

Cathepsin B inhibition blocks neurite outgrowth in cultured neurons by regulating lysosomal trafficking and remodeling

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論 文 名	Cathepsin B inhibition blocks neurite outgrowth in cultured neurons by regulating lysosomal trafficking and remodeling (培養神経細胞においてカテプシン B の抑制はリソソーム輸送とリモデリングを調節することで神経突起の成長を阻害する)			
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論 文 審 査 の 結 果 の 要 旨

Lysosomes are known to mediate neurite outgrowth in neurons. However, the principal lysosomal molecule controlling that outgrowth is unclear. We studied primary mouse neurons in vitro and found that they naturally develop neurite outgrowths over time and as they did so the lysosomal cysteine protease cathepsin B (CTSB) mRNA levels dramatically increased. Surprisingly, we found that treating those neurons with CA-074Me, which inhibits CTSB, prevented neurites. As that compound also inhibits another protease, we evaluated a N2a neuronal cell line in which the CTSB gene was deleted (CTSB knockout, KO) using CRISPR technology and induced their neurite outgrowth by treatment with retinoic acid. We found that CTSB KO N2a cells failed to produce neurite outgrowths but the wild-type (WT) did. CA-074Me is a cell permeable prodrug of CA-074, which is cell impermeable and a specific CTSB inhibitor. Neurite outgrowth was and was not suppressed in WT N2a cells treated with CA-074Me and CA-074, respectively. Lysosome-associated membrane glycoprotein 2-positive lysosomes traffic to the plasma cell membrane in WT but not in CTSB KO N2a cells. Interestingly, no obvious differences between WT and CTSB KO N2a cells were found in neurite outgrowth regulatory proteins, PI3K/AKT, ERK/MAPK, cJUN, and CREB. These findings show that intracellular CTSB controls neurite outgrowth and that it does so through regulation of lysosomal trafficking and remodeling in neurons. This adds valuable information regarding the physiological function of CTSB in neural development.

The present study indicates the importance of CTSB expression on the development of neurite outgrowth via PI3K/AKT, ERK/MAPK, cJUN, and CREB. The present work could be recommended for a candidate for Doctor of Philosophy (Dental Science) degree in Graduate School of Dentistry, Kyushu University.