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Laser microdissection method for neurodegenerative diseases

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Abstract

Neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease raise prevalence with age. The structure of the causative protein is impaired in many neurodegenerative diseases. Therefore, abnormal accumulation of proteins is observed within and outside the cell. Many of these diseases are sporadic and idiopathic with an uncertain cause, and the clues to elucidate pathophysiology are aggregates of these disease-derived proteins. However, there are no examples in which all the elements have been clarified. The study of aggregated proteins is important for correct diagnosis and selecting suitable therapies or the development of therapies and prevention. The laser microdissection (LMD) technique that can cut the submicron order region has been used for neurodegenerative disease studies in recent years. The LMD approach is also useful for isolating only particular cells from the central nervous system from the tissue. This paper provides examples of LMD study in neurodegenerative disease research and discusses their efficacy.

Introduction

It is not well understood how neurodegenerative diseases occur in a specific person and when they start, but since they tend to develop in the elderly, aging itself is considered a risk. Thus, in many countries where life expectancy is growing, the number of patients continues to increase, but unfortunately there is no preventive or curative treatment.

Most neurodegenerative diseases are protein aggregation diseases such as Alzheimer's disease and Parkinson's disease characterized by the accumulation of intracellular and extracellular deposits made up of highly aggregated pathogenic proteins.

Knowing when, where and how these intracellular aggregates are formed is perhaps the most relevant knowledge for pathophysiology clarity. However, the answer has not yet been issued. One reason is that the tissue in the central nervous system contains various types of cells in a complicated way, and it is challenging to separate only particular cells, such as neurons or glial cells. Another reason is that even though a single cell could be isolated, it is tough to highly purify the protein aggregates only from the cell using the conventional biochemical analysis process. Therefore, experimental results are unreliable due to contaminants.

Laser Microdissection (LMD), which has grown in the number of users in recent years, is an efficient way to solve these problems. This is because LMD is a device that can eliminate accidental contamination as much as possible. After all, the target will be cut when visually viewing the target under a microscope. The first inventor of the LMD process was Sergei Stepanovich Chashotin (1883-1973) and commonly used as a microsurgery instrument in the early 1960s. LMD currently has two distinct types of lasers, primarily infrared (IF) and ultraviolet (UV). Over the decades, it has been updated and improved from ultraviolet (UV) laser beams to high-energy nitrogen, infrared and carbon dioxide lasers. LMD allows the precise separation of uniform cell populations or single cells from heterogeneous populations and also allows the separation of live cells in culture dishes [1]. Thus, LMD is also a fast cell isolation method and is an excellent tool for the preservation of genomic molecules. Currently, LMD is commonly used in various fields of medical research, from neuroscience, cancer, scientific research to biomarker discovery and clinical diagnosis.

Neurodegenerative disorders cause degeneration and damage to individual neurons, but the remaining cells are largely unaffected [2]. LMD is especially useful for studying neurodegenerative diseases because it can separate the specific cells with selective fragility from tissues, however, there are still many disadvantages. The LMD itself and related consumables are costly, so even though it is known that high purity purification is possible and more accurate results can be achieved, classical biochemical analysis is required. Furthermore, while the performance of LMD has improved, it is still uneasy about extracting submicron-order deposits produced within cells using commercially available LMD.

Here, we will present some typical examples examined by LMD technique, focusing on the application of LMD findings for neurodegenerative diseases to pathological research.

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Parkinson’s disease

Parkinson's disease (PD) is a polyphyletic neurodegenerative disease with progressive deterioration of motor neuron. Prevalence rises gradually with age [3] and is the second most prevalent neurodegenerative disorder [4,5]. In developing countries, it is commonly estimated to be 0.3% of the total population and approximately 1% of people over the age of 60. PD exhibits ataxia, bradykinesia, hypokinesia, postural dysfunction, stiffness, leaning posture, tremor, and worsens bilateral vocal cord paralysis [6]. In addition to dysfunction of motor neuron, it has been shown that certain non-motor disfunctions such as olfactory dysfunction, visual disturbances, ocular motility disorders, neuropsychiatric symptoms such as depression and anxiety, and autonomic dysfunction are known as prodromal symptoms. Urological impairment, mood disorders and other neurobehavioral disturbances have also been identified [7,8].

