., Bellaiche M.M.J., Ruggeri F.S., Sanguanini M., Idini I., Kumita J.R., Sparr E., Linse S., Dobson C.M., Knowles T.P.J., Vendruscolo M. 2018. Cholesterol catalyses Aβ42 aggregation through a heterogeneous nucleation pathway in the presence of lipid membranes. Nat. Chem. V. 10. P. 673.
https://doi.org/10.1038/s41557-018-0031-x

Hachiya N., Fulek M., Zajączkowska K., Kurpas D., Trypka E., Leszek J. 2021. Cellular prion protein and amyloid-β oligomers in Alzheimer's disease – there are connections? Preprints. 2021050032.
https://doi.org/10.20944/preprints202105.0032.v1

Hamano T., Hayashi K., Shirafuji N., Nakamoto Y. 2018. The implications of autophagy in Alzheimer's disease. Curr. Alzheimer Res. V. 15. P. 1283.
https://doi.org/10.2174/1567205015666181004143432

Hardenberg M., Horvath A., Ambrus V., Fuxreiter M., Vendruscolo M. 2020. Widespread occurrence of the droplet state of proteins in the human proteome. Proc. Natl. Acad. Sci.

USA. V. 117. P. 33254.
https://doi.org/10.1073/pnas.2007670117

Hardenberg M.C., Sinnige T., Casford S., Dada S.T., Poudel C., Robinson E.A., Fuxreiter M., Kaminksi C.F., Kaminski Schierle G.S., Nollen E.A.A., Dobson C.M., Vendruscolo M. 2021. Observation of an α-synuclein liquid droplet state and its maturation into Lewy body-like assemblies. J. Mol. Cell Biol. V. 13. P. 282.
https://doi.org/10.1093/jmcb/mjaa075

Hashimoto M., Masliah E. 1999. Alpha-synuclein in Lewy Body Disease and Alzheimer's Disease. Brain Pathology. V. 9. P. 707.
https://doi.org/10.1111/j.1750-3639.1999.tb00552.x

Hevroni B.L., Major D.T., Dixit M., Mhashal A.R., Das S., Fischer B. 2016. Nucleoside-2', 3'/3', 5'-bis (thio) phosphate antioxidants are also capable of disassembly of amyloid beta 42-Zn (ii)/Cu (ii) aggregates via Zn (ii)/Cu (ii)-chelation. Organic Biomol. Chem. V. 14. P. 4640.
https://goi.org/10/1039/C6OB00613B

Hideshima M., Kimura Y., Aguirre C., Kakuda K., Takeuchi T., Choong C.J., Doi J., Nabekura K., Yamaguchi K., Nakajima K., Baba K., Nagano S., Goto Y., Nagai Y., Mochizuki H., Ikenaka K. 2022. Two-step screening method to identify α-synuclein aggregation inhibitors for Parkinson's disease. Sci. Rep. V. 12. P. 351.
https://doi.org/10.1038/s41598-021-04131-9

Hijaz B.A., Volpicelli-Daley L.A. 2020. Initiation and propagation of α-synuclein aggregation in the nervous system. Mol. Neurodegener. V. 15. P. 19.
https://doi.org/10.1186/s13024-020-00368-6

Hillen H. 2019. The beta amyloid dysfunction (BAD) hypothesis for Alzheimer's disease. Front. Neurosci. V. 13. P. 1154.
https://doi.org/10.3389/fnins.2019.01154

Hurst L.R., Fratti R.A. 2020. Lipid rafts, sphingolipids, and ergosterol in yeast vacuole fusion and maturation. Front. Cell Dev. Biol. V. 8. P. 539.
https://doi.org/10.3389/fcell.2020.00539

Jackson K., Barisone G.A., Diaz E., Jin L.W., DeCarli C., Despa F. 2013. Amylin deposition in the brain: a second amyloid in Alzheimer disease? Ann. Neurol. V. 74. P. 517.
https://doi.org/10.1002/ana.23956

Jacobs H.I.L., Hedden T., Schultz A.P., Sepulcre J., Perea R.D., Amariglio R.E., Papp K.V., Rentz D.M., Sperling R.A., Johnson K.A. 2018. Structural tract alterations predict downstream tau accumulation in amyloid-positive older individuals. Nat. Neurosci. V. 21. P. 424.
https://doi.org/10.1038/s41593-018-0070-z

