

MINI-REVIEW

Nucleolar alterations in brain aging and Alzheimer's disease

Bin Wu^{1†} , Juan Zhang^{2†} , Yao Lu^{1*} , and Qiang Liu^{3,4,5*} 

¹Department of Anesthesiology, The First Affiliated Hospital of Anhui Medical University, Key Laboratory of Anesthesia and Perioperative Medicine of Anhui Higher Education Institutes, Anhui Medical University, Hefei, China

²Department of Pathophysiology, School of Basic Medical Sciences, Wannan Medical College, Wuhu, Anhui, China

³Hefei National Research Center for Physical Sciences at the Microscale, Center for Advanced Interdisciplinary Science and Biomedicine of IHM, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China

⁴Anhui Province Key Laboratory of Biomedical Aging Research, University of Science and Technology of China, Hefei, China

⁵Department of Anesthesiology, Institute on Aging and Brain Disorders, The First Affiliated Hospital of USTC, University of Science and Technology of China, Hefei, China

(This article belongs to the Special Issue: *Advanced Neurology 3rd Anniversary Special Issue*)

[†]These authors equally contributed to this work.

*Corresponding authors:

Yao Lu
(luyao@ahmu.edu.cn)
Qiang Liu
(liuq2012@ustc.edu.cn)

Citation: Wu B, Zhang J, Lu Y, Liu Q. Nucleolar alterations in brain aging and Alzheimer's disease. *Adv Neurol.* 2026;5(2):025310085. doi: 10.36922/AN025310085

Received: July 30, 2025

Revised: October 15, 2025

Accepted: October 17, 2025

Published online: November 10, 2025

Copyright: © 2025 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract

The nucleolus is a dynamic, non-membrane-bound nuclear organelle organized into fibrillar and granular components, serving as a central hub for ribosome biogenesis, stress responses, and cell cycle regulation. In brain aging and Alzheimer's disease (AD), it undergoes marked structural and functional alterations. Aging brains commonly exhibit cognitive decline, whereas AD is characterized by neuronal loss and biochemical abnormalities, including extracellular amyloid-beta plaques and tau hyperphosphorylation. Mounting evidence indicates that nucleolar alterations—such as impaired ribosome biogenesis, disrupted proteostasis, and activation of nucleolar stress pathways—occur early in AD pathogenesis. This review summarizes current understanding of nucleolar function, highlights its dysfunction in aging and AD, and discusses its potential as a therapeutic target.

Keywords: Brain aging; Alzheimer's disease; Nucleolus; Structure and function

1. Introduction

1.1. Epidemiology of Alzheimer's disease

Brain aging is commonly associated with progressive cognitive decline, particularly memory impairment, and increased risk for neurodegenerative diseases such as Alzheimer's disease (AD).¹⁻³ Globally, AD affects nearly 60 million individuals, with over 10 million new cases annually.⁴ The prevalence rises sharply with age, affecting more than half of individuals over 85 years old. In China alone, more than 15 million people aged 60 and above are projected to develop AD, representing over 6% of this population group.⁴

Despite its high prevalence, AD remains underdiagnosed, and treatment outcomes are generally poor.⁵

1.2. Pathological features of AD

Clinically, AD manifests as progressive memory and cognitive deficits, severely impairing daily life. Pathologically, AD is characterized by cortical neuronal damage, A β deposition, tau pathology, cholinergic dysfunction, inflammation, and oxidative stress.^{6,7} The classical amyloid cascade hypothesis, while foundational, fails to fully explain the weak correlation between A β burden and symptoms, or the limited efficacy of A β -targeted therapies.⁸

1.3. Nucleolar dysfunction in AD

The nucleolus, long regarded primarily as the site of ribosome synthesis, has emerged as a central player in cellular homeostasis and disease. Structural and functional nucleolar alterations—such as nucleolar size, ribosomal RNA (rRNA) transcription and methylation, and nucleolar stress activation—have been linked to AD pathology.^{9,10} This review aims to synthesize current knowledge on nucleolar biology, describe its alterations in brain aging and AD, and highlight its importance in neurodegeneration.

