CHAPTER EIGHT

Metabolic Syndrome and the Cellular Phase of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is characterized by cognitive dysfunction and progressive neurodegeneration. The major hallmarks of AD pathology are amyloid plaques and neurofibrillary tangles. However, AD often coexists with other brain microvascular lesions caused by comorbidities, including obesity, diabetes, hypertension, and cardiovascular diseases. The risk factors for these comorbidities are collectively referred to as metabolic syndrome (MetS). Clinical AD is preceded by decades of prodromal cellular phase. During this asymptomatic phase, systemic changes caused by MetS can play critical roles in driving neuroinflammation, an important cause of AD pathogenesis. Studies of MetS and AD have traditionally remained in distinct domains. The cross talk between MetS and the cellular phase of AD is an important area to be investigated. AD risk factors identified by genome-wide association studies (GWAS) have strongly suggested the role of microglia, the resident immune cells of the brain, in AD pathogenesis. Microglial dysregulation is caused not only by CNS-intrinsic factors but also by systemic changes. MetS appears to cause brain mitochondrial dysfunction through a defective NAD^+-sirtuin pathway. Sirtuins are a family of seven proteins that are involved in longevity and

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inflammation. Among them, SIRT3 is exclusively present in mitochondria, playing a significant role in metabolic adaptation. SIRT3 deacetylates and activates key metabolic enzymes and transcriptional regulators, utilizing NAD^+ in the process. MetS could prime microglia through the interface of blood–brain barrier (BBB). Age-dependent breakdown of the BBB has been reported in human subjects. The neurovascular unit at BBB consists of brain microvascular endothelial cells, end feet of astrocytes, and pericytes. Therapeutic targeting of the sirtuin pathway in AD with coexisting pathologies has the potential to produce profoundly beneficial effects in improving mitochondrial function and decreasing neuroinflammation.

1. ALZHEIMER'S DISEASE IS A CONVERGENT SYNDROME WITH MIXED PATHOLOGIES

Deposition of amyloid plaques and formation of neurofibrillary tangles are important causes of Alzheimer's disease (AD).[1] However, recent studies have suggested that the pure form of AD may be rare and that the coexisting brain lesions could tip the scale to clinical diagnosis of dementia.[2–4] A report reviewing the Nun Study (NS) and Honolulu-Asia Aging Study (HAAS) concluded that the total burden of comorbid brain abnormalities was the main determinant of cognitive deficits in clinically diagnosed AD.[2] The combination rather than the type of lesions played a major role. This study also leads to the understanding that there can be a broader opportunity to treat dementia. Pharmacological interventions targeting the comorbidities have improved survival from life-threatening complications. However silent neurodegenerative pathways that proceed during decades could contribute to cognitive decline. Although Alzheimer's transgenic mice expressing human mutant APP, presenilin and tau have advanced our knowledge of AD pathogenesis, studies of AD mouse models with mixed pathology are needed to recapitulate the molecular events of human AD. The comorbidities including brain hypoperfusion, silent ministrokes, diabetes, and cardiovascular dysfunction need to be incorporated into the current AD transgenic models to recapitulate CNS pathology in the human disease.[5] The boundaries that distinctively separated AD from other forms of dementias are slowly disappearing, suggesting that dementia is a confluent syndrome with contributions from multiple pathologies.[3] Comorbidities of dementia include obesity, diabetes, hypertension, and cardiovascular diseases (Fig. 1). The risk factors for these comorbidities are collectively referred to as metabolic syndrome (MetS).

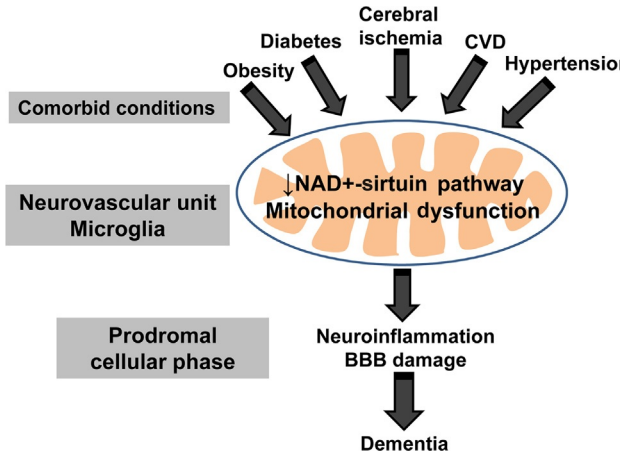

Fig. 1 Comorbidities of Alzheimer's disease. There are several comorbid conditions including obesity, diabetes, cerebral ischemia, cardiovascular diseases, and hypertension that can potentially increase the susceptibility to Alzheimer's disease. The mechanism appears to involve mitochondrial dysfunction in the neurovascular unit and in the microglia. The resulting blood brain damage and neuroinflammation during the prodromal stage of Alzheimer's disease could influence the progression of cognitive decline.