The key pathological shift is the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta of the basal ganglia, which induces neural circuit dysfunction, including the motor cortex region and the basal ganglia [9-12]. With selective neuronal failure in substantia nigra pars compacta, Lewy 's body, consisting mainly of α-synuclein and inclusion bodies due to irregular deposits, becomes noticeable [13,14]. Degeneration of dopaminergic substantia nigra striatal neurons with Lewy bodies is considered a major neuropathological correlation for movement disorders in PD. In addition, similar damage appears in glutamatergic, cholinergic, GABAergic, tryptaminergic, noradrenalinergic and adrenergic neurons [15].

PD pathology involves ion channel activity, activity associated Ca2+ homeostasis, mitochondrial dysfunction, and increased metabolic stress [16-19]. In addition, in some familial PD cases, pathogenic mutations in the familial PD genes (PARK genes) have been identified, most of which are associated with increased metabolic stress [20-22].

Neuronal Ca2+ sensor proteins (NCS) bind to various interaction partners that react to changes in intracellular Ca2+ and activate different signaling pathways [23-25]. Neuronal Calcium Sensor 1 (NCS-1) is involved in a number of neural functions such as synaptic transmission and plasticity, neuronal survival and promotes mitochondrial function [26-28]. The appearance of NCS-1 in the brain increases during the neonatal phase and decreases with growth. However, increased expression is observed again during various cell disorders [29]. For example, the altered expression of NCS-1 modifies its relationship to target proteins, leading to disruption of dopaminergic signaling in multiple diseases, including schizophrenia and PD [28,30-34]. Therefore, NCS-1 is especially important in the context of activity-related Ca2+ stress and dopaminergic neuronal vulnerability in PD [33,34].

Simons *et al*. quantified mRNA levels of Ca2+ stress-related genes during NCS-1 failure using wild-type and NCS-1 knock-out mice by integrating UV laser LMD and RT-qPCR approaches and they found that NADH-ubiquinone oxidoreductase chain 1 (ND1), neuron-specific enolase 2 (ENO2), mitochondrial uncoupling proteins UCP4 and UCP5, and a familial Parkinson's disease causative gene DJ-1 (PARK7) has been specifically decreased in the melanotic dopaminergic neurons of NCS-1 KO mice [35].

Huntington's disease

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disease that occurs in adults. HD has a specific phenotype of distinct movement disturbances, clinical symptoms, and cognitive disability. Motor neuron symptoms include chorea, dyskinesia, and dystonia. Psychiatric symptoms such as depression, anxiety, and sleep disorder appear to precede motor symptoms [36]. Cognitive deterioration presents in low concentration, difficulty in remembering newly learned information, poor language skills, disrupted speech and impaired vision. Stiffness of motor neuron and dementia predominates during the disease progresses.

HD displays neuropathological symptoms in many areas of the brain, with the most severe degeneration occurring in the caudate nucleus and putamen. The HD causative protein is huntingtin (htt) on chromosome 4. An unstable extension of the CAG (glutamine-encoding trinucleotide) repeats occurring in the first exon of the Interest Transcript 15 (IT 15) gene in HD patients. The htt glutamine tail is usually elongated 8 to 36 times in the healthy person, whereas 41 times or more in the HD group. HD can be seen with htt having 38 or more repeats of glutamine, but in rare cases it has been documented that symptoms are not evident even with up to 41 repeats [37].

Some studies have shown a clear inverse association between the number of repeats and the age at onset of HD [38-40]. Neuronal damage occurs in GABAergic neurons, which up 95% of the striatum cells [41] and dysfunction of the striatal cortical pathway and loss of pyramidal cells is widespread [42]. Striatal neurons are locally lost in HD; therefore, HD is also an attractive candidate for stem cell transplantation therapy. Transplantation of stem cells to the striatum has also been shown to improve motor and cognitive dysfunction in animal models [43,44]. In addition, mesenchymal stromal and neural stem cells (NSCs) are tested for HD stem cell therapy [45,46].