2. Nucleolar structure and function

2.1. Structure of the nucleolus

The nucleolus is a non-membrane-bound organelle essential for ribosome biogenesis.¹¹ It consists of three main compartments: The fibrillar centers (FC), which are sites of ribosomal DNA (rDNA) transcription and are marked by RNA polymerase I subunit A and upstream binding factor; the dense fibrillar component (DFC), where early rRNA processing occurs and which is marked by fibrillarin (FBL); and the granular component (GC), which hosts ribosomal subunit assembly and is marked by nucleophosmin 1 (NPM1)¹² (Figure 1). In terms of relative volume, the GC occupies the majority of the nucleolus (~75%), the DFC contributes about 20%, whereas the FC represents only ~5%.¹³ Together, these domains coordinate rRNA transcription, processing, and assembly into 40S and 60S ribosomal subunits, which are then exported to the cytoplasm.^{14–16} The nucleolus is highly dynamic: it disassembles during mitosis, then rapidly reassembles via pre-nucleolar bodies at nucleolar organizer regions.^{17,18}

Our previous studies demonstrated that the long nucleolar-specific long non-coding RNA (LoNA) serves as a molecular scaffold to tether NPM1 and FBL, thereby facilitating their liquid–liquid phase separation and driving the formation of compartmentalized nucleolar

structures.¹⁹ Moreover, embryos lacking LoNA experience developmental arrest at the two-cell stage (2C), indicating that LoNA plays a crucial role in nucleolar formation and cellular development¹⁹ (Figure 1).

2.2. Function of the nucleolus

Beyond ribosome production, the nucleolus acts as a hub for stress sensing and signal transduction. Nucleolar activity correlates with protein synthesis demand—reflected in cancer cell proliferation and neuronal growth.²⁰ In neurons, nucleolar size and number correspond to protein synthesis rates required for axonal and dendritic development.^{21–23} Importantly, nucleolar stress can induce divergent effects: triggering apoptosis in developing neurons but conferring resilience in mature neurons.^{24–27}

3. Nucleolar changes during aging

3.1. Morphological changes

Aging alters nucleolar morphology and function. Senescent cells typically display fewer but larger nucleoli compared to proliferating cells.²⁸ Nucleolar size correlates with rDNA transcriptional activity and, intriguingly, lifespan: Smaller nucleoli are observed in long-lived *Caenorhabditis elegans* and *Drosophila* mutants, suggesting a causal role in longevity.²⁹

3.2. Functional changes

Senescence is also linked to impaired ribosome biogenesis, which activates p53 and induces p21-mediated growth arrest. Nucleolar stress, triggered by oxidative damage, DNA damage, or metabolic dysregulation, leads to p53 accumulation and subsequent cell-cycle arrest or apoptosis. The severity of nucleolar stress dictates whether activation of the p53-mediated pathway results in cell-cycle arrest or apoptosis.^{30–33} Stress-induced translocation of nucleolar proteins (e.g., NPM1, FBL) to DNA damage sites further illustrates the nucleolus' role in genome integrity.³⁴

During DNA damage, the FC, DFC, and GC of the nucleolus condense and separate spatially, accompanied by the translocation of nucleolar proteins into the nucleoplasm. Many of these proteins rapidly relocate to DNA damage sites, where they assemble into repair complexes or act as scaffolds to facilitate the recruitment of DNA repair enzymes.³² In response to oxidative or ribotoxin stress, rRNA synthesis is efficiently suppressed. This stress response triggers signaling cascades that converge on c-Jun N-terminal kinase 2 (JNK2), which halts cell-cycle progression until the stress is resolved or, if unresolved, drives the cell toward apoptosis. In addition, JNK2 activation during nucleolar stress suppresses rRNA synthesis by phosphorylating TIF-1A and inhibiting

