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Invited Review

Pharmacological intervention of early neuropathy in neurodegenerative diseases

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ABSTRACT

Extensive studies have reported the significant roles of numerous cellular features and processes in properly maintaining neuronal morphology and function throughout the lifespan of an animal. Any alterations in their homeostasis appear to be strongly associated with neuronal aging and the pathogenesis of various neurodegenerative diseases, even before the occurrence of prominent neuronal death. However, until recently, the primary focus of studies regarding many neurodegenerative diseases has been on the massive cell death occurring at the late stages of disease progression. Thus, our understanding on early neuropathy in these diseases remains relatively limited. The complicated nature of various neuropathic features manifested early in neurodegenerative diseases suggests the involvement of a system-wide transcriptional regulation and epigenetic control. Epigenetic alterations and consequent changes in the neuronal transcriptome are now begun to be extensively studied in various neurodegenerative diseases. Upon the catastrophic incident of neuronal death in disease progression, it is utterly difficult to reverse the deleterious defects by pharmacological treatments, and therefore, therapeutics targeting the system-wide transcriptional dysregulation associated with specific early neuropathy is considered a better option. Here, we review our current understanding on the system-wide transcriptional dysregulation that is likely associated with early neuropathy shown in various neurodegenerative diseases and discuss the possible future developments of pharmaceutical therapeutics.

Contents

1. Introduction

Along with the increases in life expectancy of elderlies, the needs for accurate diagnosis and effective therapeutic treatments of age-related neurodegenerative diseases have become a serious issue worldwide. Among various neurodegenerative diseases, the most representative ones are Alzheimer's disease (AD), Parkinson's disease (PD), Lou Gehrig's disease/Amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). Being the most common neurodegenerative diseases, AD is partly associated with genetic risk factors such as mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1), presenilin 2 (PSEN2), and apolipoprotein E (APOE) [1]. Following AD, PD is the second most prevalent neurodegenerative disease [2]. PD has two distinct types of cause: one is environmen-

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tal factors primarily responsible for sporadic cases, constituting approximately 90%–95% of PD, and the other is genetic risk factors primarily responsible for the remaining familial cases [3,4]. ALS is a fatal neurodegenerative disease whose pathoetiology is partly associated with genetic mutations in superoxide dismutase 1 (SOD1), TAR DNA-binding protein 43 (TDP-43), fused in sarcoma/translocated in liposarcoma (FUS/TLS), and chromosome 9 open reading frame 72 (C9orf72) genes. Finally, HD belongs to a group of neurodegenerative diseases known as polyglutamine (polyQ) diseases, which are solely caused by expansion of CAG repeats encoding glutamines (Qs) within the coding regions of the disease-responsible genes [5,6]. Depending on the associated genes, they are categorized into at least nine subgroups, including HD and several types of ataxias [7,8].

Although detailed molecular and cellular mechanisms of these neurodegenerative diseases appear to be extremely complex and different from each other, interestingly, there exist certain features shared among them. The most prominent and well-studied characteristic commonly shared by these neurodegenerative diseases is massive neuronal death primarily observed at the late stages of the disease progression [9]. However, previous studies have also notably reported a broad spectrum of neuropathic features (Fig. 1) commonly acquired in many cases of these diseases, such as dendrite defects [10], impaired axonal transport [11–16], and mitochondrial perturbations [17], even much earlier than the occurrence of neuronal cell death in afflicted neurons. These neuropathic features evident at the early stages of the diseases might be more responsible for the initiation and progression of diverse disease symptoms than neuronal cell death. Given that reversing deleterious neuronal problems is extremely difficult once neurons die, further studies specifically focusing on early neuropathy are highly demanded in order to develop effective therapeutics for neurodegenerative diseases.