Fetal tissue contains different cells, so it is important to isolate the correct source of the cells.

In order to pick up the cells correctly, Andre *et al*, established a new experimental method for the LMD extraction of samples from brain slices [47]. The optimum tissue section thickness for LMD is usually 4-15 μm [48], but some studies have been conducted with slices up to 200 μm using UV laser cutting [49]. In their experiments, they successfully cut 400 μm organ-type slices using LMD, further separating the HD transplanted stem cells from the surrounding host tissues and analyzing them with RT-qPCR.

Multiple system atrophy

Multiple System Atrophy (MSA) is an adult sporadic neurodegenerative disorder. Olivopontocerebellar atrophy (OPCA), striatonigral degeneration (SND) and Shy-Drager syndrome (SDS) are all included in the MSA. MSA affects approximately 3/ 100,000 people annually [50,51]. The average age at onset is between 50 and 75 years [52,53]. The incidence rises to approximately 12 per 100,000 over 70 years of age [54].

MSA causes a relatively rapid deterioration of the central nervous system with an overall survival period of 6-10 years [55,56]. 20-75% of MSA patients include prodromal stages of non-motor symptoms, including cardiovascular autonomic dysfunction, genitourinary and sexual dysfunction, orthostatic hypotension, REM sleep behavior disorder, and respiratory disorders preceding movement disorders. as well [57]. There are two distinct clinical subtypes, the MSA-P (mainly Parkinsonism) and the MSA-C (mainly cerebellar ataxia). MSA-P refers to patients with signs of Parkinson's disease, such as postural stiffness and dysfunction, bradykinesia, and tremor. This definition includes patients that have historically been diagnosed with SND.

MSA-C contains more prevalent cerebellar signs such as eye movement dysfunction, cerebellar dysarthria, and ataxia in the limb. MSA-C typically involves patients previously known as OPCA classical. Both phenotypes are usually observed in patients at the later stage of the disease [58-64].

MSA confirms high-density ubiquitinated α-synuclein aggregates containing protein aggregates known as argyrophilic glial cytoplasmic inclusion bodies (GCI) in oligodendrocytes [53,65-68]. GCIs are emerging from the early stages of neuronal failure, and found to remain even though several of the cells have lost. It is also present in the nucleus of oligodendrocytes and the cytoplasm [52].

It is suspected that α-synuclein aggregation contributes to disruption of oligodendrocytes in the process of neuronal myelination, leading to microglial activation, and subsequent release of α-synuclein from defective oligodendrocytes. Adjacent neurons can take extracellularly released α synuclein. This initiates the next aggregation inside the neuron cell. In addition, it is thought that toxic α-synuclein will spread to neurons in other synaptic brain regions in a prion-like manner [69-75]. The lack of practical support for local neurons for oligodendrocytes and the effects on neurons of α -synuclein inclusion bodies eventually contribute to axonal dysfunction, neuronal cell death and reactive astrocytes [53,76].

A genome-wide expression profiling analysis was performed by preparing RNA samples from cerebellar white matter of MSA patients and healthy individuals using LMD [77]. NF1 (neurofibromatosis 1) associated with the myelination process, PLP1 (proteolipid protein 1) involved in the development of oligodendrocytes and maintenance of axons, and ERMN (Ermin) involved in the formation of myelin and in the maintenance and stabilization of myelin sheaths, were down-regulated in patients with MSA-C. Whereas GGCX (gamma-glutamyl carboxylase) gene (OMIM: 137167) was upregulated in MSA patients that are specifically functionally associated with myelination. GGCX is necessary for the activation of vitamin K-dependent proteins [78] and mutations in this gene cause "GGCX syndrome" (OMIM: 137167). Vitamin K has been shown to postpone fibrosis of α-synuclein in vitro by the interaction of α-synuclein at a particular site at the N-terminus [79].