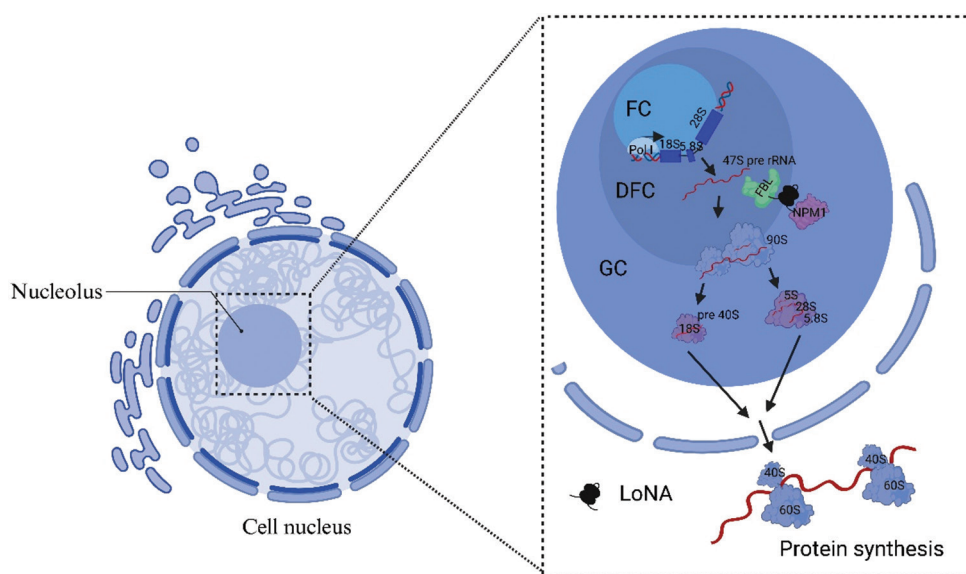


Figure 1. The nucleolus comprises three distinct substructures: the FC, the DFC, and the GC. The nucleolus primarily orchestrates rRNA transcription and processing, as well as the assembly of ribosomal subunits. Long non-coding RNA LoNA plays a crucial role in maintaining nucleolar structural integrity and supporting its proper function. Image created by the authors.

Abbreviations: FC: Fibrillar center; DFC: Dense fibrillar component; GC: Granular component; rRNA: Ribosomal RNA; LoNA: Long non-coding RNA.

polymerase I, thereby linking stress signaling to ribosome shutdown³⁵ (Figure 2).

Together, these findings highlight that nucleolar changes during aging are multifaceted, encompassing alterations in size, transcriptional activity, protein mobilization, and stress signaling. Such changes are not only hallmarks of cellular aging but also contributors to the decline of neuronal resilience, setting the stage for age-associated neurodegenerative diseases (Table 1).

4. Nucleolar changes in AD

4.1. Morphological changes

Neuronal function relies heavily on protein synthesis, making the nucleolus essential for neuronal health. In AD, a variety of structural and functional changes in the nucleolus have been observed. Morphologically, studies have reported increased nucleolar volume in asymptomatic individuals at risk for AD, which is thought to reflect early compensatory upregulation of rRNA transcription.^{36,37} By contrast, in symptomatic AD patients, nucleoli appear smaller and less active, suggesting a decline in ribosome biogenesis as the disease progresses.^{38,39}

4.2. rRNA levels

Alterations in ribosomal RNA further support this notion. Levels of 18S, 28S, 5S, and 5.8S rRNAs are reduced in AD brains and are even detectable in peripheral blood, often accompanied by oxidative modifications that impair their stability and function.³⁹⁻⁴² Such changes compromise

Table 1. Nucleolar alterations in aging brain and Alzheimer's disease

Change type	Specific manifestations	Possible mechanism
Nucleolar size	Nucleolar atrophy	Ribosome biogenesis capacity
Ribosome biogenesis capacity	rRNA levels	rRNA transcription and processing
Ribosome dysfunction	Protein synthesis malfunction	Ribosome assembly
Nucleolar stress response	JNK2, p53 upregulation	DNA damage, oxidative stress, apoptosis
Nucleolar protein abnormality	Ribosome malfunction	Nucleolar protein expression and distribution

Abbreviations: rRNA: Ribosomal RNA; JNK2: c-Jun N-terminal kinase 2.

ribosome assembly and global protein synthesis, potentially undermining synaptic maintenance and plasticity. Beyond rRNA itself, nucleolar non-coding RNAs also play important roles.⁴³ The nucleolar long non-coding RNA LoNA, for instance, regulates rRNA transcription and ribosome biogenesis. Dysregulation of LoNA in AD models impairs memory, whereas its normalization rescues cognitive deficits, highlighting a functional link between nucleolar non-coding RNA regulation and disease pathology.⁴⁴

4.3. Nucleolar proteins

Nucleolar protein alterations also contribute to nucleolar dysfunction in AD. Nucleolin, which facilitates ribosome

