Development of new therapeutic drugs for glioma targeting choline transporter-like protein 1

Masato Inazu[1,2], Saiichiro Watanabe[1], Nozomi Nishijima[1], Kaho Hirai[1], Akane Hase[1], Kaoru Shibata[1], Riko Gido[1], Tsuyoshi Yamanaka[2]

[1]Inst. Med. Sci., Tokyo Med. Univ., [2]Dept. Mol. Preventive Med., Tokyo Med. Univ.

Choline is an organic cation that plays a critical role in the structure and function of biological membranes. Intracellular choline accumulation through choline transporters is the rate-limiting step in phospholipid metabolism, and it is a prerequisite for cell proliferation. In this study, we examined the functional characterization of choline transporters in U251MG glioma cells. Furthermore, we searched for compounds that inhibit choline uptake as well as cell proliferation in a plant-derived natural organic compound library. Choline transporter-like protein 1 (CTL1) and CTL2 mRNA are highly expressed. CTL1 and CTL2 were located in the cell membrane and intracellular compartment, respectively. [^{3}H]Choline uptake was mediated by a single Na^+-independent, intermediate-affinity transport system. We found two hit compounds that inhibit choline uptake and cell proliferation from 500 plant-derived natural organic compounds. These hit compounds reduced cell survival and enhanced caspase-3/7 activity. One of the compounds inhibited tumor growth in U251MG cell xenograft model mice. These results suggest that CTL1 is functionally expressed in glioma cells and are also involved in abnormal proliferation. Identification of this CTL1-mediated choline transport system provides a potential new target for glioma therapy.