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal motor neuron disease characterized by degenerative changes in both upper and lower motor neurons [80,81]. 10% of ALS is known as familial ALS (FALS). Almost all these cases are inherited in an autosomal dominant manner. The remaining 90-95% of cases of ALS are sporadic ALS (SALS) with no family history [82].

Superoxide dismutase1 (SOD1) is a 153 amino acid metal enzyme, one of the three superoxide dismutase presents in humans, and was the first molecule shown to be associated with ALS [83]. SOD1 binds to copper and zinc in order to form a very stable homodimer. Mutations in the SOD1 gene are associated with a 50-80% reduction in enzyme activity [83,84] indicating that loss of dismutase activity results in disease. However, later studies have shown that dismutase activity is not associated with disease severity, suggesting that toxic acquisition of functional mechanisms could be working [85]. Recent meta-analyses data have shown that pathogenic variants in SOD1 account for approximately 15-30% of FALS and less than 2% of SALS cases [86]. The majority of SOD1 gene mutations are missense mutations, and the D90A variant is the most common in the world.

TAR DNA-binding protein 43 (TDP-43) is an etiological protein of ALS present in ubiquitinated inclusion bodies located in spinal cord neuron cytoplasm in patients with SALS [87-89]. The accumulation of ubiquitin-positive TDP-43 in the brain and spinal cord is considered a pathological characteristic of ALS [90-92]. TDP-43 is composed of 414 amino acids and has a signal for nuclear localization and export [93]. It is normally located in the nucleus and is involved in multiple RNA processing steps including pre-mRNA splicing, mRNA stability control, mRNA transport, translation, and non-coding RNA regulation [94-96].

Homozygous TDP-43 null mice are non-viable, suggesting that TDP-43 is central to embryonic development [97-99].

ALS is one of the diseases mostly used in the study of LMD, and its efficacy is being studied [100-103]. Recently, Krach *et al.* isolated motor neurons from the lumbar area of SALS patients with early respiratory failure using LMD and profiled the expression of RNA [104]. As a consequence, they found that the CK1E protein encoded by CSNK1E, a member of the CK1 family of serine-threonine protein kinases, plays a key role in various cellular processes, such as DNA replication and repair, interacted with TDP-43. Increased expression of CK1E resulted in increased TDP-43 phosphorylation and thus these findings suggest that CK1E can influence TDP-43 phosphorylation and may be a therapeutic target for ALS.

Alzheimer's disease

Alzheimer's disease (AD) accounts for up to 80% of all dementia diagnoses [105]. Postmortem brain tissue assessment is needed for a definitive diagnosis of AD. Relatively new clinical parameters such as biomarker identification of cerebrospinal fluid (CSF) and positron emission tomography (PET) have also become useful in recent years [88]. Available drug therapy in patients at all stages of AD dementia is an inhibitor of cholinesterase. Memantine is also used for mild to severe AD dementia. These medicines have been shown to enhance the quality of life of both patients and caregivers when prescribed for the disease at the right time however, they do not slow down or reverse the progression of disease [106].

Most cases of AD are sporadic. Multiple factors, such as environmental exposure, genetic risk factors, mitochondrial haplotypes, age and gender, have been identified, but the cause of AD development remains unknown [88,107,108]. Approximately 1% of AD cases are associated with familial mutations in either the amyloid protein precursor (APP) or the presenilin 1 (PS1) and presenilin 2 (PS2) genes specifically involved in APP processing.

Cleavage of APP on the cell membrane by α-secretase does not form pathological amyloid-β (Aβ) peptides. On the other hand, cleavage by β and γ-secretase produces the disease-causing Aβ 40 or Aβ 42 peptide, which is released into the extracellular space and becomes a major component of the extracellular aggregate amyloid plaque [106,109-112]. In several in vitro and in vivo studies using human tissues and transgenic mice, extracellular Aβ accumulates prior to the formation of extracellular plaques that directly affect synaptic function and has been shown to cause severe memory loss [113-115]. It has also been documented that Aβ is present in neurons, develops β-and γ-secretase cleavage in the trans-Golgi network [116], endoplasmic reticulum (ER), endosomes, lysosomes [117], mitochondrial membrane.