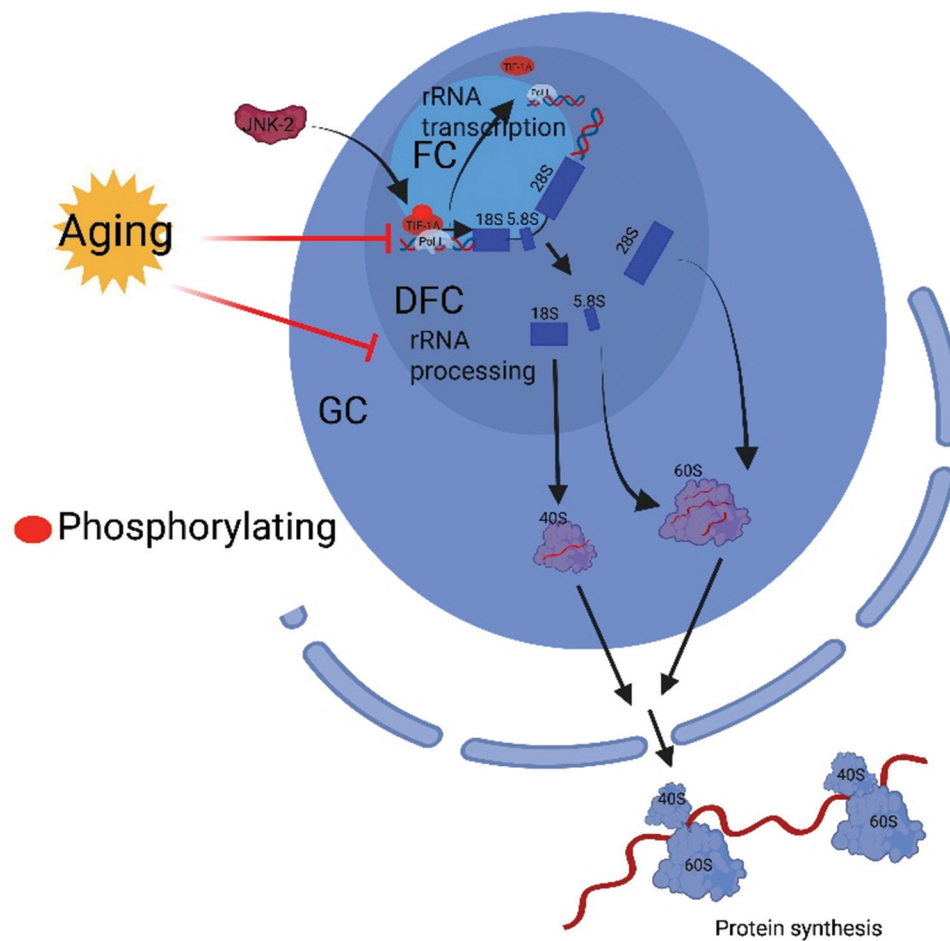


Figure 2. Aging suppresses RNA polymerase I activity, thereby reducing rRNA transcription and the synthesis of the 40S and 60S ribosomal subunits, and ultimately resulting in diminished rRNA production and functional capacity. Image created by the authors.

Abbreviations: DFC: Dense fibrillar component; FC: Fibrillar center; GC: Granular component; rRNA: Ribosomal RNA.

assembly and stabilizes *APP* messenger RNA,⁴⁵ shows region- and stage-specific differences: Its expression is reduced in the frontal cortex of late-stage AD patients but elevated in the somatosensory cortex of early-stage *APP/PS1* transgenic mice.¹⁰ Another critical protein, FBL, methylates rRNA and thereby modulates ribosome structure and function. Dysregulation of FBL contributes to rDNA hypermethylation and ribosome dysfunction, with downstream effects on synaptic activity.^{44,46} Ribosomal proteins and regulators such as S6K1 are similarly perturbed in AD brains, further impairing protein synthesis capacity in neurons.⁴⁷

4.4. Nucleolar stress

Finally, nucleolar stress responses are closely intertwined with AD pathology. Oxidative damage, metabolic dysregulation, and ribotoxin exposure activate stress pathways, leading to rRNA suppression and

redistribution of nucleolar proteins. These processes engage signaling cascades involving JNK2 and p53, both of which influence neuronal fate.^{48,49} In addition, abnormal aggregation of G-quadruplex DNA structures within the nucleolus has been observed in AD, correlating with tau hyperphosphorylation and synaptic dysfunction. Such stress-related changes not only disrupt ribosome production but also amplify pathological signaling cascades central to neurodegeneration⁵⁰ (Figure 3).

Taken together, these lines of evidence demonstrate that nucleolar dysfunction in AD is multifaceted, encompassing structural alterations, impaired rRNA metabolism, dysregulation of nucleolar proteins and non-coding RNAs, and maladaptive stress responses. These interconnected disturbances converge on impaired protein synthesis and disrupted neuronal homeostasis, reinforcing the idea that the nucleolus plays a pivotal role in the onset and progression of AD (Table 1).

