Analysis on Autophagy Dysfunction in Alzheimer's Disease and Revelant Bioethic Issues in Its Healthcare

Jiaze Gao[1,*]

[1]China Medical University-Queen's University Belfast Joint College, China Medical University, Shenyang, Liaoning, China, 110122
[*]Corresponding author. Email: jiazegao2001@hotmail.com

ABSTRACT
Alzheimer's disease is a common degenerative disease that manifests itself primarily as tau tangles and amyloid beta protein plaques. In the last five years, studies on lysosomes have sparked interest in autophagy and autophagic dysfunction, yet the specific role of autophagy in the pathogenesis of Alzheimer's disease is still not particularly clear. This paper focuses on the mechanisms of autophagy and the role of autophagy in the pathogenesis of Alzheimer's disease, while exploring the biosynthesis of lysosomes and identifying abnormal autophagy as a major cause of the development of Alzheimer's disease. Finally, the paper discussed the bioethical issues and moral dilemmas that patients, family members, caregivers and clinicians may face in Alzheimer's disease, while highlighting the importance of conducting predictive testing and maintaining patient autonomy.

Keywords: *Lysosome, Beta-amyloid, Autophagy, Alzheimer's disease, Bioethical issue*

1. INTRODUCTION

Alzheimer's disease is a degenerative brain disease that worsens over time and is the leading cause of dementia in the elderly [1]. Its main features manifest themselves in the accumulation of extracellular amyloid β plaques (Aβ) and intracellular neurofibrillary tangles (NFT). As it unfolds, overproduction or low clearance of Aβ leads to the deposition of Aβ plaques in the brain, while phosphorylation of tau proteins leads to the formation of neurofibrillary tangles. These induce the onset of cognitive impairment [2]. However, the pathogenesis of Alzheimer's disease remains controversial and in this paper we describe the biogenesis of lysosomes and explore the role of autophagy in this disease with respect to the pathogenesis of Alzheimer's disease. As a neurodegenerative disease, people with Alzheimer's experience a long goodbye. With the gradual deterioration of physical and cognitive functions, patients also lose their mental and executive abilities, which not only affects their physical and mental health, but also places a heavy burden on families and induces ethical controversies. Autonomy and self-determination are two of the most important components of bioethics [13], and the different stages of Alzheimer's disease will also raise different bioethical issues.

Lysosomes are acidic, degrading organelles and their biogenesis is a complex regulated process that has not been particularly well studied [3]. Recent studies have shown that there are multiple pathways for the biological synthesis of lysosomes. The protein reaches the lysosome directly via the trans-Golgi network (TGN) and can also be transported to the lysosome via the endosome (early endosome EE, recycling endosome RE and late endosome LE) [4]. The transport of lysosomal soluble proteins requires post-translational modification and after glycosylation in the endoplasmic reticulum, they are transported to the Golgi apparatus, after which they are modified once more to expose M6P residues. Finally, the protein tagged with the M6P residue is transported to the lysosome by the mannose-6-phosphate receptor [5].

2. AUTOPHAGY

Lysosomes are also important for autophagy. Autophagy is the cellular process that enables the isolation and degradation of long-lived protein dysfunctional organelles and invading pathogens [4]. There are three types of autophagy: macroautophagy, microautophagy and chaperone mediated autophagy, each type involves a different mechanism of substrate delivery to the lysosome, but lysosomal digestion remains the common underlying feature [6].

2.1. Macroautophagy

Macroautophagy is a kind of multiple-step complex process which occurs in ER-derived double lipid membrane organelles known as autophagosome, which fuses with the lysosome to form autolysosomes [4]. Macroautophagy can occur selectively or non-selectively. Besides, it could be responsible for the bulk turnover of the cytoplasm which is the only mechanism of organelle turnover in the cell.

Microautophagy is the process by which autophagic cargoes in the cytoplasm are entrapped in the lysosomal membrane by invagination into the lysosome or endosome to form luminal vesicles. During this process, the luminal vesicles are degraded together with their contents through the action of mitochondria, peroxisomes and lipid droplets [4]. Microautophagy can be non-selective or highly selective, degrading material that is randomly incorporated into the cytoplasm or selectively degrading peroxisomes directly in the lysosome.