2. CELLULAR PHASE OF AD

Sporadic late-onset AD, the most common form of dementia, is characterized by slow progression over several decades. Cognitive reserve and the ability of brain cells to cope with stress can delay the onset of clinical dementia. There are multiple factors that drive the cellular phase of AD. For example, impaired brain metabolism in early stages appears to play a significant role in cognitive decline.[6] Specifically, defects in frontal and temporoparietal glucose metabolism could contribute to disease progression.[7] Mitochondrial dysfunction is another early event during the prodromal stage of AD[8,9] and it plays an important role in the initiation of neuroinflammation. Linking of these two pathways has provided new insights through the generation of inflammasome,[10–12] a multiprotein cytosolic complex that is generated in response to infection, cellular damage, and metabolic dysregulation.[13] Inflammasome formation leads to the activation of caspase-1 and to the proteolytic cleavage and secretion of the cytokines IL-1β and IL-18.[14] Sterile inflammasomes in response to cellular stress causes neuronal injury.[15] During the disease progression, inflammation gets exacerbated as a result of feed-forward loops and synergistic actions of transcription factors.

For example, secreted inflammatory mediators support astrogliosis and cytokine-activated transcription factors including NF-κB, STAT-1, and c-jun (AP-1) act synergistically to induce more cytokines and chemokines. Many of these events during the presymptomatic phase of this complex disease can become independent self-sustaining pathways later. Presence of comorbidities during the cellular phase of AD can potentially facilitate the progression toward clinical AD. Comorbidities can significantly influence the trajectory of prodromal stage to symptomatic AD. It is being increasingly recognized that the therapeutic targeting of AD needs to start at the prodromal cellular phase.[16] For example, although epidemiological studies have linked the use of antiinflammatory drugs with reduced risk of AD,[17] clinical trials with NSAIDs have failed (reviewed in Ref. [18]), suggesting that the interventions need to start early. Advances in biomarker-based diagnostic criteria can facilitate early interventions.[19,20]

3. CROSS TALK BETWEEN MetS AND THE CELLULAR PHASE OF AD

The major challenge in understanding the complexity of AD pathogenesis is its long cellular phase.[21] This is the stage at which comorbidities can potentially cross talk with AD pathogenesis in mid-life. MetS is a combination of five risk factors including abdominal obesity, hypertriglyceridemia, insulin resistance, high blood pressure, and low levels of good cholesterol (HDL). Current reports are suggesting that around 35% of adults have MetS.[22] The role of comorbidities needs to be examined during the prodromal stage rather than at the time of clinical AD diagnosis, because aged population with comorbidities takes diverse paths in terms of disease management and the type of medications used. Although genetic risk factors play significant roles in susceptibility to AD the role of modifiable risk factors cannot be ignored. A combination of genetic predisposition with unhealthy life styles can dramatically affect the susceptibility to cognitive decline. Consumption of Western diet and lack of physical activities could play important roles during the cellular phase of AD. Although MetS is a known risk factor for cardiovascular disease, diabetes, and stroke, MetS as a risk factor for dementia has received less attention because of mixed results from epidemiological studies.[23–26] An Italian longitudinal study in MCI patients reported that MetS independently predicted an increased risk of progression to dementia in a 3.5-year follow-up.[27] The French three-city study reported association between MetS and vascular dementia (VaD) but not with AD.[28] MetS

late in life was found to be not associated as a risk factor for dementia.[25] The mechanism appears to be microvascular damage leading to disrupted cortical connectivity. Insulin resistance has been suggested to be an important link between MetS and cognitive dysfunction. Visceral fat during MetS is characterized by infiltration of macrophages which produce proinflammatory cytokines. The increased levels of circulating cytokines can cross BBB and produce sustained chronic inflammation through an inflammatory loop the mechanism of which we have described in a recent study.[29]

4. TARGETING SIRT3 TO IMPROVE METABOLIC ADAPTATION DURING THE CELLULAR PHASE OF AD

Mitochondrial dysfunction is an early event during the prodromal stage of AD[9] and it plays an important role in the initiation of neuroinflammation. For the therapeutic targeting of these defects, sirtuins appear to show promise.[30] The silent information regulator (SIRT) genes (sirtuins) comprise a highly conserved family of seven proteins that use NAD^+ as a cosubstrate to catalyze the deacetylation and/or the mono-ADP ribosylation of target proteins.[31] They regulate diverse biological mechanisms including longevity, genomic stability, and inflammation. Among the seven members, SIRT3 is exclusively present in mitochondria, where it plays a central role in metabolic regulation[32] (Fig. 2). Acetylation is an

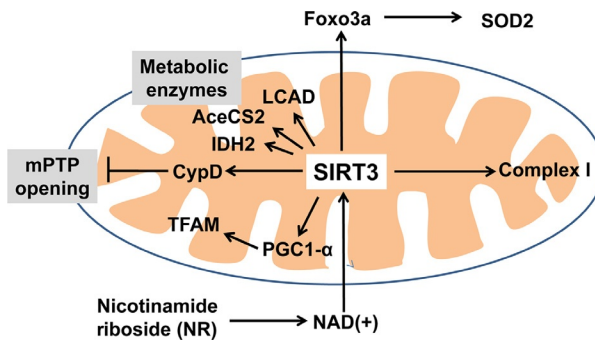

Fig. 2 SIRT3 and metabolic adaptation. SIRT3 deacetylates and activates metabolic enzymes, transcription factors, and other critical proteins in mitochondria. The metabolic enzymes include long chain fatty acid acyl-coA dehydrogenase (LCAD), acetyl CoA synthetase 2 (AceCS2), and isocitrate dehydrogenase (IDH). Overall, SIRT3 mediates adaptive response to metabolic stress especially during the aging process. SIRT3 can be targeted therapeutically by supplementation with nicotinamide riboside, a precursor of NAD^+.