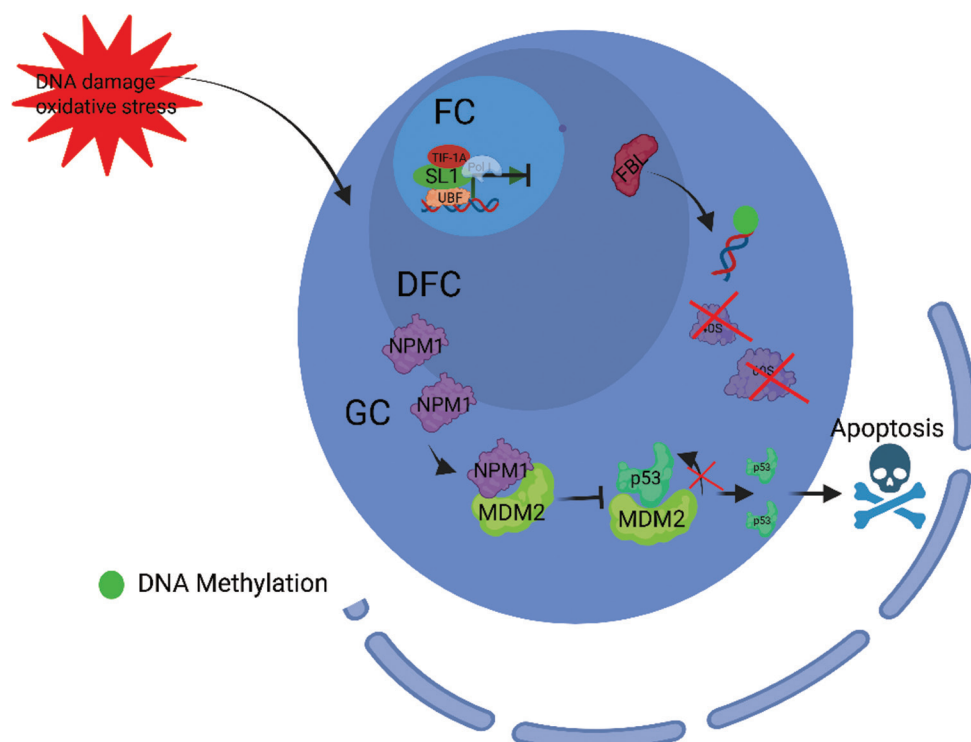


Figure 3. Nucleolar stress induces the translocation of key nucleolar proteins, including NPM1, UBF, and FBL, leading to impaired rRNA synthesis and disruption of 40S and 60S ribosomal subunit biogenesis. Mislocalization of NPM1 promotes p53 stabilization and activation, ultimately inducing apoptosis. Image created by the authors.

Abbreviations: NPM1: Nucleophosmin 1; UBF: Upstream binding factor; FBL: Fibrillarin; DFC: Dense fibrillar component; FC: Fibrillar center; GC: Granular component; rRNA: Ribosomal RNA.

5. Conclusion

The nucleolus is not only a site of ribosome production but also a central hub that integrates signals of cellular stress, genome stability, and protein homeostasis. Evidence from aging and AD highlights that nucleolar alterations—whether in rRNA transcription, ribosomal assembly, or stress pathway activation—appear early and may act as drivers rather than mere consequences of neuronal decline. By disrupting protein synthesis and altering stress responses, these changes compromise neuronal resilience and set the stage for neurodegeneration.

Neurons are particularly susceptible to nucleolar dysfunction during aging and in AD. Structural and molecular alterations in nucleolus—including nucleolar shrinkage, reduced rRNA transcription, and disruption of nucleolar proteins such as FBL and NPM1—are especially predominant in pyramidal neurons of the hippocampus and cortex, which are highly vulnerable to age- and AD-related pathology. These nucleolar changes correlate with early synaptic and metabolic decline and can occur before overt neuronal loss.

Recognizing the nucleolus as both a marker and mediator of pathological processes opens new

opportunities for intervention. Future work should integrate molecular biology, genetics, and neuroscience to dissect its precise roles and explore therapeutic strategies. Targeting nucleolar pathways may ultimately provide a means to preserve proteostasis, protect neuronal networks, and improve clinical outcomes in AD and age-related cognitive decline.

Acknowledgments

None.

Funding

This work was supported by the National Key R&D Program of China (2021YFA0804900 and 2020YFA0509300), the National Natural Science Foundation of China (82125009, 82330045, 82071185, 92149303, 32121002 and 82470279), the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB39000000), CAS Project for Young Scientists in Basic Research (YSBR-013), Plans for Major Provincial Science & Technology Projects (202303a07020004), Research Funds of Center for Advanced Interdisciplinary Science and Biomedicine of IHM (QYZD20220003), the Major Frontier Research

Project of the University of Science and Technology of China (LS9100000002), the Hefei Comprehensive National Science Center Hefei Brain Project, and the USTC Research Funds of the Double First-Class Initiative.