The complicated nature of the aforementioned neuropathic features manifested early in neurodegenerative diseases surmises the involvement of a system-wide transcriptional regulation and epigenetic control. Epigenetic alterations are heritable, potentially reversible, and influenced by environment without any changes in DNA sequences [18,19]. These include DNA methylation, post-translational modifications (PTMs) of histones (e.g., acetylation, methylation, phosphorylation, and ubiquitination), deposition/eviction of histone variants, and chromatin remodeling, generally accompanying transcriptional changes [20,21]. In the case of DNA methylation, a methyl group is attached to the 5′ position of the cytosine in 5′-CpG-3′ dinucleotides with the help of DNA methyltransferases (DNMTs), which generates heritable patterns that directly influence the transcription of subsets of genes by inhibiting transcription factor binding or recruiting methyl CpG-binding proteins [22,23]. Like PTMs of histones, this relatively stable modification is reversible through the action of ten-eleven translocation (TET) proteins, which catalyze conversion of 5-mehtylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC), 5-formylcytosine (5-fC), and 5-carboxycytosine (5-caC) [24]. These oxidized cytosines are then converted to unmethylated cytosines via base excision repair that is mediated by thymidine DNA glycosylase [25]. Another well-defined epigenetic marker, histone acetylation, generally correlates with gene expression activation [26,27]. An acetyl group is transferred to histones by histone acetyltransferases (HATs), which neutralizes their positive charge and thus decreases their affinity to negatively charged DNA. Histone acetylation consequently leads to an open chromatin structure, thereby promoting gene transcription [28]. These acetyl marks can be reversibly removed by histone deacetylases (HDACs), leading to a closed chromatin structure. Based on sequence similarity and their cognate cofactors, HDACs are classified into two categories: zinc-dependent classes (I, II, and IV) and nicotinamide adenine dinucleotide (NAD)-dependent class (III) [29]. In the following sections, we review our current understanding on the potential link between a system-wide transcriptional dysregulation involving epigenetic changes and early neuropathy of neurodegenerative diseases and provide our perspective on the possible future directions in developing pharmaceutical therapeutics for these diseases.

1.1. Various neuropathic features manifested at the early stages of neurodegenerative diseases

Perturbations of numerous cellular features and processes preceding massive neuronal death (Fig. 1) have been reported in various neurodegenerative diseases [30–32]. These neuropathic features include prominent morphological changes and intracellular defects in diseased neurons (Fig. 1), as presented below. Related to morphological changes of neurons, defective formation and maintenance of dendrites and/or axons have been observed in many neurodegenerative disease cases [33–41]. These morphological changes of neurons generally lead to synaptic loss and thus are considered to contribute to disease progression. These apparent changes of neuronal morphology often involve alterations in intracellular components such as cytoskeletal alterations [10]. Consistently, a number of studies on neurodegenerative diseases have reported alterations in the distribution and dynamics of filamentous actin (F-actin) in afflicted neurons [42–45]. For example, a previous study on polyQ diseases demonstrated that the F-actin structures were absent in the distal dendrites of afflicted neurons [43]. Another study on polyQ diseases also reported a shift in actin polymerization because of a perturbed ratio of F-actin to globular actin (G-actin) caused by toxic polyQ proteins [44]. Moreover, abnormal bundling and accumulation of F-actin by the expression of hyperphosphorylated tau have been revealed in both *Drosophila* and mouse models of AD [42]. Likewise, the formation of abnormal actin structures such as cofilin-actin rods (actin aggregates) and Hirano bodies has been implicated in AD pathogenesis [45].

Among various intracellular components altered in neurodegenerative disease conditions, mitochondria are the most well described and heavily studied ones. Mitochondria play essential roles in diverse biological processes, such as intracellular signaling, calcium homeostasis, ATP synthesis, and apoptosis [46–48]. There are many studies showing not only morphological, but also functional problems of mitochondria in various neurodegenerative diseases, such as AD [49], PD [49–51], ALS [52,53], and HD [54–57]. As one detailed example, Wang et al. showed that APP overexpression caused mitochondrial defects at multiple levels, such as fragmented mitochondria, abnormal distribution of mitochondria accumulating around the perinuclear regions of the cell, elevated reactive oxygen species levels, decreased ATP synthesis, and reduced mitochondrial membrane potential [49]. In addition, other types of intracellular defects such as axonal transport impairment [58–60], Golgi fragmentation [61–63], disturbed secretory pathway [31], and defective endosome trafficking [51] have been characterized in various neurodegenerative disease conditions. However, detailed molecular mechanisms underlying the early neuropathy of these neurodegenerative diseases still remain uncharted in many cases.

1.2. System-wide transcriptional dysregulation potentially associated with early neuropathy

Transcriptional dysregulation has been very often observed in the contexts of neurodegenerative diseases and is suspected to be one possible molecular mechanism underlying the aforementioned neuropathic features. It tends to occur in a system-wide manner, which has been evident in extensive studies on AD [64–66], PD [67,68], ALS [69–74], and HD [75–78], presenting significant