important posttranslational modification that plays a critical role in metabolic regulation.[33] Around 300 acetylation sites have been identified in mitochondrial proteins.[34] SIRT3 is essential for adaptive response to metabolic stress. Targets of SIRT3 deacetylation include metabolic enzymes including long chain fatty acid acyl-CoA dehydrogenase (LCAD), acetyl CoA synthetase 2 (AceCS2), and isocitrate dehydrogenase (IDH), the transcription factor FOXO3a, transcriptional coactivator PGC1-α, antioxidant enzyme SOD2, mitochondrial OPA1 and complex1 proteins.[35] SIRT3 mediates adaptive response to metabolic stress, which is critical during aging. SIRT3 is transcriptionally upregulated by dietary restriction and fasting.[35] Homozygous $SIRT3^{-/-}$ mice are viable and do not display any gross physical or behavioral abnormalities.[36] However, when fed with energy-rich diet, they develop MetS due to impaired mitochondrial metabolism.[37] Single-nucleotide polymorphism of human SIRT3 is associated with susceptibility for MetS.[38] Nicotinamide adenine dinucleotide (NAD^+) is a coenzyme for metabolic pathways and it is also a cosubstrate for many enzymes including sirtuins.[39,40] Depletion of NAD^+ plays a critical role in neurodegeneration.[40–42] Replacing the NAD^+ levels is emerging as an important therapeutic approach.[43] Increasing the cellular level of NAD^+ by administration of nicotinamide riboside (NR), a precursor of NAD^+, is an effective strategy to activate the sirtuin pathway.[44] Other approaches to increase NAD^+ with nicotinamide mononucleotide (NAM), NAD^+, and nicotinic acid have undesirable effects.[45–47]

5. MICROGLIAL PRIMING DURING MetS

Microglia, the resident immune cells of the brain, constitute 5%–10% of the brain cells with region-specific variations. Microglia originate from erythromyeloid precursors in the embryonic yolk sac and migrate to the brain before the blood–brain barrier (BBB) is formed.[48] Microglial synaptic pruning by a complement-dependent pathway plays an important role in the establishment of neuronal network during development.[49] Genome-wide association studies (GWAS) of AD patients have shown that a large number of genetic polymorphisms of risk factor genes are involved in immune regulatory pathways, especially in microglia.[50] Microglia are known to be activated in the vicinity of amyloid plaques in the Alzheimer's brain and they are believed to reduce Aβ burden by phagocytosis. Landreth and coworkers[51] demonstrated that phagocytosis of β amyloid by microglia can be significantly improved with the use of RXR agonist bexarotene, leading to

decrease in β amyloid load in AD mouse models. However, uncontrolled chronic inflammation results in the release of neurotoxic factors including proinflammatory cytokines and reactive oxygen species by glial cells, resulting in the neurodegenerative process. In response to injury, microglia change their phenotype and response. Recent reports have suggested that M1/M2 polarization of microglia is an oversimplification. Deep sequencing studies have revealed unique molecular signatures of microglia when compared to other immune cells as well as other brain cells.[52–55] Microglial gene expression patterns are important markers because they reflect the neurodegenerative environment and the detrimental cues sent by MetS from the periphery. Microglia also play crucial intermediary roles in the CNS effects of gut microbiota.[56] For example, mice in germ-free environment with less developed microbiota have immature microglia. Microbiota-generated short chain fatty acids (SCFA) act on GPR34, a SCFA receptor on microglia, leading to its maturation.[56] SCFAR KO mice have microglia with immature phenotype. Western diet causes significant decreases in SCFA and GPR34.[57]

6. PERIPHERAL AND CENTRAL INFLAMMATION CONNECTION

Bidirectional cross talk between peripheral and central inflammation is an important component of AD pathogenesis.[58] Aging-associated chronic low-grade inflammation has been referred to as "inflammaging."[59] The expression of genes in the inflammatory pathways is significantly elevated even during cognitively normal aging.[60] The expression patterns in this study suggest activation of microglia and perivascular macrophages. The progression of neurodegenerative diseases is known to be exacerbated by systemic infection and inflammation.[61] Villeda *et al.* made an interesting observation that exposure of aged animal to young blood reverses the effects of aging at the molecular and functional levels.[62] Microglia in their entire life span, do not directly come in contact with the systemic circulation.[48] Induction of cytokines and chemokines in hippocampus is observed, following systemic challenge with IL-1β and TNFα in mice.[63] Higher peripheral concentrations of proinflammatory cytokines have been reported in Alzheimer's patients.[64] Framingham study has reported elevated circulating IL-1β and TNF-α as markers for the risk of AD.[65] Elevated levels of circulating TNF-α, associated with acute and chronic systemic inflammation, have

been shown to contribute cognitive decline in AD.[66] Proinflammatory cytokines are known to pass through BBB.[67–69] Microglia are known to be primed in the aging brain and they respond to peripheral inflammation with greater severity and duration.[70] BBB damage observed during aging further adds to the exacerbation of CNS inflammation with the entry of immune cells into the brain. Activated microglia in the perivascular region can induce the expression of the adhesion molecules through secreted proinflammatory cytokines. Vascular adhesion molecules play important roles in immune cell entry. The cascade involves, rolling adhesion with E-selectin and P-selectin and firm adhesion with ICAM1 and VCAM1, followed by the entry of immune cells. Availability of FDA-approved drugs that can modulate microglial activation and improve brain microvascular function are promising.