Conflict of interest

Qiang Liu is an Editorial Board Member of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: Qiang Liu, Yao Lu

Visualization: Bin Wu

Writing—original draft: Bin Wu

Writing—review & editing: Juan Zhang, Yao Lu, Qiang Liu

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

- Livingston G, Huntley J, Sommerlad A, *et al.* Dementia prevention, intervention, and care: 2020 report of the lancet commission. *Lancet*. 2020;396(10248):413–446.
doi: 10.1016/s0140-6736(20)30367-6
- Gaspar-Silva F, Trigo D, Magalhaes J. Ageing in the brain: Mechanisms and rejuvenating strategies. *Cell Mol Life Sci*. 2023;80(7):190.
doi: 10.1007/s00018-023-04832-6
- Huang S, Lu Y, Fang W, Huang Y, Li Q, Xu Z. Neurodegenerative diseases and neuroinflammation-induced apoptosis. *Open Life Sci*. 2025;20(1):20221051.
doi: 10.1515/biol-2022-1051
- Jia L, Du Y, Chu L, *et al.* Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60 years or older in China: A cross-sectional study. *Lancet Public Health*. 2020;5(12):e661–e671.
doi: 10.1016/s2468-2667(20)30185-7
- Jin S, Lu W, Zhang J, *et al.* The mechanisms, hallmarks, and therapies for brain aging and age-related dementia. *Sci Bull (Beijing)*. 2024;69(23):3756–3776.
doi: 10.1016/j.scib.2024.09.005
- Twarowski B, Herbet M. Inflammatory processes in Alzheimer's disease-pathomechanism, diagnosis and treatment: A review. *Int J Mol Sci*. 2023;24(7):6518.
doi: 10.3390/ijms24076518
- Neary D, Snowden JS, Mann DM, *et al.* Alzheimer's disease: A correlative study. *J Neurol Neurosurg Psychiatry*. 1986;49(3):229–237.
doi: 10.1136/jnnp.49.3.229
- Li D, Zhang J, Liu Q. Mechanistic insights on non-coding RNAs in learning and memory. *Sci Bull (Beijing)*. 2023;68(15):1591–1594.
doi: 10.1016/j.scib.2023.07.005
- Zhou H, Xia Y, Zhu R, *et al.* Ribosomal DNA and neurological disorders. *Curr Mol Med*. 2025;25(5):556–566.
doi: 10.2174/0115665240292079240513093708
- Hernández-Ortega K, Garcia-Esparcia P, Gil L, Lucas JJ, Ferrer I. Altered machinery of protein synthesis in Alzheimer's: From the nucleolus to the ribosome. *Brain Pathol*. 2016;26(5):593–605.
doi: 10.1111/bpa.12335
- Garland W, Comet I, Wu M, *et al.* A functional link between nuclear RNA decay and transcriptional control mediated by the polycomb repressive complex 2. *Cell Rep*. 2019;29(7):1800–1811.e6.
doi: 10.1016/j.celrep.2019.10.011
- Lafontaine DLJ, Riback JA, Bascetin R, Brangwynne CP. The nucleolus as a multiphase liquid condensate. *Nat Rev Mol Cell Biol*. 2021;22(3):165–182.
doi: 10.1038/s41580-020-0272-6
- Hua L, Yan D, Wan C, Hu B. Nucleolus and nucleolar stress: From cell fate decision to disease development. *Cells*. 2022;11(19):3017.
doi: 10.3390/cells11193017
- Puvion-Dutilleul F, Puvion E, Bachellerie JP. Early stages of pre-rRNA formation within the nucleolar ultrastructure of mouse cells studied by *in situ* hybridization with a 5'ETS leader probe. *Chromosoma*. 1997;105(7-8):496–505.
doi: 10.1007/bf02510486
- Hernandez-Verdun D. Assembly and disassembly of the nucleolus during the cell cycle. *Nucleus*. 2011;2(3):189–194.
doi: 10.4161/nucl.2.3.16246
- Olson MO, Dundr M, Szebeni A. The nucleolus: An old factory with unexpected capabilities. *Trends Cell Biol*. 2000;10(5):189–196.
doi: 10.1016/s0962-8924(00)01738-4

