REVIEW

Brain organoids and insights on human evolution [version 1; peer review: 4 approved]

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Abstract

Human brain organoids, generated from pluripotent stem cells, have emerged as a promising technique for modeling early stages of human neurodevelopment in controlled laboratory conditions. Although the applications for disease modeling in a dish have become routine, the use of these brain organoids as evolutionary tools is only now getting momentum. Here, we will review the current state of the art on the use of brain organoids from different species and the molecular and cellular insights generated from these studies. Besides, we will discuss how this model might be beneficial for human health and the limitations and future perspectives of this technology.

Keywords

brain organoids, evolution, pluripotent stem cells

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Introduction

What is it that makes us uniquely human? Among several features of our species, perhaps the most impactful characteristic consists of our sophisticated brains and all the abilities and advanced lifestyles we all enjoy. However, a complex brain came with a cost. The vulnerability for human-specific neurological disorders might well be an undesired evolutionary trade-off. Although many genetic mutations might also cause diseases in other animals, the genomic landscape of humans makes our species more susceptible to certain neurological disorders.

Gaining a clearer understanding of human brain evolution is crucial to interpreting how human genetic variants lead to disease. Therefore, understanding the evolutionary path of the modern human brain will likely illuminate the origins of conditions such as autism, dementia, or schizophrenia, which are considerable burdens to all present and future human societies.

Our knowledge of human brain development is deficient and there are gaps in the critical steps leading to the cellular organization and the formation of functional networks that are the basis of cognition. The limited accessibility of the human (and also non-human primate, or NHP) brain has blocked our understanding of neurodevelopment, especially at very early stages. During embryogenesis, a limited number of pluripotent embryonic stem cells will give rise to a multi-cellular and complex nervous system in the brain, which orchestrates many of the autonomous and non-autonomous functions of the body. In utero experimental access to ape brains is not always possible. Instead, scientists have relied on less invasive passive alternatives, such as ultrasound and functional imaging. Most of our understanding of normal and pathological brain conditions comes from postmortem tissues that represent only a blurry snapshot of a highly dynamic tissue. Also, the neuroanatomical and functional heterogeneity that individuals have because of their genetic and environmental backgrounds adds another obstacle to fully understanding the typical and unhealthy progression of neurodevelopment.

Brain organoids, generated from pluripotent stem cells, are multi-cellular, three-dimensional self-assemble miniaturized structures that mimic the dynamic organization and molecular profile of the developing human embryonic and fetal brain. These structures can grow free floating in media or embedded in matrigel and develop different brain regions using endogenous patterning cues. Alternatively, cells could be patterned early on by exposure to specific cocktails of factors, coaxing the identity of the cells toward a specific brain region. Differently patterned organoids independently created could be fused, exchanging signals among the different brain regions, stimulating cell exchange or reciprocal projections. The “lego-organoid” approach can recreate specific circuit formations in a more controlled and reproducible fashion than non-patterned cerebral organoids.

Brain organoids have recently contributed to the understanding of several neurological conditions (reviewed extensively in), including typically human conditions such as schizophrenia and autism. Interestingly, the fact that brain organoids can be generated from induced pluripotent stem cells (iPSCs), reprogrammed from somatic cells of any species, offered an unprecedented opportunity to compare early stages of human neurodevelopment with those of other primates, including our closest NHP relatives: the chimpanzees and bonobos. These three species have very similar genomes, including nearly 98% of alignable genomic sequence. However, cellular and molecular phenotypes, especially at similar stages of development, are difficult to establish, mainly owing to limited access to live embryonic material from humans and NHPs. Thus, the study and manipulation of brain organoids in a dish are novel and promising evolutionary tools.

LINEs might be responsible for human-specific diseases

The first comparative study between human and NHP iPSCs revealed unexpected differential regulation of long interspersed element-1 (L1, also known as LINE-1) endogenous retrotransposons. L1 elements are autonomous mobile elements present in around 20% of the mammalian genomes and have remained active during evolution. Mobilization of L1s can impact the human genome and is associated with several human disorders. Among the top 50 genes that were differentially expressed between human and NHP iPSCs, two L1-restricting factors—APOBEC3B (also known as A3B) and PIWIL2—were found upregulated in human cells. The experimental manipulation of A3B and PIWIL2 levels in the pluripotent stem cells supported a causal inverse relationship with L1 retrotransposition. Increased levels of L1 retrotransposition suggested that NHP-derived iPSCs would be more susceptible or permissive to new insertions. An increased copy number of species-specific L1 elements in the genome of chimpanzees was observed when compared with humans. The data support the idea that increased L1 mobility in NHPs might not be limited to the pluripotent stage and may also occur in the germline during primate evolution. Thus, it is possible to speculate that the activity of L1 elements has differentially shaped the human genome and still has adaptive significance.

