



Title	TDP-43 transports ferritin heavy chain mRNA to regulate oxidative stress in neuronal axons
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論文内容の要旨
Synopsis of Thesis

氏名 Name	神野 隼輝
論文題名 Title	TDP-43 transports ferritin heavy chain mRNA to regulate oxidative stress in neuronal axons (TDP-43は、フェリチン重鎖mRNAの軸索輸送に関わり、軸索での酸化ストレスを調整する)
論文内容の要旨 〔目的(Objective)〕 Amyotrophic lateral sclerosis (ALS) is characterized by the mislocalization and abnormal deposition of TAR DNA-binding protein 43 (TDP-43). This protein plays important roles in RNA metabolism and transport in motor neurons and glial cells. We have previously demonstrated that TDP-43 downregulation significantly affects the expression of ferritin heavy chain (<i>Fth1</i>) mRNA in the axonal regions of neurons. The ferritin heavy chain regulates iron homeostasis in conjunction with the ferritin light chain, converting ferrous ions (Fe^{2+}) to ferric ions (Fe^{3+}) through its ferroxidase activity. This process allows ferritin to store iron and protect cells from reactive oxygen species (ROS), mainly hydroxyl radicals ($\cdot\text{OH}$), generated via the Fenton reaction ($\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \cdot\text{OH}$). Oxidative stress and changes in iron homeostasis are believed to be involved in the pathophysiology of ALS, but the mechanisms by which TDP-43 contributes to oxidative stress and iron accumulation in the central nervous system remain elusive. In this study, we aimed to investigate whether <i>Fth1</i> mRNA is a target transported to the axon by TDP-43 using biophysical and biochemical analyses. Moreover, we evaluated whether changes in ferritin heavy chain in axons lead to the increase of Fe^{2+} and ROS signal using probes that specifically react with Fe^{2+} and ROS, and molecularly elucidated the involvement of oxidative stress in the pathophysiology of ALS. 〔方法ならびに成績(Methods/Results)〕 Primary cortical neurons from embryonic day 15 (E15) B6J mice were cultured using insert chambers, and axonal and cell body fractions were collected for biochemical analyses such as quantitative PCR and western blotting. We confirmed that <i>Fth1</i> mRNA and ferritin heavy chain decreased in axonal fractions of cortical neurons by TDP-43 knockdown, though no significant difference was observed in the cell body fraction. Moreover we demonstrated that <i>Fth1</i> mRNA co-localized with TDP-43 via the 5'UTR or 3'UTR using imaging analysis. Next, live cell imaging of cortical neurons cultured in microfluidics chambers (with 450 μm microgrooves) using confocal microscopy showed Fe^{2+} increase in the axonal area of cortical neurons following TDP-43 knockdown. The Fe^{2+} signal was also enhanced in the cell body, and similarly, the ROS signal showed the increase throughout the whole neuron. 〔総括(Conclusion)〕 In this study, we demonstrated that TDP-43 knockdown lead to the decrease in <i>fth1</i> mRNA and ferritin heavy chain protein in the axonal fraction of neuronal cells, which subsequently resulted in the increase in Fe^{2+} and ROS levels throughout the whole neuronal cells. These findings suggest that oxidative stress and changes in iron homeostasis are involved in the pathophysiology of ALS.	

論文審査の結果の要旨及び担当者

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	論文審査の結果の要旨
	筋萎縮性側索硬化症 (ALS) は、TAR DNA結合タンパク質43 (TDP-43) の細胞質への局在化によって特徴づけられ、同タンパク質は運動ニューロンにおけるRNA代謝および輸送において重要な役割を果たす。また、ALS患者・モデル動物の病理組織や検体より、鉄代謝異常と酸化ストレスは、ALSの病態に関わると考えられる。本研究では、マイクロアレイ解析でTDP-43のdown-regulationによって、軸索分画で減少が確認されたFth1 (フェリチン重鎖) mRNAが、TDP-43によって軸索に輸送されることを明らかにし、TDP-43の減少下では軸索でのフェリチン重鎖の減少を通じて、鉄イオンの状態変化・酸化ストレスの増強が起こることを示した。本研究は、TDP-43が神経細胞において、鉄を媒介した酸化ストレスを制御し、ALSの病態に寄与する可能性を示すもので、学位に値するものと認める。