論 文 審 査 の 結 果 の 要 旨

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（論文審査の結果の要旨）

Glioblastoma is the most aggressive brain tumor with poor prognosis. Nox4 expression was previously reported to be upregulated in glioblastoma cells and consider to play a role in cellular functions related to the malignant phenotype, but its regulatory mechanism is largely unknown. His principal aim of this study was to characterization of the regulation and function of the Nox4 and to dissect the pathway downstream of Nox4 redox signaling involved in the bioactivities of glioma cells.

It was found that,

1. Nox4 mRNA was prominently expressed and involved in spontaneous ROS production in glioma cells.
2. Silencing of Nox4 expression by Nox4-targeted siRNA suppressed cell growth and motility of glioblastoma U87 cells.
3. Nox4-derived ROS oxidized and inactivated protein tyrosine phosphatase (PTP):1B: PTP1B in its active form downregulates cell proliferation and migration.
4. Tyrosine-phosphorylated coronin-1C was identified as a substrate of PTP1B.
5. Ablation of coronin-1C attenuated the proliferative and migratory activity of U87 cells.
6. Coronin-1C, associated with malignancy of glioblastoma is tyrosine-phosphorylated.
7.Tyrosine phosphorylation level was suppressed by Nox4 inhibition, suggesting that tyrosine-phosphorylation of coronin-1C is regulated by the Nox4-PTP1B pathway.

In summary, his study establishes the Nox4-PTP1B-coronin 1C axis as a novel redox signaling pathway contributing to glioblastoma development. Thus, the discovery suggests a critical mediating role of Nox4 redox signaling in gliomagenesis. Nox4 may serve as a potential molecular target in the development of therapeutic agents for malignant gliomas.

主査、副査は一致して本論文を学位論文として価値があるものと認めた。