Jacquier N., Choudhary V., Mari M., Toulmay A., Reggiori F., Schneiter R. 2011. Lipid droplets are functionally connected to the endoplasmic reticulum in *Saccharomyces cerevisiae*. J. Cell Sci. V. 124. P. 2424.
https://doi.org/10.1242/jcs.076836

Jomova K., Vondrakova D., Lawson M., Valko M. 2010. Metals, oxidative stress and neurodegenerative disorders. Mol. Cell Biochem. V. 345. P. 91.
https://doi.org/10.1007/s11010-010-0563-x

Kalaitzakis M.E., Graeber M.B., Gentleman S.M., Pearce R.K. 2008. Striatal beta-amyloid deposition in Parkinson disease with dementia. J. Neuropathol. Exp. Neurol. V. 67. P. 155.
https://doi.org/10.1097/NEN.0b013e31816362aa

Kieran D., Hafezparast M., Bohnert S., Dick J.R., Martin J., Schiavo G., Fisher E.M., Greensmith L. 2005. A mutation in dynein rescues axonal transport defects and extends the life span of ALS mice. J. Cell Biol. V. 169. P. 561.
https://doi.org/10.1083/jcb.200501085

König A.S., Rösener N.S., Gremer L., Tusche M., Flender D., Reinartz E., Hoyer W., Neudecker P., Willbold D., Heise H. 2021. Structural details of amyloid β oligomers in complex with human prion protein as revealed by solid-state MAS NMR spectroscopy. J. Biol. Chem. V. 296. P. 100499.
https://doi.org/10.1016/j.jbc.2021.100499

Konstantoulea K., Louros N., Rousseau F., Schymkowitz J. 2021. Heterotypic interactions in amyloid function and disease. FEBS J. V. 289. P. 2025.
https://doi.org/10.1111/febs.15719

Koopman M.B., Ferrari L., Rüdiger S.G.D. 2022. How do protein aggregates escape quality control in neurodegeneration? Trends Neurosci. V. 45. P. 257.
https://doi.org/10.1016/j.tins.2022.01.006

LaFerla F.M., Green K.N., Oddo S. 2007. Intracellular amyloid-beta in Alzheimer's disease. Nat. Rev. Neurosci. V. 8. P. 499.
https://doi.org/10.1038/nrn2168

Lambert M.P., Velasco P.T., Chang L., Viola K.L., Fernandez S., Lacor P.N., Khuon D., Gong Y., Bigio E.H., Shaw P., De Felice F.G., Krafft G.A., Klein W.L. 2007. Monoclonal antibodies that target pathological assemblies of Abeta. J. Neurochem. V. 100. P. 23.
https://doi.org/10.1111/j.1471-4159.2006.04157.x

Li D., Liu C. 2022. Spatiotemporal dynamic regulation of membraneless organelles by chaperone networks. Trends Cell. Biol. V. 32. P. 1.
https://doi.org/10.1016/j.tcb.2021.08.004

Li F., Calingasan N.Y., Yu F., Mauck W.M., Toidze M., Almeida C.G., Takahashi R.H., Carlson G.A., Flint Beal M., Lin M.T., Gouras G.K. 2004. Increased plaque burden in brains of APP mutant MnSOD heterozygous knockout mice. J. Neurochem. V. 89. P. 1308.
https://doi.org/10.1111/j.1471-4159.2004.02455.x

Liang C., Savinov S.N., Fejzo J., Eyles S.J., Chen J. 2019. Modulation of amyloid-β42 conformation by small molecules through nonspecific binding. J. Chem. Theory Comput. V. 15. P. 5169.
https://doi.org/10.1021/acs.jctc.9b00599

Limbocker R., Staats R., Chia S., Ruggeri F.S., Mannini B., Xu C.K., Perni M., Cascella R., Bigi A., Sasser L.R., Block N.R., Wright A.K., Kreiser R.P., Custy E.T., Meisl G. et al. 2021. Squalamine and its derivatives modulate the aggregation of amyloid-β and α-synuclein and suppress the toxicity of their oligomers. Front. Neurosci. V. 15. P. 680026.
https://doi.org/10.3389/fnins.2021.680026

Lindersson E., Beedholm R., Højrup P., Moos T., Gai W., Hendil K.B., Jensen P.H. 2004. Proteasomal inhibition by alpha-synuclein filaments and oligomers. J. Biol. Chem. V. 279. P. 12924.

