



## Nagoya City University Academic Repository

学位の種類	博士 (医学)
報告番号	甲第1619号
学位記番号	第1154号
氏名	吉田 嵩
授与年月日	平成 30年 3月 26日
学位論文の題名	<p>Potent anti-tumor activity of a syringolin analog in multiple myeloma: A dual inhibitor of proteasome activity targeting <math>\beta 2</math> and <math>\beta 5</math> subunits (<math>\beta 2</math> と <math>\beta 5</math> サブユニットのプロテアソーム活性を阻害するシリングリン誘導体の多発性骨髄腫における強力な抗腫瘍活性)</p> <p>Oncotarget; accepted for publication</p>
論文審査担当者	主査： 稲垣 宏 副査： 岡本 尚, 飯田 真介

## ABSTRACT

### [Introduction]

Proteasome inhibitors (PI), mainly targeting the  $\beta 5$  subunit of the 20S proteasome, are widely used in the treatment of multiple myeloma (MM). However, PI resistance remains an unresolved problem in the therapy of relapsed and refractory MM. To develop a new PI that targets other proteasome subunits, we examined the anti-MM activity of a novel syringolin analog, syringolog-1, which inhibits the activity of both the  $\beta 5$  and  $\beta 2$  subunits.

### [Methods and Results]

Syringolog-1 exhibited marked cytotoxicity against various MM cell lines and anti-tumor activity towards bortezomib (Btz)-resistant MM cells through the dual inhibition of chymotrypsin-like ( $\beta 5$  subunit) and trypsin-like ( $\beta 2$  subunit) activities. MM cells, including Btz-resistant cells, showed elevated CHOP and NOXA expression after syringolog-1 treatment, indicating the induction of excessive endoplasmic reticulum stress during syringolog-1 treatment. Similar activities of syringolog-1 were also observed in freshly prepared MM cells derived from patients. To clarify the anti-tumor mechanism of dual inhibition of both the  $\beta 5$  and  $\beta 2$  subunits of the proteasome, PSMB5 and PSMB7 were co-inhibited in MM cells. This resulted in increased apoptosis of MM cells accompanied by accumulation of ubiquitinated proteins compared to inhibition of either PSMB7 or PSMB5 alone, indicating an enhanced effect by double inhibition of  $\beta 2$  and  $\beta 5$  activities.

### [Discussion]

In conclusion, this syringolin analog, a dual inhibitor of proteasome  $\beta 2$  and  $\beta 5$  activities, exhibited potent anti-tumor effects on MM cells and may be useful for overcoming Btz-resistance in the treatment of MM.