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651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Potential Significance of CTPS1 in Multiple Myeloma

Han-Ying Huang[1], *Yang Liang, MDPhD*[2]

[1] State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China
[2] Sun Yat-sen University Cancer Center, Guangzhou, China

Introduction
With the increasing interest to the metabolism of multiple myeloma (MM), a number of metabolic genes and their associated regulatory networks are essential for MM progression. Our team's prior work indicated that high expression of metabolism-related gene CTPS1 (CTP synthase 1) correlated with poor prognosis of MM. However, the mechanism of CTPS1 in MM is unknown.

Methods
The difference in CTPS1 expression level in patients with plasma cell malignancies, various stages, and drug-resistant recurrence was examined using publicly available data. MM cell lines were engineered to overexpress or knockdown CTPS1. RNA-seq was used to unbiased interrogate the downstream effector genes modulated by CTPS1. Severe immunodeficient NRG-SGM mice expressing humanized myeloid cytokines were used to determine the effect of CTPS1 on MM proliferation *in vivo*.

Results
CTPS1 expression levels varied substantially in various plasma cell malignancies. High CTPS1 expression was associated with shorter overall survival and progression-free survival in newly diagnosed MM patients. Moreover, there was a strong correlation between CTPS1 and sex, albumin, $\beta 2$ microglobulin, lactate dehydrogenase, and ISS/R-ISS stage. *In vitro*, CTPS1 overexpressing cells proliferated more quickly than CTPS1 knockdown cells. NRG-SGM3 mouse experiments demonstrated that tumor growth was significantly accelerated *in vivo* in the CTPS1 overexpression group. In the pharmacological experiment, CTPS1 overexpression group's sensitivity to 20 nM bortezomib reduced, but CTPS1 down-knocked group's sensitivity to 20 nM bortezomib rose. CTPS1 was also shown to be involved in metabolism and synthesis, notably mRNA metabolism, DNA metabolism, chromosomal combination, cell cycle, spliceosome, and cellular senescence. Furthermore, Myc was found to be tightly connected to CTPS1 in both MM cell lines and newly diagnosed MM.

Conclusions
This study found that increased CTPS1 expression is associated with a poor prognosis and reduced sensitivity to bortezomib in MM. Additionally, CTPS1 upregulated Myc-signaling genes, which promoted progression of MM.

Disclosures No relevant conflicts of interest to declare.

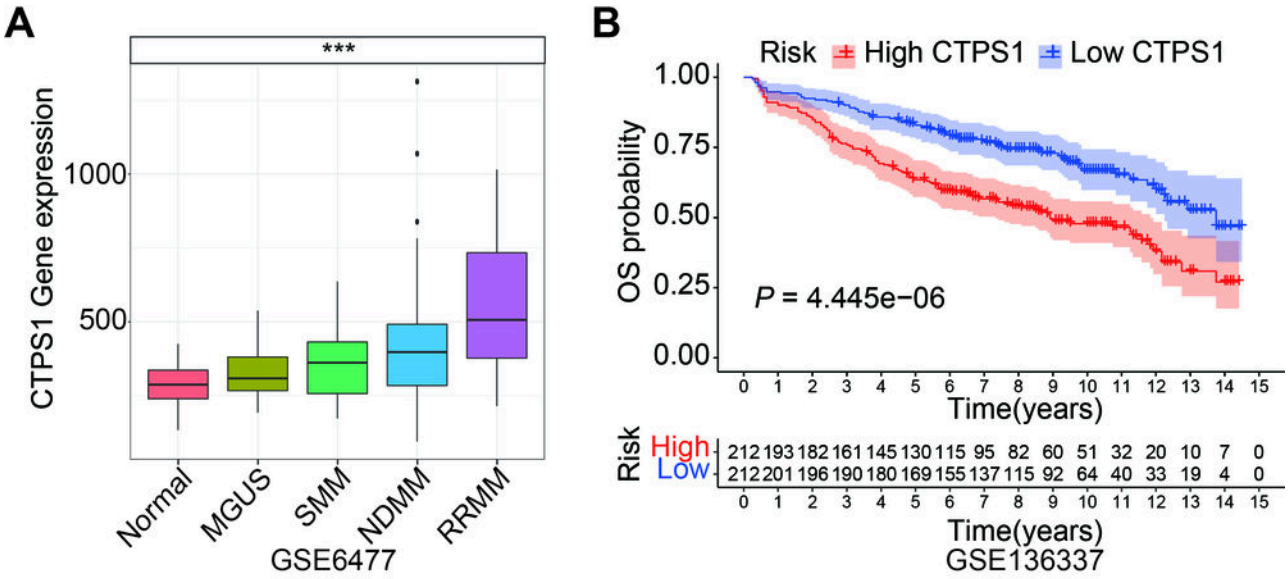

Figure. Potential significance of CTPS1 in multiple myeloma.
(A) CTPS1 expression levels in different plasma cell malignancies.
(B) CTPS1's impact on overall survival in MM.
MGUS=Monoclonal gammopathy of undetermined significanc.
SMM=Smoldering multiple myeloma.
NDMM=Newly diagnosed multiple myeloma.
RRMM=Relapsed and refractory multiple myeloma.
OS=Overall survival.

Figure 1

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