Lorenzen N., Nielsen S.B., Yoshimura Y., Vad B.S., Andersen C.B., Betzer C., Kaspersen J.D., Christiansen G., Pedersen J.S., Jensen P.H., Mulder F.A., Otzen D.E. 2014. How epigallocatechin gallate can inhibit α-synuclein oligomer toxicity in vitro. J. Biol. Chem. V. 289. P. 21299.
https://doi.org/10.1074/jbc.M114.554667

Luth E.S., Stavrovskaya I.G., Bartels T., Kristal B.S., Selkoe D.J. 2014. Soluble, prefibrillar α-synuclein oligomers promote complex I-dependent, Ca2(+)-induced mitochondrial

dysfunction. J. Biol. Chem. V. 289. P. 21490. https://doi.org/10.1074/jbc.M113.545749

Macreadie I., Lotfi-Miri M., Mohotti S., Shapira D., Bennett L., Varghese J. 2008. Validation of folate in a convenient yeast assay suited for identification of inhibitors of Alzheimer's amyloid-β aggregation. J. Alzheimers Dis. V. 15. P. 391. https://doi.org/10.3233/JAD-2008-15305

Margulis B., Tsimokha A., Zubova S., Guzhova I. 2020. Molecular chaperones and proteolytic machineries regulate protein homeostasis in aging cells. Cells. V. 9. P. 1308. https://doi.org/10.3390/cells9051308

Masliah E. 2001. Recent advances in the understanding of the role of synaptic proteins in Alzheimer's disease and other neurodegenerative disorders. J. Alzheimers Dis. V. 3. P. 121. https://doi.org/10.3233/jad-2001-3117

Mizuno H., Fujikake N., Wada K., Nagai Y. 2010. α-Synuclein transgenic Drosophila as a model of Parkinson's disease and related synucleinopathies. Parkinsons Dis. V. 2011. P. 212706. https://doi.org/10.4061/2011/212706

Nevzglyadova O.V., Mikhailova E.V., Soidla T.R. 2022. Yeast red pigment, protein aggregates, and amyloidoses: a review. Cell Tiss. Res. V. 388. P. 211. https://doi.org/10.1007/s00441-022-03609-w

Niewiadomska G., Niewiadomski W., Steczkowska M., Gasiorowska A. 2021. Tau oligomers neurotoxicity. Life (Basel). V. 11. P. 28. https://doi.org/10.3390/life11010028

Nygaard H.B., van Dyck C.H., Strittmatter S.M. 2014. Fyn kinase inhibition as a novel therapy for Alzheimer's disease. Alzheimers Res. Ther. V. 6. P. 8. https://doi.org/10.1186/alzrt238

Opazo C., Huang X., Cherny R.A., Moir R.D., Roher A.E., White A.R., Cappai R., Masters C.L., Tanzi R.E., Inestrosa N.C., Bush A.I. 2002. Metalloenzyme-like activity of Alzheimer's disease beta-amyloid. Cu-dependent catalytic conversion of dopamine, cholesterol, and biological reducing agents to neurotoxic H(2)O(2). J. Biol. Chem. V. 277. P. 40302. https://doi.org/10.1074/jbc.M206428200

Palhano F.L., Lee J., Grimster N.P., Kelly J.W. 2013. Toward the molecular mechanism(s) by which EGCG treatment remodels mature amyloid fibrils. J. Am. Chem. Soc. V. 135. P. 7503. https://doi.org/10.1021/ja3115696

Paslawski W., Mysling S., Thomsen K., Jorgensen T.J., Otzen D.E. 2014. Co-existence of two different α-synuclein oligomers with different core structures determined by hydrogen/deuterium exchange mass spectrometry. Angew. Chem. Int. Ed. Engl. V. 53. P. 7560. https://doi.org/10.1002/anie.201400491

Pena-Diaz S., Ventura S. 2022. One ring is sufficient to inhibit α-synuclein aggregation. Neural Regen. Res. V. 17. P. 508. https://doi.org/10.4103/1673-5374.320973

Penke B., Bogár F., Paragi G., Gera J., Fülöp L. 2019. Key peptides and proteins in Alzheimer's disease. Curr. Protein Pept. Sci. V. 20. P. 577. https://doi.org/10.2174/1389203720666190103123434