17. Carron C, Balor S, Delavoie F, *et al.* Post-mitotic dynamics of pre-nucleolar bodies is driven by pre-rRNA processing. *J Cell Sci.* 2012;125(Pt 19):4532-4542.
doi: 10.1242/jcs.106419
18. Sen Gupta A, Sengupta K. Lamin B2 modulates nucleolar morphology, dynamics, and function. *Mol Cell Biol.* 2017;37(24):e00274-17.
doi: 10.1128/mcb.00274-17
19. Li D, Cao R, Li Q, *et al.* Nucleolus assembly impairment leads to two-cell transcriptional repression via NPM1-mediated PRC2 recruitment. *Nat Struct Mol Biol.* 2023;30(7):914-925.
doi: 10.1038/s41594-023-01003-w
20. Lafita-Navarro MC, Conacci-Sorrell M. Nucleolar stress: From development to cancer. *Semin Cell Dev Biol.* 2023;136:64-74.
doi: 10.1016/j.semcdb.2022.04.001
21. Casafont I, Bengoechea R, Navascués J, Pena E, Berciano MT, Lafarga M. The giant fibrillar center: A nucleolar structure enriched in upstream binding factor (UBF) that appears in transcriptionally more active sensory ganglia neurons. *J Struct Biol.* 2007;159(3):451-461.
doi: 10.1016/j.jsb.2007.05.004
22. Lafarga M, Villegas J, Crespo D. Changes in nucleolar morphology and volume of the supraoptic nucleus neurons during postnatal development of the rat. *Brain Res.* 1985;354(2):310-313.
doi: 10.1016/0165-3806(85)90185-3
23. Clark P, Jones KJ, LaVelle A. Ultrastructural and morphometric analysis of nucleolar and nuclear changes during the early growth period in hamster facial neurons. *J Comp Neurol.* 1990;302(4):749-760.
doi: 10.1002/cne.903020407
24. Pietrzak M, Smith SC, Geraldts JT, Hagg T, Gomes C, Hetman M. Nucleolar disruption and apoptosis are distinct neuronal responses to etoposide-induced DNA damage. *J Neurochem.* 2011;117(6):1033-1046.
doi: 10.1111/j.1471-4159.2011.07279.x
25. Parlato R, Kreiner G, Erdmann G, *et al.* Activation of an endogenous suicide response after perturbation of rRNA synthesis leads to neurodegeneration in mice. *J Neurosci.* 2008;28(48):12759-12764.
doi: 10.1523/jneurosci.2439-08.2008
26. Casafont I, Palanca A, Lafarga V, Berciano MT, Lafarga M. Effect of ionizing radiation in sensory ganglion neurons: Organization and dynamics of nuclear compartments of DNA damage/repair and their relationship with transcription and cell cycle. *Acta Neuropathol.* 2011;122(4):481-493.
doi: 10.1007/s00401-011-0869-0
27. Zhang H, Wang JC, Liu LF. Involvement of DNA topoisomerase I in transcription of human ribosomal RNA genes. *Proc Natl Acad Sci U S A.* 1988;85(4):1060-1064.
doi: 10.1073/pnas.85.4.1060
28. Bemiller PM, Lee LH. Nucleolar changes in senescing WI-38 cells. *Mech Ageing Dev.* 1978;8(6):417-427.
doi: 10.1016/0047-6374(78)90041-6
29. Tiku V, Jain C, Raz Y, *et al.* Small nucleoli are a cellular hallmark of longevity. *Nat Commun.* 2017;8:16083.
doi: 10.1038/ncomms16083
30. Yang K, Wang M, Zhao Y, *et al.* A redox mechanism underlying nucleolar stress sensing by nucleophosmin. *Nat Commun.* 2016;7:13599.
doi: 10.1038/ncomms13599
31. Marquez-Lona EM, Tan Z, Schreiber SS. Nucleolar stress characterized by downregulation of nucleophosmin: A novel cause of neuronal degeneration. *Biochem Biophys Res Commun.* 2012;417(1):514-520.
doi: 10.1016/j.bbrc.2011.11.152
32. Tsekrekou M, Stratigi K, Chatzinikolaou G. The nucleolus: In genome maintenance and repair. *Int J Mol Sci.* 2017;18(7):1411.
doi: 10.3390/ijms18071411
33. Boulon S, Westman BJ, Hutten S, Boisvert FM, Lamond AI. The nucleolus under stress. *Mol Cell.* 2010;40(2):216-227.
doi: 10.1016/j.molcel.2010.09.024
34. Lee C, Smith BA, Bandyopadhyay K, Gjerset RA. DNA damage disrupts the p14ARF-B23(nucleophosmin) interaction and triggers a transient subnuclear redistribution of p14ARF. *Cancer Res.* 2005;65(21):9834-9842.
doi: 10.1158/0008-5472.Can-05-1759
35. Ren X, Hu B, Song M, *et al.* Maintenance of nucleolar homeostasis by CBX4 alleviates senescence and osteoarthritis. *Cell Rep.* 2019;26(13):3643-3656.e7.
doi: 10.1016/j.celrep.2019.02.088
36. Iacono D, O'Brien R, Resnick SM, *et al.* Neuronal hypertrophy in asymptomatic Alzheimer disease. *J Neuropathol Exp Neurol.* 2008;67(6):578-589.
doi: 10.1097/NEN.0b013e3181772794
37. Mann DM, Marcyniuk B, Yates PO, Neary D, Snowden JS. The progression of the pathological changes of Alzheimer's disease in frontal and temporal neocortex examined both at biopsy and at autopsy. *Neuropathol Appl Neurobiol.* 1988;14(3):177-195.
doi: 10.1111/j.1365-2990.1988.tb00880.x
38. Honda K, Smith MA, Zhu X, *et al.* Ribosomal RNA in Alzheimer disease is oxidized by bound redox-active iron.