The RNA from L1 elements might also have an impact on human health. Aicardi–Goutières syndrome (AGS) type I is characterized by a dramatic neuronal loss, leading to lifelong disability. AGS can be caused by mutations in the three-prime repair exonuclease 1 (TREX1) gene. Curiously, rodent models of AGS do not mimic the severe neurological aspect of the human condition. However, AGS-derived brain organoids do mimic the neurodegeneration and striking microcephaly seen during patient neurodevelopment in utero. Neuronal death in the brain organoids was caused, at least partially, by a substantial exposure of type I interferon, a pro-inflammatory cytokine secreted by astrocytes. The innate immune reaction in the astrocytes was triggered by the accumulation of L1 retrotransposons in the cell because of TREX1 absence. L1 elements are different between humans and other animals. Evidence that L1 activity could contribute to other neurological disorders, such as Huntington’s disease, Down syndrome, and Alzheimer’s disease, and aging has recently been provided. It is an attractive hypothesis that the sequence-specific L1 differences might contribute to several human conditions, creating the potential for a more adaptive evolutionary tool.
Emergent viruses and brain defects
Endogenous viruses are not the only ones affecting human evolution. Human brain organoids played an essential role in the causal link demonstration between the Brazilian Zika virus and the microcephaly outbreak in Brazil. The relatively slow human neurodevelopment, compared with that of other experimental animal models mimicked by the human brain organoids in a dish, allowed investigators to dissect how the virus could infect neural progenitor cells leading to defects in the cortical plate\(^4\text{–}^6\). Moreover, brain organoids from NHPs revealed differences in viral replication rates of the Brazilian strain compared with the African Zika virus at the same developmental stage. This observation might suggest that the Zika virus can adapt to different primates. Evidence for specific mutations in the circulating Brazilian Zika virus has emerged\(^7\) but it is unclear whether these variants were responsible for the dramatic phenotypes seen in the affected human babies. The abundance of human brain organoids was also a positive feature to rapidly screen for drugs that could prevent infection\(^8,^9\) or block viral replication and eventual vertical transmission\(^10\).

Exploring cortical development
In the past, testing hypotheses about human brain evolution was restricted to manipulations in animals or non-relevant cell types. Owing to cellular reprogramming, it is now possible to compare differences and similarities between human neurodevelopment and that of other primates without the use of embryonic materials that are ethically and technically difficult to access\(^10\text{–}^11\). The ability to create cortical brain organoids from human and other NHP iPSCs provides a unique opportunity to study the expansion of the neocortex in a dish\(^12\text{–}^13\). By contrasting brain organoids of humans with those of chimpanzees, it was possible to determine a subtle differentiation between timing and lengthening of prometaphase-metaphase in human apical mitosis that is specific to proliferating neural progenitor cells\(^14\text{–}^16\). It is possible that subtle differences at very early stages have a more dramatic impact later in development and thus set humans apart from other primates.

Cortical tissues generated from human, chimpanzee, orangutan, and rhesus iPSC-derived brain organoids were also used for a dynamic transcriptional analysis\(^17\). Several long non-coding RNAs (lncRNAs) were detected in specific cell types and stages of differentiation in all of the species. LncRNAs are implicated in several molecular mechanisms, including the regulation of neurodevelopment\(^18\text{–}^19\). The conservation of pattern expression on these tissue-specific lncRNAs in all of these primates indicates a possible role in transition stages during neurodevelopment. Another recent work that contrasted brain organoids from human and NHP iPSCs also described gene network conservation among primates while identifying a set of 261 genes that are human-specific\(^20\). Some of these genes overlap with recent chromosomal segmental duplications\(^21\). Interestingly, increased activation of the PI3K/AKT/mTOR pathway was validated in the radial glia cells of the outer subventricular zone of human fetal brain tissues, possibly contributing to the neocortex expansion during evolution. The creation of a “brain organoid zoo”, which has representatives of different primates and other species, might help us to resolve critical molecular and cellular steps to comprehend brain evolution better.