[118] In addition, secreted Aβ peptides can be internalized by receptor-mediated and non-receptor-mediated endocytosis [119-121]. Extensive studies also support the notion that soluble Aβ oligomers are the most toxic species affecting multiple early molecular pathways that lead to synaptic dysfunction in AD [120].

The discovery of familial AD mutations in the APP, PS1, and PS2 genes led to an amyloid cascade hypothesis that attributed the emergence of Aβ to disease. In fact, overproduction of Aβ peptide is observed early in patients who develop AD and is important for AD pathology [122]. However, there have been studies of cases in which cognitive dysfunction does not occur while having substantial Aβ [123,124] and it is difficult to understand AD on its own with an amyloid cascade hypothesis.

Intracellular neurofibrillary tangles (NFTs) are another essential component of AD. Tau is a microtubule-stabilizing protein that, when hyperphosphorylated, falls out of microtubules, leading to tau destabilizing and disrupting transport mechanisms [125]. Memory impairment in AD is closely correlated with hippocampal synaptic defect [126-128]. As a promoter of axonal microtubule assembly, tau plays a role in sustaining neuronal projection and influencing synaptic function. Loss of tau binding to microtubules is leading to synaptic dysfunction. However, it is unclear how tau mechanically retains synaptic plasticity or how the pathogenic version of tau impairs it. The widespread presence of Aβ in the brain does not seem to contribute to the development of AD unless the tau is present in the affected area. These findings support the idea that synergistic interactions between Aβ and Tau are necessary to cause neurodegeneration in AD [129,130].

The hippocampus and its surrounding area are critical for memory function and are severely impaired in the early stages of AD. The pathology seen in the hippocampus consists of extreme neuronal loss, severe plaque deposition, neurofibrillary tangle (NFT) formation, and neuroinflammatory reactions. The anterior hippocampal limb, one area of the hippocampus, tends to have a distinct pathological AD profile relative to the other regions of the medial temporalis region.

Early in the AD disease phase, deposits containing "lake-like" diffusive Aβ occur in the anterior hippocampal limb, with no aggregate morphology seen when forming with amyloid fibrils [131,132]. Components of this particular diffuse Aβ deposit were studied in conjunction with LMD and mass spectrometry in both sporadic AD, inherited and familial AD, and Familial British Dementia (FBD) and Familial Danish Dementia (FDD) brain amyloidosis and found that the deposit contain three forms of amyloid peptides Aβ, ABri, and ADan. ABri and Adan are molecules formed by the cleaving of a type II transmembrane protein called an endogenous 2B membrane protein (BRI 2). ABri and ADan cause deposits of amyloid in the blood vessels and brain. Since BRI 2 interacts with APP, the interaction between Aβ and ABri or ADan may also be relevant to influence the rate of amyloid production or this aggregation [133-135].

Endosomal dysfunction is one of the early pathologies observed in the brain of AD [136]. The endosomal pathway performs many of the main functions of the neurons, including the internalization of nutrients and growth factors, the recycling of receptors and the signaling of appropriate intracellular pathways. A group of small ras-related GTPase (rab) proteins control vesicular transport to early late endosomes and other organelles along the endosome-lysosomal pathway [137]. Early endosome effector rab5 and late endosome component rab7 regulate nervous growth factor (NGF) signaling [138,139]. Ginsberg *et al.* collected a population of neurons only from deceased subjects using LMD and analyzed endosomal markers selected by a customized microarray analysis. As a result, there has been a significant upregulation of the early endosome effector genes, including the late endosome genes rab4 and rab5 [140].