Penke B., Szűcs M., Bogár F. 2020. Oligomerization and conformationalchange turn monomeric β-Amyloid and tau proteins toxic: their role in Alzheimer's pathogenesis. Molecules. V. 25. P. 1659. https://doi.org/10.3390/molecules25071659

Perni M., Flagmeier P., Limbocker R., Cascella R., Aprile F.A., Galvagnion C., Heller G.T., Meisl G., Chen S.W., Kumita J.R., Challa P.K., Kirkegaard J.B., Cohen S.I.A., Mannini B., Barbut D. et al. 2018. Multistep inhibition of α-synuclein aggregation and toxicity *in vitro* and *in vivo* by trodusquemine. ACS Chem. Biol. V. 13. P. 2308. https://doi.org/10.1021/acschembio.8b00466

Perni M., van der Goot A., Limbocker R., van Ham T.J., Aprile F.A., Xu C.K., Flagmeier P., Thijssen K., Sormanni P., Fusco G., Chen S.W., Challa P.K., Kirkegaard J.B., Laine R.F., Ma K.Y. et al. 2021. Comparative studies in the A30P and A53T α-synuclein *C. elegans* strains to investigate the molecular origins of Parkinson's disease. Front. Cell Dev. Biol. V. 9. P. 552549. https://doi.org/10.3389/fcell.2021.552549

Rajasekhar K., Suresh S.N., Manjithaya R., Govindaraju T. 2015. Rationally designed peptidomimetic modulators of aβ toxicity in Alzheimer's disease. Sci Rep. V. 30. P. 8139. https://doi.org/10.1038/srep08139

Russo R., Borghi R., Markesbery W., Tabaton M., Piccini A. 2005. Neprylisin decreases uniformly in Alzheimer's disease and in normal aging. FEBS Lett. V. 579. P. 6027. https://doi.org/10.1016/j.febslet.2005.09.054

Sangkaew A., Kojornna T., Tanahashi R., Takagi H., Yompakdee C. 2022. A novel yeast-based screening system for potential compounds that can alleviate human α-synuclein toxicity. J. Appl. Microbiol. V. 132. P. 1409. https://doi.org/10.1111/jam.15256

Santos J., Pallarès I., Ventura S. 2022. Is a cure for Parkinson's disease hiding inside us? Trends Biochem. Sci. V. 19. P. S0968-0004(22)00025-1. https://doi.org/10.1016/j.tibs.2022.02.001

Schepers J., Behl C. 2021. Lipid droplets and autophagy-links and regulations from yeast to humans. J. Cell Biochem. V. 122. P. 602. https://doi.org/10.1002/jcb.29889

Scudamore O., Ciossek T. 2018. Increased oxidative stress exacerbates α-synuclein aggregation *in vivo*. J. Neuropathol. Exp. Neurol. V. 77. P. 443. https://doi.org/10.1093/jnen/nly024

Silva J.L., Vieira T.C., Cordeiro Y., de Oliveira G.A.P. 2022. Nucleic acid actions on abnormal protein aggregation, phase transitions and phase separation. Curr. Opin. Struct. Biol. V. 73. P. 102346. https://doi.org/10.1016/j.sbi.2022.102346

Simonsen A., Wollert T. 2022. Don't forget to be picky – selective autophagy of protein aggregates in neurodegenerative diseases. Curr. Opin. Cell Biol. V. 75. P. 102064. https://doi.org/10.1016/j.ceb.2022.01.009

Stefani M., Dobson C.M. 2003. Protein aggregation and aggregate toxicity: new insights into protein folding, misfolding diseases and biological evolution. J. Mol. Med. (Berl.). V. 81. P. 678. https://doi.org/10.1007/s00109-003-0464-5

Stefanis L. 2012. α-Synuclein in Parkinson's disease. Cold Spring Harb. Perspect. Med. V. 2. P. a009399. https://doi.org/10.1101/cshperspect.a009399

Su L.J., Auluck P.K., Outeiro T.F., Yeger-Lotem E., Kritzer J.A., Tardiff D.F., Strathearn K.E., Liu F., Cao S., Hamamichi S., Hill K.J., Caldwell K.A., Bell G.W., Fraenkel E., Cooper A.A. et al. 2010. Compounds from an unbiased chemical screen reverse both ER-to-Golgi trafficking defects and mito-

chondrial dysfunction in Parkinson's disease models. Dis. Model. Mech. V. 3. P. 194. https://doi.org/10.1242/dmm.004267