Discussion and future perspectives
Our natural interest in understanding the processes that make us human goes beyond mere anthropocentrism and philosophical debates about the human condition. Novel knowledge gained from interspecies comparisons can potentially contribute to biomedical advances. For example, humans and other primates can be distinguished by AIDS progression\(^22\), malaria vulnerability (immunity against \textit{Plasmodium falciparum})\(^13\), Alzheimer’s disease (absence of neurofibrillary tangles)\(^23\), and susceptibility to certain cancers\(^24\) as well as other differences\(^24\text{–}^45,^49\). The identification and characterization of the cellular and molecular mechanism that distinguishes humans from our closest relatives at early stages of embryogenesis and in specific types of cells are likely to become a new resource for evolutionary studies\(^26\).

In this context, recent advances in iPSC-derived neural progenitor cells and brain organoids are an attractive tool to dissect cellular and molecular events that contribute to the uniqueness of the human brain. However, this artificial \textit{in vitro} approach is not without serious inherent limitations. Most comparative studies are standardizing the growth of the brain organoids using human culture conditions. This “humanized” situation is likely masking important differences among species. The use of “neutral backgrounds”, such as transplanting different primate cells in the mouse brain\(^4\), could mitigate this concern. Other limitations are intrinsic to the brain organoid model: lack of specific cell types, cellular stress, organized brain regions, and endogenous vascularization. The use of patterned brain organoids might help to reduce experimental variability and increase confidence in the data, especially when differences are subtle. Thus, owing to these limitations, validation or confirmation of findings in primary tissues\(^56,^65\) or even intact functional brain\(^66\) is the gold standard in this field.

Nonetheless, it is expected that some of these technical shortcomings might be resolved in the next few years (reviewed in \textit{18,69}). In the future, evolutionary studies using brain organoids would benefit from genome editing for candidate approaches. More sophisticated comparisons will also incorporate functional readouts, such as the emergence of network activity and oscillatory waves in long-term, mature brain organoids\(^68\). Finally, the perspective to extrapolate the comparative approach of modern humans to other extinct hominins, such as Neanderthals and Denisovans, by using human brain organoids carrying ancestral genetic variants will lead to an entire new field\(^69\).

Abbreviations
AGS, Aicardi-Goutières syndrome; iPSC, induced pluripotent stem cell; L1 or LINE-1, long interspersed element-1; lncRNA, long non-coding RNA; NHP, non-human primate; TREX1, three-prime repair exonuclease I.
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References

1. Dennis MY, Eichler EE: Human adaptation and evolution by segmental duplication, Curr Opin Genet Dev. 2016; 41: 44–52. Published Abstract | Publisher Full Text | Free Full Text

2. Turner TN, Eichler EE: The Role of De Novo Noncoding Regulatory Mutations in Neurodevelopmental Disorders, Trends Neurosci. 2019; 42(2): 115–27. Published Abstract | Publisher Full Text | Free Full Text

3. Geschwind DH, Flint JJ: Genetics and genomics of psychiatric disease. Science. 2015; 349(6255): 1489–94. Published Abstract | Publisher Full Text | Free Full Text

4. Einak M, Watanabe K, Matsuo-Takasaki M, et al.: Self-organized formation of polarized cortical tissues from ESCs and its active manipulation by extrinsic signals. Cell Stem Cell. 2008; 3(5): 519–32. Published Abstract | Publisher Full Text | Free Full Text

5. Kadoshima T, Sakaguchi H, Nakano T, et al.: Self-organization of axial polarity, inside-out layer pattern, and species-specific progenitor dynamics in human ES cell-derived neocortex. Proc Natl Acad Sci U S A. 2013; 110(50): 20284–9. Published Abstract | Publisher Full Text | Free Full Text

6. Lancaster MA, Renner M, Martin CA, et al.: Cerebral organoids model human brain development and microcephaly. Nature. 2013; 501(7467): 373–9. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

7. Camp JG, Badsha F, Florio M, et al.: Human cerebral organoids recapitulate gene expression programs of fetal neocortex development. Proc Natl Acad Sci U S A. 2015; 112(51): 15672–7. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

