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

Targeting Glutamine Dependence through GLS1 Inhibition Suppress Multiple Myeloma and Phenomenon of Sars-Cov-2 Infectious Disease

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Introduction:
Multiple myeloma (MM) is characterized by the clonal expansion of plasma cells in the bone marrow. The treatment of MM patients has been dramatically changed by new agents, however, many patients will relapse even if new agents provide therapeutic advantages. Therefore, a new strategy is still needed to increase MM patient survival. Metabolic reprogramming is recognized as one of the hallmarks of cancer cells. Glutamine is the most abundant circulating amino acid in blood, glutamine metabolism through glutaminolysis may be associated with myeloma cell survival. The outbreak of coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, has rapidly spread to more than 196 countries worldwide. Myeloma patients present an increased risk for severe COVID-19 infection and poor outcomes.
Materials and Methods:
In this study, we investigated whether glutaminase (GLS) inhibitor, telaglenastat could suppress myeloma cells and enhance the sensitivity of myeloma cells to histone deacetylase (HDAC) inhibition. We also investigated whether telaglenastat suppress the SARS-CoV-2 phenomenon by using mouse macrophage cell line, RAW264.
Results:
We first investigated the GLS gene expression against MM patients from the online Gene Expression Omnibus (GEO) data. GLS1 expression was increased in monoclonal gammopathy of undetermined significance (MGUS) and myeloma patients compared to normal controls. We next investigated the glutaminolysis in myeloma cells. Deprivation of glutamine from the culture medium revealed that cellular growth inhibition and increased caspase 3/7 activity. We next evaluated the effect of GLS inhibitor, telaglenastat. MM cells were inhibited by telaglenastat in a dose dependent manner. Cellular cytotoxicity was also increased. Glutamine is converted by GLS into glutamate and alpha-ketoglutarate (α-KG), and related nicotinamide adenine dinucleotide phosphate (NADP) production. Intracellular α-KG and NADPH were reduced by telaglenastat. As metabolites are the substrates used to generate chromatin modification including acetylation of histone, we investigated HDAC inhibitor, panobinostat in myeloma cells. Myeloma cells were inhibited by panobinostat and histone acetylation, caspase 3/7 activity and cytotoxicity were increased. Combined treatment with panobinostat and telaglenastat caused more cytotoxicity. Sub-G1 phase was increased by cell cycle analysis. Caspase 3/7 activity and cellular cytotoxicity were also increased. Proteasomal activity was reduced. Immunoblot analysis revealed cleaved caspase 3 and γ- H2AX were increased by panobinostat and telaglenastat treatment. GLS shRNA transfectant cells were inhibited cellular proliferation and GLS shRNA transfectant cells were increased the sensitivity of panobinostat. We next investigated the effects of COVID-19 S1 protein and teragrenastat by using RAW264 cells. Gene expression of inflammatory cytokines, such as tumor necrosis factor α (TNFα) was induced by COVID-19 S1 protein treatment and inhibited by telaglenastat. Intracellular reactive oxygen species (ROS) and NFkB-p65 (Ser536) phosphate activity was increased by COVID-19 S1 protein and inhibited by telaglenastat.
Conclusion:
The GLS is involved myeloma progress and GLS inhibitor suppresses myeloma cells and enhance cytotoxic effects of HDAC inhibitor. We also provide the GLS inhibitor is effective to SARS-CoV-2 phenomenon and promising clinical relevance as a candidate drug for treatment of myeloma patients in COVID-19 pandemic.

Disclosures Gotoh: *Abbvie:* Honoraria; *AstraZeneca:* Honoraria; *Sanofi:* Honoraria; *Pfizer Japan:* Honoraria; *Janssen Pharmaceutical:* Honoraria; *Bristol Myers Squibb:* Honoraria; *Kyowa Kirin:* Honoraria; *Nihon Pharmaceutical:* Honoraria; *Nippon Shinyaku:* Honoraria; *Takeda Pharmaceutical:* Honoraria; *Novartis:* Honoraria; *Asahi Kasei Pharma:* Research Funding; *Daiichi*

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