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Short Communication

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A novel prodrug of gamma glutamylcyclotransferase inhibitor has anti-proliferative activity in-vitro and anti-cancer activity in-vivo

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Abstract:

C7orf24 was discovered as a highly expressed protein in bladder cancers by a proteomic analysis and later identified as the -glutamylcyclotransferase (GGCT). The silencing of GGCT using siRNA inhibited cancer cell proliferation and tumor growth in mice inoculated with cancer cells. However, the relationship between GGCT enzymatic activity and these phenotypes remained unknown. Therefore, we tried to identify a potent GGCT inhibitor and investigated its anti-cancer activity in vitro and in a xenograft mouse model. We performed a screening of GGCT inhibitors from 41 candidate compounds, and identified N-glutaryl-L-Ala (GA) that showed the highest inhibitory activity. Next, we used a NBD fluorochrome-tagged GA, Nα-glutaryl-L-Lys (NBD), to evaluate cell permeability. However, no signal derived from NBD was observed inside cells. In order to improve its permeability, we generated a less polar prodrug "Nα-methoxyglutaryl-L-Lys(NBD)-OCH2OCOCH3 (Me-gKFA-AM)" where carboxylates in the structure of the parent inhibitor were substituted by alkyl esters. As had been expected, Me-gKFA-AM was successfully internalized into the cells and conversion of the prodrug into the parent drug in MCF-7 breast cancer cells was confirmed by HPLC. We demonstrated anti-proliferative activity of the methyl-acetoxymethyl ester prodrug of GA (pro-GA) in human MCF7, HL-60, and PC3 cancer cells in vitro. Moreover, pro-GA administration exhibited anti-cancer effects in a xenograft model using immunocompromised mice inoculated with PC3 cells. These results indicate that the pro-GA may be promising as a lead compound to inhibit GGCT activity for the novel cancer therapeutic strategy.

Biography:

Hiromi Ii has completed her PhD at Kyoto Pharmaceutical University in 2008 and postdoctoral studies at University of Washington. She is an assistant professor of the Department of Clinical Oncology, Kyoto Pharmaceutical University.