7. OVERLAP OF VaD WITH AD

Because 20% of total energy consumption is in the brain, it is highly vascularized to facilitate the uptake of oxygen and nutrients. VaD is the second most common form of dementia after AD. However, significant overlap between these two forms is being recognized. The overlap ranges from AD with vascular dysfunction to mixed type of dementia.[71] When cerebrovascular lesions are often observed in aged brains, it is difficult to consider VaD as a distinct type.[72] Deteriorating vascular function and the progressive neurodegenerative process need to be viewed as converging pathogenic mechanisms. Two-hit vascular hypothesis suggests that defective brain microvascular circulation (first hit) acts as a trigger for the pathological events leading to the second hit of Aβ accumulation.[73] In line with this hypothesis, primary vascular events caused by the comorbidities could trigger a chain of events leading to neurodegeneration. Both VaD and AD share common risk factors including obesity, diabetes, hypertension, and smoking. Dementia could result from combined burden of vascular and neurodegenerative pathology. Cerebral amyloid angiopathy (CAA), observed in majority of AD patients, can cause intracerebral hemorrhage and microbleeds.[74] Thus additive and synergistic effects between VaD and AD can be expected. Understanding the contribution of vascular dysfunction to AD pathogenesis is critical for the development of effective therapeutic targets. Promoting the vascular health in the aging brain can be an important therapeutic strategy.

8. NEUROVASCULAR UNIT FACILITATES MetS–AD CROSS TALK

Comorbidities of AD can exert their deleterious CNS effects through neurovascular unit (NVU) (Fig. 3). NVU contributes to the development of VaD as well as its progression. A recent MRI study in human subjects has reported age-dependent breakdown of BBB.[75] Studies in rodents have shown that feeding of energy-rich diet leads to compromised BBB integrity.[76–78] BBB damage in the aging brain leads to accumulation of blood-derived proteins including immunoglobulins, albumin, fibrinogen, and thrombin.[73] Bien-Ly *et al.* reported lack of BBB permeability in AD mouse models.[79] Essentially this study raises doubt regarding the plasma Aβ-mediated BBB disruption. It appears that BBB damage could be a feature of AD with mixed pathologies. NVU consists of brain microvascular endothelial cells (BMECs), end feet of astrocytes, and pericytes. To meet the high energy demand of active transport across BBB, endothelial cells contain high number of mitochondria. Studies with BMEC have revealed that their susceptibility to oxidative stress.[80] Silencing of SIRT3 leads to decreased viability of endothelial cells.[81] BMECs are uniquely different from other

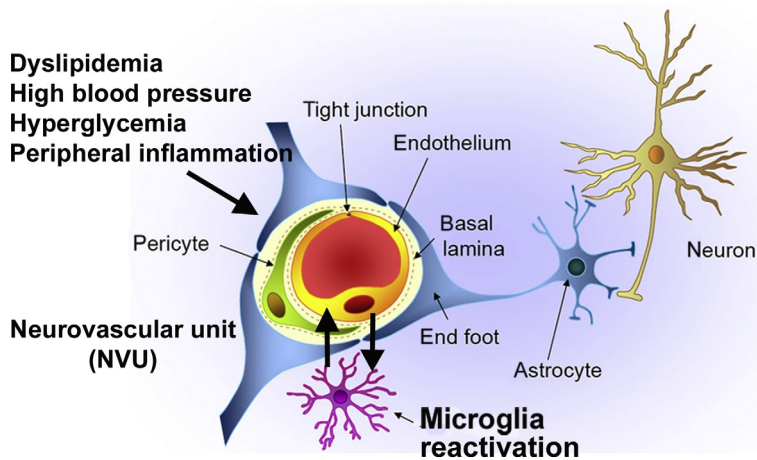

Fig. 3 Metabolic syndrome and the neurovascular unit (NVU). NVU consists of brain microvascular endothelial cells, end feet of astrocytes, and pericytes. Cerebrovascular endothelial cells are critical sensors of dyslipidemia, hyperglycemia, and peripheral inflammation and play critical roles as mediators of microglial activation. Two-way communications between these cell types are critical to maintain homeostasis.

vascular endothelial cells because they are glued together by tight-junction (TJ) proteins including occludin and claudins.[82] As they line the luminal side, they are in constant contact with circulating factors and in communication with circulating immune cells. Therefore, cerebrovascular endothelial cells are critical sensors of peripheral inflammation and mediators of microglial activation. Microglia act as sensors of these signals leading to it reactivation. Microglia not only responds to the cues on the environment in the parenchyma but also to the signals generated by NVU. Microglia play biphasic role in terms of BBB integrity in a context-dependent manner. Following BBB injury, juxtavascular microglia migrate to the site and close the leak through their processes with P2RY12 receptor.[83] However, proinflammatory cytokines released from activated microglia are also known to decrease the expression of TJs and increase the expression of matrix metalloproteinase (MMP-9) which degrades TJ proteins.[84] Higher levels of circulating MMP-9 caused by MMP-9 gene variant are associated with a higher risk for MetS.[85] TNF-α causes microvascular endothelial permeability by activation of MMP-9.[84] Individuals with history of hypertension and high plasma levels of MMP-9 develop white matter hyperintensities.[86] Hyperglycemia-mediated induction of MMP-9 causes astrocyte migration.[87] Circulating MMP-9 levels are higher in children with diabetic ketoacidosis.[88]