2.2. Chaperone-mediated autophagy

Chaperone-mediated autophagy (CMA) is a process that relies on the selective degradation of soluble proteins with KFERQ which contains Lysine, Phenylalanine, Glutamic acid, Arginine and Glutamine by HSPA8, Hsc70 or Hsc90 [7]. Heat shock proteins recognise and bind to the KFERQ motif and then deliver the target protein to the lysosomal surface where it binds to the lysosomal transmembrane protein LAMP2A. Prior to binding, LAMP2A exists as a homodimer or monomer. After binding, LAMP2A multimers begin to form translocation complexes and carry the unfolded protein into the lumen of the lysosome where it is rapidly degraded by proteases [4]. Some proteins also contain a small amount of PTM-induced motifs, which demonstrates that the CMA pathway is the main pathway for protein degradation [8]. However, the selective degradation of CMA also interacts with macroautophagy and proteasome activity, with the CMA pathway being enhanced if macroautophagy is inhibited.

3. REGULATION OF AUTOPHAGY IN ALZHEIMER'S DISEASE

In recent years, lysosomes have achieved widespread interest in Alzheimer's disease research. Autophagy takes a large part of the impaired lysosomal function in Alzheimer's disease. There is evidence that autophagy can alter the course of Alzheimer's disease [9]. Alzheimer's disease consists of sporadic AD and familial AD, the vast majority of which is sporadic AD. Familial AD is mainly due to mutations in the three genes below: amyloid precursor protein, presenilin 1 and presenilin 2. Mutations in the presenilin 1 gene could affect lysosomal function and autophagy and the increase in amyloid could lead to an over formation of Aβ. Autophagy also regulates Aβ protein levels. Interaction of NFB2 with APP promotes lysosomal disposal, however overexpression of NRBF2 would decrease Aβ level [8]. It has been shown that autophagy activation in microglia is also associated with Alzheimer's disease. Ablation of genes encoding surface receptors on microglia (TREM2) in response to neurodegeneration can dysregulate MTORC1 activation, causing abnormal microglia metabolic function and therefore abnormal autophagosome function. Under these conditions, Aβ plaque formation is exacerbated and neuronal decay is accelerated [10]. The onset of cognitive impairment and neuronal dystrophy are major factors in neuronal decay in Alzheimer's disease [11].

In addition, chaperone-mediated autophagy can degrade tau proteins, but acetylation of tau proteins can inhibit their degradation, which can inhibit CAM function. It has been shown that reduced CMA activity occurs in the brains of Alzheimer's patients [11, 12], and therefore, the suppression of CAM function may also contribute to the development of Alzheimer's disease.

4. BIOETHICAL ISSUES IN THE COURSE OF ALZHEIMER'S DISEASE

4.1. Early stage

In the early stages of Alzheimer's disease, the first thing that occurs is memory loss. Patients often forget things, and because the symptoms are not obvious, many people do not notice that Alzheimer's is occurring. As research into the pathogenesis of Alzheimer's disease has continued in recent years, the results of biomarker tests can be used as a basis for early Alzheimer's diagnosis. However, as a degenerative disease, Alzheimer's means that the patient becomes increasingly frail and less able to care for himself or herself, which brings a great deal of stigma. After testing, the patient's family and healthcare professionals are likely to use non-malicious ethical principles to conceal the condition in order to prevent the patient from being devastated. Such concealment deprives patients of their autonomy and right to know, and patients have a right to know their condition and clinicians should be truthful about it. Predictive testing is highly uncertain and misdiagnosis can occur even with a 90% diagnosis rate [13], and patients want to be informed of their diagnosis, which may enable earlier detection and timely initiation of treatment to delay the course of Alzheimer's disease. It is important to note that this initiative may raise ethical issues. Even before the disease has manifested itself, those tested are already labelled as having the disease, and their lives will be filled with worry and anxiety, and they will be discriminated against in terms of employment and insurance. It has been shown that the benefits of predictive testing for Alzheimer's patients far outweigh the risks [14]. In other words, by receiving a predictive diagnosis, patients and their families will not only know if they are at risk of