In another case of the use of LMD for the study of AD, the expression profile of hippocampal CA1 pyramidal neurons in aged Ts65Dn mice, a mice model of Down's Syndrome (DS) and Alzheimer's Disease (AD), was examined. Alldred *et al* isolated CA1 pyramidal neurons only by use of LMD and found that there was a down-regulation of the neurotrophin-associated receptor [141]. Neurotrophin receptors, especially BDNF and TrkB, are potent regulators of synaptic plasticity, learning, and memory [142].

Frontotemporal lobar degeneration

Frontotemporal lobar degeneration (FTLD) is a progressive neuropathy with severe behavioral, personal and verbal symptoms. It accounts for around 20% of dementia diseases [143]. The main FTLD syndromes are frontotemporal dementia (bvFTD) with prominent personality, behavioral abnormalities, progressive non-fluent aphasia (PNFA) and semantic dementia (SD) in which the meaning of terms and products is not understood. Even if the pathological form is different, the clinical picture appears according to the topography of the lesion. Pathologically, the majority of FTLD examples aggregate particular proteins in nerve or glial cells to form inclusion bodies. Tau, TDP-43, and fused in sarcoma (FUS) have been described as major constituent proteins, comprising three major pathological groups: FTLD-tau, FTLD-TDP, and FTLD-FUS.

The histopathological characteristic of FTLD-U is ubiquitin-positive, tau, and α-synuclein-negative intraneuronal inclusions primarily in the dentate gyrus and frontotemporal cortex of the hippocampus [144]. LMD was used to isolate the ubiquitinated inclusion of hippocampal dentate gyrus in patients with FTLD-U and the components were detected by LC-MS/MS. 73 candidate proteins with FTLD-U-specific expression changes were detected, of which 54 were found to be selectively increased in expression and 19 were found to be decreased in FTLD-U [145].

Pick's disease is a disease included in FTLD and is characterized as a constituent by Pick 's body containing phosphorylate tau. Eight of a total of 16 alternative splicing exons have six central nervous system (CNS) isoforms and six additional peripheral nervous system (PNS) isoforms [125]. Alternative splicing mainly affects the N-terminal projection region and the microtubule binding domains (MBDs), producing 4-repeat (4R) and 3-repeat (3R) tau. These two isoforms are preserved in a balanced ratio (1:1) in the adult brain and disruption of the 3R to 4R tau expression ratio induces AD and other tauopathy [146]. The most studied function of Tau is to promote the construction and stability of microtubules, supported primarily by studies using cell-free in vitro systems, and it has been found that 4R tau has more robust microtubule support activity than 3R tau [147]. Using LMD method, Ohkubo *et al.* was isolated by approximately 500 of Pick bodies and analyzed by a mass spectrometer. Consequently, they found that phosphorylate tau (69 kDa, tau 69) isoforms were accumulated in Pick bodies [148].

Conclusions

Protein aggregation disorders are often caused by aging and the number of patients is expected to continue to increase as life expectancy rises. However, many mechanisms behind these diseases have not yet been explained. In addition, unfortunately, there are currently no known preventive or curative approaches.

One of the key reasons for this is that the components of protein aggregates and disease-specific deposits have not been clarified.

As we have seen in the study of neurodegenerative diseases, it has become possible to isolate only particular cells from a complex mixture

of tissues with LMD and to examine the components of nucleic acids and proteins. LMD is now used to address these issues in the field of neurodegenerative diseases. High-precision target separation using LMD approach is expected to accurately identify disease-derived deposit components when combined with high-sensitivity mass spectrometry. It would be fantastic if this could soon elucidate the real pathophysiology of protein aggregation and improve treatment and preventive methods.

The current pathological classification of neurodegenerative diseases associated with protein aggregation deposits is based on proteins with irregular accumulation. In order to make an appropriate diagnosis based on clinical evidence, it is important to explain the pathophysiology of neurodegenerative diseases. High-definition extraction of the research targets by the LMD device and the establishment of a highly accurate sample-based analysis method would become more important.

Declaration of competing interest

The authors declare no competing financial interests.

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