8. Luo C, Lancaster MA, Castanon R, et al.: Cerebral Organoids Recapitulate Epigenomic Signatures of the Human Fetal Brain. Cell Rep. 2016; 17(12): 3136–46. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

9. Giandomenico SL, Lancaster MA: Probing human brain evolution and development in organoids. Curr Opin Cell Biol. 2017; 44: 36–43. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

10. Renner M, Lancaster MA, Bian S, et al.: Self-organized developmental patterning and differentiation in cerebral organoids. EMBO J. 2017; 36(10): 1316–29. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

11. Papa AM, Sloan SA, Clarke LE, et al.: Functional cortical neurons and astrocytes from human pluripotent stem cells in 3D culture. Nat Methods. 2015; 12(7): 671–8. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

12. Je J, Xiao Y, Sun AX, et al.: Midbrain-like Organoids from Human Pluripotent Stem Cells Contain Functional Dopaminergic and Neuromelanin-Producing Neurons. Cell Stem Cell. 2016; 19(2): 248–57. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

13. Watanabe K, Kamiya D, Nishiyama A, et al.: Directed differentiation of telencephalic precursors from embryonic stem cells. Nat Neurosci. 2005; 8(3): 288–96. Published Abstract | Publisher Full Text | F1000 Recommendation

14. Sloan SA, Andersen J, Papa AM, et al.: Generation and assembly of human brain region-specific three-dimensional cultures. Nat Protoc. 2018; 13(9): 2062–85. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

15. Xiang Y, Yoshiaki T, Patterson B, et al.: Generation and Fusion of Human Cortical and Medial Ganglionic Eminence Brain Organoids. Curr Protoc Stem Cell Biol. 2018; 4(1): e1. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

16. Xiang Y, Tanaka Y, Patterson B, et al.: Fusion of Regionally Specified hiPSC-Derived Organoids Models Human Brain Development and Interneuron Migration. Cell Stem Cell. 2017; 21(3): 383–398.e7. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

17. Xiang Y, Tanaka Y, Cakir B, et al.: hESC-Derived Thalamic Organoids Form Reciprocal Projections When Fused with Cortical Organoids. Cell Stem Cell. 2019; 24(3): 487–497.e7. Published Abstract | Publisher Full Text | F1000 Recommendation

18. Trejiljo CA, Muoti AR: Brain Organoids and the Study of Neurodevelopment. Trends Mol Med. 2018; 24(12): 982–90. PubMed Abstract | Publisher Full Text | Free Full Text

19. Chen Hl, Song H, Ming GL: Applications of Human Brain Organoids to Clinical Problems. Dev Dyn. 2019; 248(1): 59–64. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

20. Sun AX, Ng HH, Tan EK: Translational potential of human brain organoids. Ann Clin Transl Neurol. 2018; 5(2): 226–35. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

21. Stachowiak EK, Benson CA, Narla ST, et al.: Cerebral organoids reveal early cortical maldevelopment in schizophrenia-computational anatomy and genomics, role of FGFR1. Transl Psychiatry. 2017; 7(11): e6. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

22. Manani J, Coppola G, Zhang P, et al.: FOXG1-Dependent Dysregulation of GABA/Glutamate Neuron Differentiation in Autism Spectrum Disorders. Cell. 2015; 162(2): 375–90. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

23. Takahashi K, Tanabe K, Okumura K, et al.: Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007; 131(5): 861–72. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

24. Oki K, Ichisaka T, Yamanaka S: Generation of germline-competent induced pluripotent stem cells. Nature. 2007; 448(7151): 313–7. PubMed Abstract | Publisher Full Text | F1000 Recommendation

25. Hryvko-Mihic B, Marchetto MC, Gage FH, et al.: Novel tools, classic techniques: evolutionary studies using primate pluripotent stem cells. Biol Psychiatry. 2014; 75(12): 929–35. PubMed Abstract | Publisher Full Text | Free Full Text

26. Hryvko-Mihic B, Bienvenu T, Stefancic L, et al.: Evolution, development, and plasticity of the human brain: from molecules to bones. Front Hum Neurosci. 2013; 7: 707. PubMed Abstract | Publisher Full Text | Free Full Text

27. Mora-Bermúdez F, Badsha F, Kanton S, et al.: Differences and similarities between human and chimpanzee neural progenitors during cerebral cortex development. eLife. 2016; 5: e11863. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