developing the disease, but this also gives healthcare professionals the space and time to intervene in the course of Alzheimer's disease with medication and other treatments to delay the onset of the disease. Although there are cases of misdiagnosis, the diagnosis does allow for earlier treatment to be initiated. Therefore, predictive tests including biomarker tests can be used by medical institutions and hospitals to detect whether a patient is at risk of developing Alzheimer's disease, provided that the person gives permission and confidentiality is maintained. Thus protecting the right to privacy and autonomy from discrimination is necessary. At this stage, to facilitate the formation of memory habits, families could place important items such as keys, wallets and mobile phones in the same place. At the same time, it is important to ensure that the patient carries identification and a mobile phone with a location function so that the patient's family can be contacted at the first opportunity to find out exactly where the patient is. If finding the condition getting worse, sending the patient to hospital is of great importance.

4.2. Intermediate stage

The intermediate stage of Alzheimer's disease is typically the longest stage which could last for several years. During this stage, patients might confuse words and have difficulty expressing their ideas, which makes it difficult for them to perform everyday tasks alone. As the disease progresses, the patient gradually loses short and medium-term memory, and motor deficits cause difficulties in mobility, speech and swallowing, which can cause significant difficulties in daily communication and travel, leading to emotional disturbances. In response to this situation, a number of jurisdictions have enacted laws to safeguard the rights of the patients with mental incapacity and to guarantee their right to exercise autonomy over their future health care. However, this autonomy is limited to cases where the patient has not lost mental capacity. As long as the patient is mentally competent, they should be consulted to make decisions, regardless of the stage of the course of the illness. At the same time, patients at this stage experience a variety of negative emotions such as fear, confusion, anger, depression. In such cases, it is important for the family to provide timely guidance, listen patiently, provide emotional support and maintain their dignity.

4.3. Late stage

In the late stage of Alzheimer's disease, the dementia becomes particularly pronounced and the patient becomes unable to respond to the outside environment and gradually loses contact with the outside world. In this case, communication becomes increasingly difficult and the patient needs the help of personal care around the clock. The most difficult ethical dilemmas usually arise in the later stages of Alzheimer's. In terms of treatment, in addition to patient autonomy, the core principles of medical ethics of kindness, non-maleficence, justice and respect must be taken into account, which means that treatment is carried out in such a way that the patient benefits and is not harmed while at the same time being treated equally [15]. At this stage, the patient's physical and psychological overdependence can place a great burden on the caregiver, and the heavy burden and futile treatment can raise a number of ethical issues. It is well known that treatment in the later stages of Alzheimer's disease can extend life but not improve quality of life, in other words, life-sustaining measures such as cardiopulmonary resuscitation can only maintain the physical characteristics of the patients, which would not provide relief nor comfort. This treatment is known as futile treatment, which does not necessarily harm or benefit the patient [15]. The decision to proceed with treatment should be based on the patient's wishes at the time of self-awareness and the advice of the medical team. Refusal to take medication and agitation are also common in the later stages of the disease. In such cases, caregivers may conceal medication in food to induce the patient to take it, and may use physical and chemical means to calm the patient, which not only deceives the patient but also violates the patient's autonomy. If the benefits of these measures far outweigh the harm to the patient, then they may be considered, otherwise they should be discontinued.

5. CONCLUSION

This paper outlined the biogenesis of lysosomes, including sorting and the available biogenic pathways. We also discussed the mechanisms of autophagy and its role in Alzheimer's disease, found that both disruption of lysosomal function and dysfunctional autophagy are causative factors in Alzheimer's disease. Autophagy dysregulation disrupts the nutritional balance of neurons and causes them to decay, which drives the pathogenic process of Alzheimer's disease. As autophagy has been studied in recent years, we have gained a better understanding of the pathways and mechanisms of autophagy, however these are far from sufficient and the role of autophagy in Alzheimer's disease is still worth investigating. People with Alzheimer's disease are a vulnerable group in the society, so people should take care of them in terms of medical and health care, even mental health. Whatever the stage of the disease, they should be treated with respect and their rights should be upheld, with the principles of kindness, justice and non-malice, such as choosing to conceal their condition in order to alleviate their psychological stress, restricting their movement by confining them in consideration of personal safety issues such as preventing them from wandering off and preventing them from injuring themselves in an unstable mood, it is worth noting that these acts for personal safety must not cause physical or

psychological harm to the patient, while maximising their daily interests and dignity.