9. CEREBRAL ISCHEMIA AND AD

The progression of cognitive decline in AD patients is faster with coexisting cerebral infarction.[89] Cerebral ischemia by tMCAO in CX3CR1/GFP mouse model with the loss of function of microglia showed decreased stroke size.[90] Biphasic functions of microglia after stroke have been reported, suggesting that suppressing microglial activation may not be an effective therapeutic strategy.[91] Microinfarcts are commonly observed in the aging brain.[92,93] The incidence of microinfarcts increases further in VaD patients.[94] Silent infarcts have been shown to be associated with MetS.[95,96] These microinfarcts are generally microscopic in nature. These silent infarcts are typically identified in postmortem examination. Compared to global cerebral ischemia, less information is available with experimental microinfarcts models. A mouse microinfarct model has been developed by Nedergaard and colleagues.[97] This model is generated by unilateral injection of cholesterol crystals. Unlike the classic MCAO model in which

neuronal loss is irreversible after 3 h, in the microinfarct model, neuronal loss is delayed over a 24-day period. The chronic effects of microinfarcts could be due to hypoxia resulting from diffuse hypoperfusion, oxidative stress, and inflammation resulting from glial activation. Overall, microinfarcts are considered to contribute independently to cognitive decline. Even in the absence of dementia, they are associated with decreased cognitive function score. These asymptomatic brain lesions can collectively contribute to the progression of AD pathology in additive or synergistic manner.

REFERENCES

1. Selkoe DJ. Alzheimer's disease: genes, proteins and therapy. *Physiol Rev*. 2001;81:741–766.
2. White LR, Edland SD, Hemmy LS, Montine KS, Zarow C, et al. Neuropathologic comorbidity and cognitive impairment in the Nun and Honolulu-Asia Aging Studies. *Neurology*. 2016;86:1000–1008.
3. Montine TJ, Sonnen JA, Montine KS, Crane PK, Larson EB. Adult Changes in Thought study: dementia is an individually varying convergent syndrome with prevalent clinically silent diseases that may be modified by some commonly used therapeutics. *Curr Alzheimer Res*. 2012;9:718–723.
4. Kawas CH, Kim RC, Sonnen JA, Bullain SS, Trieu T, et al. Multiple pathologies are common and related to dementia in the oldest-old: the 90+ study. *Neurology*. 2015;85:535–542.
5. Snyder HM, Hendrix J, Bain LJ, Carrillo MC. Alzheimer's disease research in the context of the national plan to address Alzheimer's disease. *Mol Aspects Med*. 2015;43–44:16–24.
6. Habeck C, Risacher S, Lee GJ, Glymour MM, Mormino E, et al. Relationship between baseline brain metabolism measured using [(1)(8)F]FDG PET and memory and executive function in prodromal and early Alzheimer's disease. *Brain Imaging Behav*. 2012;6:568–583.
7. Herholz K. Cerebral glucose metabolism in preclinical and prodromal Alzheimer's disease. *Expert Rev Neurother*. 2010;10:1667–1673.
8. Caldwell CC, Yao J, Brinton RD. Targeting the prodromal stage of Alzheimer's disease: bioenergetic and mitochondrial opportunities. *Neurotherapeutics*. 2015;12:66–80.
9. Du H, Guo L, Yan S, Sosunov AA, McKhann GM, et al. Early deficits in synaptic mitochondria in an Alzheimer's disease mouse model. *Proc Natl Acad Sci USA*. 2010;107:18670–18675.
10. Gurung P, Lukens JR, Kanneganti TD. Mitochondria: diversity in the regulation of the NLRP3 inflammasome. *Trends Mol Med*. 2015;21:193–201.
11. Sorbara MT, Girardin SE. Mitochondrial ROS fuel the inflammasome. *Cell Res*. 2011;21:558–560.
12. West AP, Khoury-Hanold W, Staron M, Tal MC, Pineda CM, et al. Mitochondrial DNA stress primes the antiviral innate immune response. *Nature*. 2015;520(7548):553–557.
13. Lamkanfi M, Dixit VM. Mechanisms and functions of inflammasomes. *Cell*. 2014;157:1013–1022.
14. Laudisi F, Spreafico R, Evrard M, Hughes TR, Mandriani B, et al. Cutting edge: the NLRP3 inflammasome links complement-mediated inflammation and IL-1beta release. *J Immunol*. 2013;191:1006–1010.