- J Biol Chem.* 2005;280(22):20978-20986.
doi: 10.1074/jbc.M500526200
39. Ding Q, Markesbery WR, Cekarini V, Keller JN. Decreased RNA, and increased RNA oxidation, in ribosomes from early Alzheimer's disease. *Neurochem Res.* 2006;31(5):705-710.
doi: 10.1007/s11064-006-9071-5
40. Ding Q, Markesbery WR, Chen Q, Li F, Keller JN. Ribosome dysfunction is an early event in Alzheimer's disease. *J Neurosci.* 2005;25(40):9171-9175.
doi: 10.1523/jneurosci.3040-05.2005
41. Da Silva AM, Payão SL, Borsatto B, Bertolucci PH, Smith MA. Quantitative evaluation of the rRNA in Alzheimer's disease. *Mech Ageing Dev.* 2000;120(1-3):57-64.
doi: 10.1016/s0047-6374(00)00180-9
42. Tavares WM, Sperança MA, De Labio RW, *et al.* Apolipoprotein E4 allele and ribosomal genes in Alzheimer's disease. *J Alzheimers Dis.* 2004;6(4):391-395; discussion 443-449.
doi: 10.3233/jad-2004-6406
43. Mercer TR, Dinger ME, Sunkin SM, Mehler MF, Mattick JS. Specific expression of long noncoding RNAs in the mouse brain. *Proc Natl Acad Sci U S A.* 2008;105(2):716-721.
doi: 10.1073/pnas.0706729105
44. Li D, Zhang J, Wang M, *et al.* Activity dependent LoNA regulates translation by coordinating rRNA transcription and methylation. *Nat Commun.* 2018;9(1):1726.
doi: 10.1038/s41467-018-04072-4
45. Zaidi SH, Malter JS. Nucleolin and heterogeneous nuclear ribonucleoprotein C proteins specifically interact with the 3'-untranslated region of amyloid protein precursor mRNA. *J Biol Chem.* 1995;270(29):17292-17298.
doi: 10.1074/jbc.270.29.17292
46. Lin J, Lai S, Jia R, *et al.* Structural basis for site-specific ribose methylation by box C/D RNA protein complexes. *Nature.* 2011;469(7331):559-563.
doi: 10.1038/nature09688
47. Caccamo A, Branca C, Talboom JS, *et al.* Reducing ribosomal protein S6 kinase 1 expression improves spatial memory and synaptic plasticity in a mouse model of Alzheimer's disease. *J Neurosci.* 2015;35(41):14042-14056.
doi: 10.1523/jneurosci.2781-15.2015
48. Zhu X, Raina AK, Rottkamp CA, *et al.* Activation and redistribution of c-jun N-terminal kinase/stress activated protein kinase in degenerating neurons in Alzheimer's disease. *J Neurochem.* 2001;76(2):435-441.
doi: 10.1046/j.1471-4159.2001.00046.x
49. Proctor CJ, Gray DA. GSK3 and p53 - is there a link in Alzheimer's disease? *Mol Neurodegener.* 2010;5:7.
doi: 10.1186/1750-1326-5-7
50. Comptdaer T, Tardivel M, Schirmer C, Buée L, Galas MC. Cell redistribution of G quadruplex-structured DNA is associated with morphological changes of nuclei and nucleoli in neurons during tau pathology progression. *Brain Pathol.* 2025;35(2):e13262.
doi: 10.1111/bpa.13262