AUTHORS' CONTRIBUTIONS

This paper is independently completed by Jiaze Gao.

ACKNOWLEDGMENTS

Firstly, I would like to thank Professor Cheng for providing me the theoretical knowledge on degenerative diseases and the lysosomal endoplasmic reticulum, which sparked my interest in research on autophagy and Alzheimer's disease. I would also like to thank my thesis supervisor for her guidance. Finally, I would like to thank my parents for their support and care, which has helped me tremendously.

REFERENCES

[1] 2021 Alzheimer's disease facts and figures. Alzheimers Dement. 2021, pp.327-406. doi:10.1002/alz.12328.

[2] Porsteinsson, A. P. Isaacson, R. S. Knox, S. et al. Diagnosis of Early Alzheimer's Disease: Clinical Practice in 2021. J Prev Alzheimers Dis 8, 2021, pp.371-386. https://doi.org/10.14283/jpad.2021.23.

[3] Saffi G. T. Botelho R. J. Lysosome Fission: Planning for an Exit. Trends Cell Biol. 2019, pp.635-646. doi:10.1016/j.tcb.2019.05.003.

[4] Trivedi P. C. Bartlett J. J. Pulinilkunnil T. Lysosomal Biology and Function: Modern View of Cellular Debris Bin. Cells. 2020, pp.1131. Published 2020 May 4. doi:10.3390/cells9051131.

[5] Bajaj L. Lotfi P. Pal R. Ronza AD, Sharma J, Sardiello M. Lysosome biogenesis in health and disease. J Neurochem. 2019, pp.573-589. doi:10.1111/jnc.14564.

[6] Van Weering JRT, Scheper W. Endolysosome and Autolysosome Dysfunction in Alzheimer's Disease: Where Intracellular and Extracellular Meet. CNS Drugs. 2019, pp.639-648. doi:10.1007/s40263-019-00643-1.

[7] Kaushik S. Cuervo A. M. The coming of age of chaperone-mediated autophagy. Nat Rev Mol Cell Biol. 2018, pp.365-381. doi:10.1038/s41580-018-0001-6.

[8] Lahiri V. Hawkins W. D. Klionsky D. J. Watch What You (Self-) Eat: Autophagic Mechanisms that Modulate Metabolism. Cell Metab. 2019, pp.803-826. doi:10.1016/j.cmet.2019.03.003.

[9] Bostancıklıoğlu M. An update on the interactions between Alzheimer's disease, autophagy and inflammation. Gene. 2019, pp.157-166. doi:10.1016/j.gene.2019.04.040.

[10] Ulland TK. Song WM. Huang SC, et al. TREM2 Maintains Microglial Metabolic Fitness in Alzheimer's Disease. Cell. 2017, pp.649-663. doi:10.1016/j.cell.2017.07.023.

[11] Klionsky DJ, Petroni G, Amaravadi RK, et al. Autophagy in major human diseases. EMBO J. 2021;40(19):e108863. doi:10.15252/embj.2021108863.

[12] Caballero B. Bourdenx M. Luengo E, et al. Acetylated tau inhibits chaperone-mediated autophagy and promotes tau pathology propagation in mice. Nat Commun. 2021;12(1):2238. Published 2021 Apr 14. doi:10.1038/s41467-021-22501-9.

[13] Vanderschaeghe G. Dierickx K. Vandenberghe R. Review of the Ethical Issues of a Biomarker-Based Diagnoses in the Early Stage of Alzheimer's Disease. J Bioeth Inq. 2018, pp.219-230. doi:10.1007/s11673-018-9844-y

[14] Low JA. Ho E. Managing Ethical Dilemmas in End-Stage Neurodegenerative Diseases. Geriatrics (Basel). 2017;2(1):8. Published 2017 Jan 20. doi:10.3390/geriatrics2010008.

[15] Watt AD. Jenkins NL. McColl G. Collins S. Desmond PM. Ethical Issues in the Treatment of Late-Stage Alzheimer's Disease. J Alzheimers Dis. 2019, pp.1311-1316. doi:10.3233/JAD-180865.