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学 位 論 文 要 旨
Dissertation Abstract

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学位論文題目：
Title of Dissertation

Evaluation of Anti-Proliferative Activity of Rare Aldohexoses, and Development of D-Allose Derivatives with Biological Activities (希少アルドヘキソースのがん細胞増殖抑制活性の評価および生物活性を有するD-アロース誘導体の開発)

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Sugars are important as energy sources and component materials for living organisms including human. Rare sugars are defined as monosaccharides and their derivatives rarely existing in nature. Recently, rare sugars are regarded as a promising source for the development of pharmaceutical drugs and food additives owing to their unique biological activities. Among the rare sugars, D-allose (D-All) showed plant growth-regulatory, antioxidant, and anti-proliferative activity. However, the concentration of D-All required to exhibit the activity is relatively high, which makes it difficult to use practically. Furthermore, there is no report on the anti-proliferative activity of the rare sugars other than D-All. Thus, the author attempted to develop a D-All derivative and investigate the anti-proliferative activity of rare aldohexoses.

The biological activity of D-All was known to improve by esterification. Thus, at first, the author attempted to synthesized D-All fatty acid esters with nematocidal activity. The author synthesized D-All fatty acid esters (**1**-**4**), 6-*O*-Octanoyl-D-Glc (**5**), and nonhydrolyzable alkoxy analog of D-All (**5**, **6**). Compound **3** showed nematocidal activity, and the optimum length of fatty acid chain was found to be C8. In addition, **6** not hydrolyzed within the body of *C. elegans* and exerts toxicity in its intact form. Thus, **3** and **4** might be lead compound of a novel class of anthelmintics having different mechanisms of action from those of conventional drugs.

Next, to improve the relatively weak activity of D-All, the author applied the prodrug strategy to D-allose-6-phosphate (A6P) to give it membrane permeability. The hydroxyl groups and a phosphate group in the A6P derivative (**11**) are protected by acetyl groups and a cyclosaligenyl (cycloSal) group, respectively, which can undergo hydrolysis in cells by enzymatic or non-enzymatic process. Compound **11** showed 250-fold higher anti-proliferative activity against a MOLT-4F human leukemia cell line than D-All. Although D-All induced cell cycle arrest not cell death in the MOLT-4F

cells, **11** showed cytotoxicity and completely killed the cells at 30 μM. The expression of the thioredoxin-interacting protein (TXNIP) induced by **11** was low compared with that induced by D-All, which implies the involvement of a TXNIP-independent pathway in the activity of **11**. On the other hand, D-glucose-6-phosphate derivative (**12**) and tetraacetyl-A6P (**13**) showed weak and no activity, respectively. These results suggest that protection of the phosphate group is necessary for the membrane-permeability and the cytotoxicity is partially caused by the derivatization. These results indicate that similar derivatization of phosphates of other rare monosaccharides could be a promising strategy for enhancing their biological activities.

Finally, to investigate rare sugars that show anti-proliferative activity, the author evaluated the activity of the rare aldohexoses. Among thirteen rare aldohexoses tested, D-All and D-idose (D-Ido) at 5 mM inhibited cell proliferation by 60% and 46%, respectively. To clarify the contribution of the D-Sorbose (D-Sor) which is an isomerized product of D-Ido, its anti-proliferative activity was evaluated. In addition, to reveal the importance of the hydroxy group at C-6 of D-Ido, the activity of 6-deoxy-D-Ido and L-xylose (L-Xyl) were also evaluated. D-Sor, 6-deoxy-D-Ido, and L-Xyl did not show significant activity against MOLT-4F cells. These results suggest that the aldose structure and the C-6 hydroxy group of D-Ido are important for the activity. In addition, the author found that D-Ido as well as D-All inhibited cellular glucose uptake through TXNIP independent mechanism. In addition, to investigate the mechanism of the anti-proliferative activity of D-Ido, the author examined the effect of D-Ido treatment on cellular glucose uptake and TXNIP expression. Cellular glucose uptake assay and western blotting analysis of TXNIP expression suggested that the anti-proliferative activity of D-Ido is induced by inhibition of glucose uptake via TXNIP-independent pathway.

In conclusion, this study revealed that a derivatization of rare sugar can be promising strategy to improve the biological activity and demonstrated the possibility of anti-cancer activity of rare sugars which had not been well investigated could be used as anti-cancer agent. This finding also indicates that drugs design based on monosaccharides may be possible in the development of anticancer drugs with novel mechanisms of action.