15. Kaushal V, Dye R, Pakavathkumar P, Foveau B, Flores J, et al. Neuronal NLRP1 inflammasome activation of Caspase-1 coordinately regulates inflammatory interleukin-1-beta production and axonal degeneration-associated Caspase-6 activation. *Cell Death Differ*. 2015;22(10):1676–1686.
16. Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, et al. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement*. 2016;12:292–323.
17. McGeer PL, McGeer E, Rogers J, Sibley J. Anti-inflammatory drugs and Alzheimer disease. *Lancet*. 1990;335:1037.
18. Hoozemans JJ, O'Banion MK. The role of COX-1 and COX-2 in Alzheimer's disease pathology and the therapeutic potentials of non-steroidal anti-inflammatory drugs. *Curr Drug Targets CNS Neurol Disord*. 2005;4:307–315.
19. Jack Jr CR, Holtzman DM. Biomarker modeling of Alzheimer's disease. *Neuron*. 2013;80:1347–1358.
20. Jack Jr CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010;9:119–128.
21. De Strooper B, Karran E. The cellular phase of Alzheimer's disease. *Cell*. 2016;164:603–615.
22. Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States, 2003–2012. *JAMA*. 2015;313:1973–1974.
23. Vanhanen M, Koivisto K, Moilanen L, Helkala EL, Hanninen T, et al. Association of metabolic syndrome with Alzheimer disease: a population-based study. *Neurology*. 2006;67:843–847.
24. Razay G, Vreugdenhil A, Wilcock G. The metabolic syndrome and Alzheimer disease. *Arch Neurol*. 2007;64:93–96.
25. Forti P, Pisacane N, Rietti E, Lucicesare A, Olivelli V, et al. Metabolic syndrome and risk of dementia in older adults. *J Am Geriatr Soc*. 2010;58:487–492.
26. Watts AS, Loskutova N, Burns JM, Johnson DK. Metabolic syndrome and cognitive decline in early Alzheimer's disease and healthy older adults. *J Alzheimers Dis*. 2013;35:253–265.
27. Solfrizzi V, Scafato E, Capurso C, D'Introno A, Colacicco AM, et al. Metabolic syndrome and the risk of vascular dementia: the Italian Longitudinal Study on Ageing. *J Neurol Neurosurg Psychiatry*. 2010;81:433–440.
28. Raffaitin C, Gin H, Empana JP, Helmer C, Berr C, et al. Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia: the Three-City Study. *Diabetes Care*. 2009;32:169–174.
29. Pugazhenthi S, Zhang Y, Bouchard R, Mahaffey G. Induction of an inflammatory loop by interleukin-1beta and tumor necrosis factor-alpha involves NF-kB and STAT-1 in differentiated human neuroprogenitor cells. *PLoS One*. 2013;8, e69585.
30. Min SW, Sohn PD, Cho SH, Swanson RA, Gan L. Sirtuins in neurodegenerative diseases: an update on potential mechanisms. *Front Aging Neurosci*. 2013;5:53.
31. Gan L, Mucke L. Paths of convergence: sirtuins in aging and neurodegeneration. *Neuron*. 2008;58:10–14.
32. Onyango P, Celic I, McCaffery JM, Boeke JD, Feinberg AP. SIRT3, a human SIR2 homologue, is an NAD-dependent deacetylase localized to mitochondria. *Proc Natl Acad Sci USA*. 2002;99:13653–13658.
33. Sol EM, Wagner SA, Weinert BT, Kumar A, Kim HS, et al. Proteomic investigations of lysine acetylation identify diverse substrates of mitochondrial deacetylase sirt3. *PLoS One*. 2012;7, e50545.
34. Kim HS, Patel K, Muldoon-Jacobs K, Bisht KS, Aykin-Burns N, et al. SIRT3 is a mitochondria-localized tumor suppressor required for maintenance of mitochondrial integrity and metabolism during stress. *Cancer Cell*. 2010;17:41–52.

35. Nogueiras R, Habegger KM, Chaudhary N, Finan B, Banks AS, et al. Sirtuin 1 and sirtuin 3: physiological modulators of metabolism. *Physiol Rev*. 2012;92:1479–1514.
36. Ahn BH, Kim HS, Song S, Lee IH, Liu J, et al. A role for the mitochondrial deacetylase Sirt3 in regulating energy homeostasis. *Proc Natl Acad Sci USA*. 2008;105:14447–14452.
37. Lantier L, Williams AS, Williams IM, Yang KK, Bracy DP, et al. SIRT3 is crucial for maintaining skeletal muscle insulin action and protects against severe insulin resistance in high-fat-fed mice. *Diabetes*. 2015;64:3081–3092.
38. Hirschey MD, Shimazu T, Jing E, Grueter CA, Collins AM, et al. SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome. *Mol Cell*. 2011;44:177–190.
39. Imai S, Guarente L. NAD+ and sirtuins in aging and disease. *Trends Cell Biol*. 2014;24:464–471.
40. Verdin E. NAD(+) in aging, metabolism, and neurodegeneration. *Science*. 2015;350:1208–1213.
41. Zhu XH, Lu M, Lee BY, Ugurbil K, Chen W. In vivo NAD assay reveals the intracellular NAD contents and redox state in healthy human brain and their age dependences. *Proc Natl Acad Sci USA*. 2015;112:2876–2881.
42. Zhang H, Ryu D, Wu Y, Gariani K, Wang X, et al. NAD(+) repletion improves mitochondrial and stem cell function and enhances life span in mice. *Science*. 2016;352:1436–1443.
43. Imai S. A possibility of nutriceuticals as an anti-aging intervention: activation of sirtuins by promoting mammalian NAD biosynthesis. *Pharmacol Res*. 2010;62:42–47.
44. Gong B, Pan Y, Vempati P, Zhao W, Knable L, et al. Nicotinamide riboside restores cognition through an upregulation of proliferator-activated receptor-gamma coactivator 1alpha regulated beta-secretase 1 degradation and mitochondrial gene expression in Alzheimer's mouse models. *Neurobiol Aging*. 2013;34:1581–1588.
45. Sauve AA, Wolberger C, Schramm VL, Boeke JD. The biochemistry of sirtuins. *Annu Rev Biochem*. 2006;75:435–465.
46. Bogan KL, Brenner C. Nicotinic acid, nicotinamide, and nicotinamide riboside: a molecular evaluation of NAD+ precursor vitamins in human nutrition. *Annu Rev Nutr*. 2008;28:115–130.
47. Benyo Z, Gille A, Kero J, Csiky M, Suchankova MC, et al. GPR109A (PUMA-G/HM74A) mediates nicotinic acid-induced flushing. *J Clin Invest*. 2005;115:3634–3640.
48. Crotti A, Ransohoff RM. Microglial physiology and pathophysiology: insights from genome-wide transcriptional profiling. *Immunity*. 2016;44:505–515.
49. Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science*. 2016;352:712–716.
50. Mhatre SD, Tsai CA, Rubin AJ, James ML, Andreasson KI. Microglial malfunction: the third rail in the development of Alzheimer's disease. *Trends Neurosci*. 2015;38:621–636.
51. Cramer PE, Cirrito JR, Wesson DW, Lee CY, Karlo JC, et al. ApoE-directed therapeutics rapidly clear beta-amyloid and reverse deficits in AD mouse models. *Science*. 2012;335(6075):1503–1506.
52. Beutner C, Linnartz-Gerlach B, Schmidt SV, Beyer M, Mallmann MR, et al. Unique transcriptome signature of mouse microglia. *Glia*. 2013;61:1429–1442.
53. Chiu IM, Morimoto ET, Goodarzi H, Liao JT, O'Keeffe S, et al. A neurodegeneration-specific gene-expression signature of acutely isolated microglia from an amyotrophic lateral sclerosis mouse model. *Cell Rep*. 2013;4:385–401.
54. Hickman SE, Kingery ND, Ohsumi TK, Borowsky ML, Wang LC, et al. The microglial sensome revealed by direct RNA sequencing. *Nat Neurosci*. 2013;16:1896–1905.
55. Butovsky O, Jedrychowski MP, Moore CS, Cialic R, Lanser AJ, et al. Identification of a unique TGF-beta-dependent molecular and functional signature in microglia. *Nat Neurosci*. 2014;17:131–143.