Subedi S., Sasidharan S., Nag N., Saudagar P., Tripathi T. 2022. Amyloid cross-seeding: mechanism, implication, and inhibition. Molecules. V. 27. P. 1776. https://doi.org/10.3390/molecules27061776

Tang Y., Zhang D., Liu Y., Zhang Y., Zhou Y., Chang Y., Zheng B., Xu A., Zheng J. 2022a. A new strategy to reconcile amyloid cross-seeding and amyloid prevention in a binary system of α-synuclein fragmental peptide and hIAPP. Protein Science. V. 31. P. 485. https://doi.org/10.1002/pro.4247

Tang Y., Zhang D., Zhang Y., Liu Y., Miller Y., Gong K., Zheng J. 2022b. Cross-seeding between Aβ and SEVI indicates a pathogenic link and gender difference between Alzheimer diseases and AIDS. Communications Biology. V. 5. P. 417. https://doi.org/10.1038/s42003-022-03343-7

Tanguy E., Wang Q., Moine H., Vitale N. 2019. Phosphatidic acid: from pleiotropic functions to neuronal pathology. Front. Cell Neurosci. V. 13. P. 2. https://doi.org/10.3389/fncel.2019.00002

Tardiff D.F., Jui N.T., Khurana V., Tambe M.A., Thompson M.L., Chung C.Y., Kamadurai H.B., Kim H.T., Lancaster A.K., Caldwell K.A., Caldwell G.A., Rochet J.C., Buchwald S.L., Lindquist S. 2013. Yeast reveal a druggable Rsp5/Nedd4 network that ameliorates α-synuclein toxicity in neurons. Science. V. 342. P. 979. https://doi.org/10.1126/science.1245321

Tavanti F., Pedone A., Menziani M.C. 2020. Insights into the effect of curcumin and (−)-epigallocatechin-3-gallate on the aggregation of Aβ(1–40) monomers by means of molecular dynamics Int. J. Mol. Sci. V. 21. P. 5462. https://doi.org/10.3390/ijms21155462

Tenreiro S., Munder M.C., Alberti S., Outeiro T.F. 2013. Harnessing the power of yeast to unravel the molecular basis of neurodegeneration. J. Neurochem. V. 127. P. 438. https://doi.org/10.1111/jnc.12271

Thellung S., Corsaro A., Nizzari M., Barbieri F., Florio T. 2019. Autophagy activator drugs: anew opportunity in neuroprotection from misfolded protein toxicity. Int. J. Mol. Sci. V. 20. P. 901. https://doi.org/10.3390/ijms20040901

Tuite M.F. 2019. Yeast models of neurodegenerative diseases. Prog. Mol. Biol. Transl. Sci. V. 168. P. 351. https://doi.org/10.1016/bs.pmbts.2019.07.001

Vernon R.M., Chong P.A., Tsang B., Kim T.H., Bah A., Farber P., Lin H., Forman-Kay J.D. 2018. Pi-Pi contacts are an overlooked protein feature relevant to phase separation. Elife. V. 7. P. e31486. https://doi.org/10.7554/eLife.31486

Villar-Piqué A., da Fonseca T.L., Sant'Anna R., Szegö É.M., Fonseca-Ornelas L., Pinho R., Carija A., Gerhardt E., Masaracchia C., Abad G.E., Rossetti G., Carloni P., Fernández C.O., Foguel D., Milosevic I. et al. 2016. Environmental and genetic factors support the dissociation between α-synuclein aggregation and toxicity. Proc. Natl. Acad. Sci. USA.V. 113. P. E6506. https://doi.org/10.1073/pnas.1606791113

Vivoli Vega M., Cascella R., Chen S.W., Fusco G., De Simone A., Dobson C.M., Cecchi C., Chiti F. 2019. The toxicity of misfolded protein oligomers is independent of their secondary structure. ACS Chem. Biol. V. 14. P. 1593. https://doi.org/10.1021/acschembio.9b00324

Volles M.J., Lee S.J., Rochet J.C., Shtilerman M.D., Ding T.T., Kessler J.C., Lansbury P.T. Jr. 2001. Vesicle permeabilization by protofibrillar alpha-synuclein: implications for the pathogenesis and treatment of Parkinson's disease. Biochemistry. V. 40. P. 7812. https://doi.org/10.1021/bi0102398

Wang Y., Westermark G.T. 2021. The amyloid forming peptide islet amyloid polypeptide and amyloid β interact at the molecular level. Int. J. Mol. Sci. V. 22. P. 11153. https://doi.org/10.3390/ijms222011153