28. Prüfer K, Munch K, Hellmann I, et al.: The bonobo genome compared with the chimpanzee and human genomes. Nature. 2012; 486(7404): 527–31. PubMed Abstract | Publisher Full Text | Free Full Text

29. Marchetto MCN, Narvaez I, Deri AM, et al.: Differential L1 regulation in pluripotent stem cells of humans and apes. Nature. 2013; 503(7477): 525–9. PubMed Abstract | Publisher Full Text | Free Full Text

30. Lander ES, Linton LM, Birren B, et al.: Initial sequencing and analysis of the human genome. Nature. 2001; 409(6822): 860–921. PubMed Abstract | Publisher Full Text | F1000 Recommendation

31. Gibbs RA, Weinstock GM, Metzker ML, et al.: Genome sequence of the Brown Norway rat yields insights into mammalian evolution. Nature. 2004; 428(6982): 493–521. PubMed Abstract | Publisher Full Text | F1000 Recommendation

32. Kuznetsov VV, Mochida T, Takahashi K, et al.: The bonobo and human genomes: differences and similarities. Nature. 2009; 457(7229): 342–50. PubMed Abstract | Publisher Full Text | F1000 Recommendation

33. Kuznetsov VV, Mochida T, Takahashi K, et al.: The bonobo and human genomes: differences and similarities. Nature. 2009; 457(7229): 342–50. PubMed Abstract | Publisher Full Text | F1000 Recommendation

34. Thomas CA, Paquola AC, Muoti AR: LINE-1 retrotransposition in the nervous system. Ann Rev Cell Dev Biol. 2012; 28: 555–73. PubMed Abstract | Publisher Full Text | Free Full Text

35. Suarez NA, Macia A, Muoti AR: LINE-1 retrotransposons in healthy and...
36. Crow YJ, Chase DS, Lowenstein Schmidt J, et al.: Characterization of human disease phenotypes associated with mutations in TREP1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR, and IFIH1. Am J Med Genet A. 2015; 167A(2): 296–312.

37. Crow YJ, Manel N: Aicardi-Goutières syndrome and the type I interferonopathies. Semin Cell Dev Biol. 2015; 26(5): 429–40.

38. Gall A, Treuting P, Elkon KB, et al.: Autoimmunity initiates in nonhematopoietic cells and promotes age-associated inflammation. JCI Insight. 2017; 2(12): e94157.

39. Thomas CA, Tejwani L, Trujillo CA, et al.: Modeling of TREP1-Dependent Autoimmune Disease using Human Stem Cells Highlights L1 Accumulation as a Source of Neuroinflammation. Cell Stem Cell. 2017; 21(3): 319–331.e8.

40. Xue AT, Ruggiero RP, Hickerson MJ, et al.: Differential Effect of Selection against LINE1 Retrotransposons among Vertebrates Inferred from Whole-Genome Data and Demographic Modeling. Genome Biol Evol. 2018; 10(5): 1265–81.

41. Xue AT, Ruggiero RP, Hickerson MJ, et al.: LINE-1 retrotransposons are an ancient source of interspersed repeat sequences. Nat Genet. 2018; 50(2): 177–183.

42. Lee MH, Siddoway B, Kaeser GE, et al.: Somatic APP gene recombination in Alzheimer’s disease and normal neurons. Nature. 2016; 563(7732): 639–45.

43. Fe Cocco M, Ito T, Petrasen AP, et al.: L1 drives IFN in senescent cells and promotes age-associated inflammation. Nature. 2019; 566(7742): 73–8.

44. Cugola FR, Fettman, et al.: The Brazilian Zika virus strain causes birth defects in experimental models. Nature. 2016; 534(7626): 267–71.

45. Qian X, Nguyen HN, Song MM, et al.: Brain-Region-Specific Organoids Using Mini-bioreactors for Modeling ZIKV Exposure. Cell. 2016; 165(6): 1238–54.

46. Gabriel E, Ramani A, Karow LJ, et al.: Recent Zika Virus isolates induce premature differentiation of neural progenitors in human brain organoids. Cell Stem Cell. 2017; 20(3): 397–406.e5.

47. Yuan L, Huang XY, Liu ZY, et al.: A single mutation in the prim protein of Zika virus contributes to fetal microcephaly. Science. 2017; 358(6365): 933–6.