56. Erny D, Hrabe de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, et al. Host microbiota constantly control maturation and function of microglia in the CNS. *Nat Neurosci*. 2015;18:965–977.
57. Agus A, Denizot J, Thevenot J, Martinez-Medina M, Massier S, et al. Western diet induces a shift in microbiota composition enhancing susceptibility to Adherent-Invasive E. coli infection and intestinal inflammation. *Sci Rep*. 2016;6:19032.
58. Di Filippo M, Chiasserini D, Gardoni F, Viviani B, Tozzi A, et al. Effects of central and peripheral inflammation on hippocampal synaptic plasticity. *Neurobiol Dis*. 2013;52:229–236.
59. Franceschi C. Inflammaging as a major characteristic of old people: can it be prevented or cured? *Nutr Rev*. 2007;65:S173–S176.
60. Cribbs DH, Berchtold NC, Perreau V, Coleman PD, Rogers J, et al. Extensive innate immune gene activation accompanies brain aging, increasing vulnerability to cognitive decline and neurodegeneration: a microarray study. *J Neuroinflammation*. 2012;9:179.
61. Perry VH, Cunningham C, Holmes C. Systemic infections and inflammation affect chronic neurodegeneration. *Nat Rev Immunol*. 2007;7:161–167.
62. Villeda SA, Plambeck KE, Middeldorp J, Castellano JM, Mosher KI, et al. Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. *Nat Med*. 2014;20:659–663.
63. Skelly DT, Hennessy E, Dansereau MA, Cunningham C. A systematic analysis of the peripheral and CNS effects of systemic LPS, IL-1beta, [corrected] TNF-alpha and IL-6 challenges in C57BL/6 mice. *PLoS One*. 2013;8, e69123.
64. Swardfager W, Lanctot K, Rothenburg L, Wong A, Cappell J, et al. A meta-analysis of cytokines in Alzheimer's disease. *Biol Psychiatry*. 2010;68:930–941.
65. Tan ZS, Beiser AS, Vasan RS, Roubenoff R, Dinarello CA, et al. Inflammatory markers and the risk of Alzheimer disease: the Framingham Study. *Neurology*. 2007;68:1902–1908.
66. Holmes C, Cunningham C, Zotova E, Woolford J, Dean C, et al. Systemic inflammation and disease progression in Alzheimer disease. *Neurology*. 2009;73:768–774.
67. Banks WA, Kastin AJ. Blood to brain transport of interleukin links the immune and central nervous systems. *Life Sci*. 1991;48:L117–L121.
68. Banks WA, Kastin AJ, Broadwell RD. Passage of cytokines across the blood–brain barrier. *Neuroimmunomodulation*. 1995;2:241–248.
69. Gutierrez EG, Banks WA, Kastin AJ. Murine tumor necrosis factor alpha is transported from blood to brain in the mouse. *J Neuroimmunol*. 1993;47:169–176.
70. Dilger RN, Johnson RW. Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system. *J Leukoc Biol*. 2008;84:932–939.
71. Iadecola C. The pathobiology of vascular dementia. *Neuron*. 2013;80:844–866.
72. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:2672–2713.
73. Zlokovic BV. Neurovascular mechanisms of Alzheimer's neurodegeneration. *Trends Neurosci*. 2005;28:202–208.
74. Brenowitz WD, Nelson PT, Besser LM, Heller KB, Kukull WA. Cerebral amyloid angiopathy and its co-occurrence with Alzheimer's disease and other cerebrovascular neuropathologic changes. *Neurobiol Aging*. 2015;36:2702–2708.
75. Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, et al. Blood–brain barrier breakdown in the aging human hippocampus. *Neuron*. 2015;85:296–302.
76. Freeman LR, Granholm AC. Vascular changes in rat hippocampus following a high saturated fat and cholesterol diet. *J Cereb Blood Flow Metab*. 2012;32:643–653.