Wells C., Brennan S.E., Keon M., Ooi L. 2021. The role of amyloid oligomers in neurodegenerative pathologies. Int. J. Biol. Macromol. V. 181. P. 582. https://doi.org/10.1016/j.ijbiomac.2021.03.113

Wells C., Brennan S.E., Keon M., Saksena N.K. 2019. Prionoid proteins in the pathogenesis of neurodegenerative diseases. Front. Mol. Neurosci. V. 12. P. 271. https://doi.org/10.3389/fnmol.2019.00271

Wentink A., Nussbaum-Krammer C., Bukau B. 2019. Modulation of amyloid states by molecular chaperones. Cold Spring Harb. Perspect. Biol. V. 11. P. a033969. https://doi.org/10.1101/cshperspect.a033969

Xue W.F., Hellewell A.L., Hewitt E.W., Radford S.E. 2010. Fibril fragmentation in amyloid assembly and cytotoxicity. Prion. V. 4. P. 20. https://doi.org/10.4161/pri.4.1.11378

Youn K., Ho C., Jun M. 2022. Multifaceted neuroprotective effects of (-)-epigallocatechin-3-gallate (EGCG) in Alzheimer's disease: an overview of pre-clinical studies focused on β-amyloid peptide. Food Sci. Human Wellness. V. 11. P. 483. https://doi.org/10.1016/j.fshw.2021.12.006

Younan N.D., Chen K.F., Rose R.S., Crowther D.C., Viles J.H. 2018. Prion protein stabilizes amyloid-β (βA) oligomers and enhances Aβ neurotoxicity in a *Drosophila* model of Alzheimer's disease. J. Biol. Chem. V. 293. P. 13090. https://doi.org/10.1074/jbc.RA118.003319

Young L.M., Mahood R.A., Saunders J.C., Tu L.H., Raleigh D.P., Radford S.E., Ashcroft A.E. 2015. Insights into the consequences of co-polymerisation in the early stages of IAPP and Aβ peptide assembly from mass spectrometry. Analyst. V. 140. P. 6990. https://doi.org/10.1039/c5an00865d

Zhang S., Liu Y.Q., Jia C., Lim Y.J., Feng G., Xu E., Long H., Kimura Y., Tao Y., Zhao C., Wang C., Liu Z., Hu J.J., Ma M.R., Liu Z. et al. 2021. Mechanistic basis for receptor-mediated pathological α-synuclein fibril cell-to-cell transmission in Parkinson's disease. Proc. Natl. Acad. Sci. USA. V. 118. P. e2011196118. https://doi.org/10.1073/pnas.2011196118

Zhang Y., Zhang M., Liu Y., Zhang D., Tang Y., Ren B., Zheng J. 2021. Dual amyloid cross-seeding reveals steric zipper-facilitated fibrillization and pathological links between protein misfolding diseases. J. Mat. Chem B. V. 9. P. 3300. https://doi.org/10.1039/D0TB0295K

Zhang Y., Zhao Y., Zhang L., Yu W., Wang Y., Chang W. 2019. Cellular prion protein as a receptor of toxic amyloid-β 42 oligomers is important for Alzheimer's disease. Front Cell Neurosci. V. 13. P. 339. https://doi.org/10.3389/fncel.2019.00339

Molecular Mechanisms Underlying Alzheimer's and Parkinson's Diseases and the Potential Possibility of their Neutralization

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Different protein forms inevitably load up in the cell under the influence of external and internal factors. With aging, the activity of chaperones and other components of the cell protein quality control machinery decreases. This results in accumulation of misfolded proteins with altered conformation. The most drastic alteration is the conversion of the active soluble molecules to the insoluble and inactive amyloid. Such a conformation shift of proteins is considered to lie behind the neurodegeneration process. A number of studies are devoted to neurodegeneration, but many details of the process still need to be clarified. In this review we outline some modern views on molecular mechanisms underlying the pathogenesis of the most widespread Alzheimer and Parkinson diseases. These are based on a series of interactions between Abeta and alfa-synuclein and membrane receptors and are modulated by phase separation and cross-seeding with other cell prions. Special attention is paid to natural polyfunctional compounds as promising therapeutic agents.

Keywords: amyloid, anti-amyloid compounds, non-membrane organelles, cross-seeding