Potential metabolic changes mediated by cGAMP in astrocytes in contact with brain metastatic cancer

Hiromi Sato[1], Kurumi Hara[1], Toya Okawa[1], Hiroki Tanaka[2], Daiki Shirane[2], Hiroto Hatakeyama[1], Hidetaka Akita[2], Akihiro Hisaka[1]

[1]Clinical Pharmacology & Pharmacometrics, Grad. Sch. Pharmaceut. Sci., Chiba Univ., [2]Design and Drug Disposition, Grad. Sch. Pharmaceut. Sci., Chiba Univ.

In tumor brain metastasis, a gap junction was formed between astrocytes and cancer cells, and cGAMP (Cyclic 2'3'-GMP-AMP) was reported to be transmitted to astrocytes. It is known as a ligand for STING that involves innate immune response signaling, and that also can be a material for nucleic acids and amino acids. Thus, cGAMP transmission may alter the metabolic function of astrocytes, creating a favorable environment for tumor survival. In this study, after introducing cGAMP into the cell from the outside, the amount of cGAMP in the cell and the subsequent phenotypic changes were examined. Since cGAMP is hydrophilic, lipid nanoparticles (SS-cleavable and pH-Activated-like Material: ssPalm) were used as a carrier. The ssPalm-cGAMP complex was added to the cultured astrocytes. 12 ng of cGAMP was detected by CE-MS from astrocytes to which ssPalm-cGAMP complex equivalent to 8 μg of cGAMP was added. IFNβ mRNA expression and secretion into the culture supernatant, downstream of STING, were significantly increased by 15.3 and 1.7 times, respectively. Subsequently, the complex significantly increased the 2-deoxyglucose uptake by 1.1 times. For glutamate (Glu) metabolism, cGAMP was shown to increase the secretion of Glu into the supernatant while suppressing the conversion of intracellular Glu to Gln. These results suggest that cGAMP stimulates STING in astrocytes, moreover, promotes glucose utilization and activation of Glu metabolism. It should be further investigated that how this metabolic change affects the microenvironment formation of brain metastasis.