学位論文抄録
Abstract of Thesis

Tsukushi proteoglycan maintains RNA splicing and developmental signaling network in GFAP-expressing subventricular zone neural stem/progenitor cells
（GFAP を発現する脳室下帯神経幹細胞／前駆細胞の RNA スプライシングと発生シグナルネットワークを維持するプロテオグリカン Tsukushi）

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Abstract of the Thesis

Objective: Tsukushi (TSK) proteoglycan dysfunction leads to hydrocephalus, a condition defined by excessive fluid collection in the ventricles and lateral ventricular enlargement. TSK injections into the LV at birth are effective at rescuing the lateral ventricle (LV). TSK regulates the activation of the Wnt signaling to facilitate the proper expansion of the LV and maintain the fate of the neural stem cell lineage. However, the molecular mechanism by which TSK acts on neural stem/progenitor cells (NSCs) during LV development is unknown. We demonstrated that TSK is crucial for the splicing and development-associated gene regulation of GFAP-expressing subventricular zone (SVZ) NSCs.

Method: We isolated GFAP-expressing NSCs from the SVZ of wild-type (GFAPGFP/+/TSK+/+) and TSK knock-out (GFAPGFP/+/TSK−/−) mice on postnatal day 3 and compared their transcriptome and splicing profiles.

Results: TSK deficiency in NSCs resulted in genome-wide missplicing (alteration in exon usage) and transcriptional dysregulation affecting the post-transcriptional regulatory processes (including splicing, cell cycle, and circadian rhythm) and developmental signaling networks specific to the cell (including Wnt, Sonic Hedgehog, and mTOR signaling). Furthermore, TSK deficiency prominently affected the splicing of genes encoding RNA and DNA binding proteins in the nervous SVZ and non-nervous muscle tissues.

Discussions: These results suggested that TSK is involved in the maintenance of correct splicing and gene regulation in GFAP-expressing NSCs, thereby protecting cell fate and LV development.

Conclusion: Hence, our study provides a critical insight on hydrocephalus development.