Commentary

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TDP-43: A Key of Neurodegenerative Disease

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Neurodegenerative diseases are referred to as TDP-43 proteinopathy, which are associated with the depletion of TDP-43 in the nucleus and the accumulation of TDP-43 in the cytoplasm through hyperphosphorylation, ubiquitination and cleavage [1-3]. Transactive response DNA-binding protein (TAR-TDP-43) is a RNA/DNA-binding protein encoded by TARDBP, which is a widely expressed member of heterogeneous nuclear ribonucleoprotein (hnRNP) family and was first named in 1995 [4,5].

TDP-43 consists of an N-terminal domain (NTD), two RNA recognition motifs (RRM1 and RRM2), and a C-terminal domain (CTD) [6]. It is involved in RNA metabolism, protein quality control system, mitochondrial autophagy, axonal transport, vesicle transport and stress response [7-12]. TDP-43 shuttled between cytoplasm and nucleus to fulfill its physiological functions, and controlled TDP-43 homeostasis through self-feedback autoregulation [13-15]. It regulates RNA metabolism, maintains mRNA stability, and participates in selective splicing of mRNA precursor as a component of transcription complex [11,16-18].It is also participates in classical non-homologous end junction (NHEJ) DNA repair and the formation of ribonucleoprotein (RNP) granules [18-21]. It plays a role in promoting microRNA to form RNA-induced silencing complex (RISC) [22].TDP-43 participates in the formation of stress granules through Liquid-liquid phase separation (LLPS) [1,13,17,23], carries out intracellular transport through vesicles [24], fulfills cross-synaptic transmission between cells through exosomes(controversial) [25,26], and achieves intercellular transport through tunnel nanotubes (TNTs) [27].

The pathogenesis of TDP-43 has been divided into two theories: gain of function theory and loss of function theory, that is, toxicity is obtained through overexpression and mutation, and normal function is lost through gene deletion or mutation [10,28-30]. Therefore, abnormal TDP-43 results in impaired physiological responses in which it is involved and exacerbates TDP-43 deposition.

Neurodegenerative diseases with TDP-43 pathology include Amyotrophic lateral sclerosis (ALS) [31], Frontotemporal lobar degeneration (FTLD) [12], Alzheimer's disease (AD) [32], The Guam parkinsonism–dementia complex(G-PDC) [33], Perry syndrome [34], Huntington's disease (HD) [35], Limbic-predominant age-related TDP-43 encephalopathy (LATE) [36], Hippocampal Sclerosis(HS) [37], Niemann-Pick C disease (NP-C) [38], Alexander disease (AxD) [39], Parkinson's disease and Dementia with Lewy bodies [40,41], multiple system atrophy (MSA) [42], Progressive Supranuclear palsy (PSP) [43], Corticobasal degeneration (CBD) [44].TDP-43 can be used as an indicator of pathological stage. At present, TDP-43 in ALS can be divided into five stages [45-47], FTLD into four stages [48-50], AD into six stages [51-53], and late-nc into six stages [36,54-56]. PSP is divided into five stages [43].Perry syndrome has TDP-43 pathology in six characteristic sites [57,34,58,59]. HS is divided into three stages [56].

In conclusion, TDP-43 is involved in a variety of intracellular and intercellular physiological reactions. When affected by environmental or self-related factors, TDP-43 can promote the development of neurodegenerative diseases independently or in coordination with other proteins by gaining of losing of function. TDP-43 protein pathologies often coexist with other protein pathologies, suggesting that TDP-43 may act synergistically with other proteins to promote the occurrence and development of neurological degenerative diseases. Many neurodegenerative diseases have TDP-43 deposition, so the specificity is low and cannot be used as a marker for diagnosis, but it has the significance of indicating disease staging, and can be used as a potential therapeutic target to provide direction for treatment.

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