77. Davidson TL, Monnot A, Neal AU, Martin AA, Horton JJ, et al. The effects of a high-energy diet on hippocampal-dependent discrimination performance and blood–brain barrier integrity differ for diet-induced obese and diet-resistant rats. *Physiol Behav*. 2012;107:26–33.
78. Tucsek Z, Toth P, Sosnowska D, Gautam T, Mitschelen M, et al. Obesity in aging exacerbates blood–brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus: effects on expression of genes involved in beta-amyloid generation and Alzheimer's disease. *J Gerontol A Biol Sci Med Sci*. 2014;69:1212–1226.
79. Bien-Ly N, Boswell CA, Jeet S, Beach TG, Hoyte K, et al. Lack of widespread BBB disruption in Alzheimer's disease models: focus on therapeutic antibodies. *Neuron*. 2015;88:289–297.
80. Navaratna D, Fan X, Leung W, Lok J, Guo S, et al. Cerebrovascular degradation of TRKB by MMP9 in the diabetic brain. *J Clin Invest*. 2013;123:3373–3377.
81. Liu G, Cao M, Xu Y, Li Y. SIRT3 protects endothelial cells from high glucose-induced cytotoxicity. *Int J Clin Exp Pathol*. 2015;8:353–360.
82. Haseloff RF, Dithmer S, Winkler L, Wolburg H, Blasig IE. Transmembrane proteins of the tight junctions at the blood–brain barrier: structural and functional aspects. *Semin Cell Dev Biol*. 2015;38:16–25.
83. Lou N, Takano T, Pei Y, Xavier AL, Goldman SA, et al. Purinergic receptor P2RY12-dependent microglial closure of the injured blood–brain barrier. *Proc Natl Acad Sci USA*. 2016;113:1074–1079.
84. Wiggins-Dohlvik K, Merriman M, Shaji CA, Alluri H, Grimsley M, et al. Tumor necrosis factor-alpha disruption of brain endothelial cell barrier is mediated through matrix metalloproteinase-9. *Am J Surg*. 2014;208:954–960. discussion 960.
85. Yadav SS, Mandal RK, Singh MK, Verma A, Dwivedi P, et al. High serum level of matrix metalloproteinase 9 and promoter polymorphism—1562 C:T as a new risk factor for metabolic syndrome. *DNA Cell Biol*. 2014;33:816–822.
86. Kim Y, Kim YK, Kim NK, Kim SH, Kim OJ, et al. Circulating matrix metalloproteinase-9 level is associated with cerebral white matter hyperintensities in non-stroke individuals. *Eur Neurol*. 2014;72:234–240.
87. Hsieh HL, Lin CC, Hsiao LD, Yang CM. High glucose induces reactive oxygen species-dependent matrix metalloproteinase-9 expression and cell migration in brain astrocytes. *Mol Neurobiol*. 2013;48:601–614.
88. Garro A, Chodobski A, Szmydynger-Chodobska J, Shan R, Bialo SR, et al. Circulating matrix metalloproteinases in children with diabetic ketoacidosis. *Pediatr Diabetes*. 2016. http://dx.doi.org/10.1111/pedi.12359[Epub ahead of print].
89. Sheng B, Cheng LF, Law CB, Li HL, Yeung KM, et al. Coexisting cerebral infarction in Alzheimer's disease is associated with fast dementia progression: applying the National Institute for Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences Neuroimaging Criteria in Alzheimer's Disease with Concomitant Cerebral Infarction. *J Am Geriatr Soc*. 2007;55:918–922.
90. Jolivel V, Bicker F, Biname F, Ploen R, Keller S, et al. Perivascular microglia promote blood vessel disintegration in the ischemic penumbra. *Acta Neuropathol*. 2015;129:279–295.
91. Ma Y, Wang J, Wang Y, Yang GY. The biphasic function of microglia in ischemic stroke. *Prog Neurobiol*. 2016. pii: S0301-0082(15)30070-8.
92. Brundel M, de Bresser J, van Dillen JJ, Kappelle LJ, Biessels GJ. Cerebral microinfarcts: a systematic review of neuropathological studies. *J Cereb Blood Flow Metab*. 2012;32:425–436.
93. Vinters HV, Ellis WG, Zarow C, Zaias BW, Jagust WJ, et al. Neuropathologic substrates of ischemic vascular dementia. *J Neuropathol Exp Neurol*. 2000;59:931–945.

94. Haglund M, Passant U, Sjobeck M, Ghebremedhin E, Englund E. Cerebral amyloid angiopathy and cortical microinfarcts as putative substrates of vascular dementia. *Int J Geriatr Psychiatry*. 2006;21:681–687.
95. Park K, Yasuda N, Toyonaga S, Tsubosaki E, Nakabayashi H, et al. Significant associations of metabolic syndrome and its components with silent lacunar infarction in middle aged subjects. *J Neurol Neurosurg Psychiatry*. 2008;79:719–721.
96. Bokura H, Yamaguchi S, Iijima K, Nagai A, Oguro H. Metabolic syndrome is associated with silent ischemic brain lesions. *Stroke*. 2008;39:1607–1609.
97. Wang M, Iliff JJ, Liao Y, Chen MJ, Shinseki MS, et al. Cognitive deficits and delayed neuronal loss in a mouse model of multiple microinfarcts. *J Neurosci*. 2012;32:17948–17960.