48. Shinyoung SA, Mesci P, Pinto A, et al.: Repurposing of the anti-malaria drug chloroquine for Zika Virus treatment and prophylaxis. Sci Rep. 2018; 8(1): 1218.

49. Xu M, Lee EM, Wen Z, et al.: Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen. Nat Med. 2016; 22(10): 1101–7.

50. Mesci P, Macia A, Moore SM, et al.: Blocking Zika virus vertical transmission. Sci Rep. 2018; 8(1): 47103.

51. Gallego Romero I, Pavlovic BJ, Hernando-Herraez I, et al.: A panel of induced pluripotent stem cells from chimpanzees: a resource for comparative functional genomics. eLife. 2015; 4: e07103.

52. Herculano-Houzel S: Neuronal scaling rules for primate brains: the primate advantage. Prog Brain Res. 2012; 195: 325–40.

53. Otani T, Marchetto MC, Gage FH, et al.: 2D and 3D Stem Cell Models of Primate Cortical Development Identify Species-Specific Differences in Progenitor Behavior Contributing to Brain Size. Cell Stem Cell. 2016; 18(4): 467–80.

54. Marchetto MC, Hvoj-Mihic B, Kerman BE, et al.: Species-specific maturation profiles of human, chimpanzee and bonobo neural cells. eLife. 2019; 8: pii: e37527.

55. Field AR, Jacobs FMJ, Fiddes JT, et al.: Structurally Conserved Primate LncRNAs Are Transiently Expressed during Human Cortical Differentiation and Influence Cell-Type-Specific Genes. Stem Cell Reports. 2019; 12(2): 245–57.

56. Gutman T, Donaghey J, Carey BW, et al.: LincRNAs act in the circuitry controlling pluripotency and differentiation. Nature. 2011; 477(7364): 295–300.

57. Heo JB, Sung S: Vernalization-mediated epigenetic silencing by a long intronic noncoding RNA. Science. 2011; 331(6013): 76–9.

58. Pollen AA, Bhaduri A, Andrews MG, et al.: Establishing Cerebral Organoids as Models of Human-Specific Brain Evolution. Cell. 2019; 176(4): 745–756.e17.

59. Sudmant PH, Huddleston J, Catanach CJ, et al.: Evolution and diversity of copy number variation in the great ape lineage. Genome Res. 2013; 23(9): 1373–82.

60. Novembre FJ, Sauzier M, Anderson DC, et al.: Development of AIDS in a chimpanzee infected with human immunodeficiency virus type 1. J Virol. 1997; 71(5): 4086–91.

61. Escalante AA, Ayala FJ: Phylogeny of the malarial genus Plasmodium, derived from RNA gene sequences. Proc Natl Acad Sci U S A. 1994; 91(24): 13737–7.

62. Gearing M, Rebeck GW, Hyman BT, et al.: Neurotrophin and apolipoprotein E profile of aged chimpanzees: implications for Alzheimer disease. Proc Natl Acad Sci U S A. 1994; 91(20): 9382–7.

63. Seibold HR, Wolf RH: Neoplasms and proliferative lesions in 1065 nonhuman primate necropsies. Lab Anim Sci. 1973; 23(4): 533–9.

64. Varki A: A chimpanzee genome project is a biomedical imperative. Genome Res. 2000; 10(8): 1065–70.

65. Prescott SL, Srivasan R, Marchetto MC, et al.: Enhancer divergence and cis-regulatory evolution in the human and chimp neural crest. Cell. 2015; 161(1): 68–83.

66. Chalangkarn T, Trujillo CA, Freitas BC, et al.: A human neurodevelopmental model for Williams syndrome. Nature. 2016; 536(7616): 328–33.

67. Trujillo CA, Gao R, Negraes PD, et al.: Nested oscillatory dynamics in cortical organoids model early human brain network development. bioRxiv. 2018.

68. Sethi H, Muthri AR: Brain organoids as a model system for human neurodevelopment and disease. Semin Cell Dev Biol. 2019; pii: S1084-9521(18)30091-2.

69. Cohen J: Neanderthal brain organoids come to life. Science. 2018; 360(6395): 1284.

70. Canton J: Neanderthal brain organoids come to life. Science. 2018; 360(6395): 1284.
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