**1C metabolism: a novel therapeutic target for chemo-resistant gastric cancer**

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**Abstract**

Molecular classification of gastric cancer(GC) discovered subgroup of patients showing chemo-resistance and poor prognosis, which we call as SEM (Stem like/ Epithelial-to-mesenchymal transition/ Mesenchymal) type in this study. Herein, we propose a novel treatment strategy for chemo-resistant GC patients via deciphering metabolic plasticity of SEM-type GC cells.

Transcriptome of GC patients who had undergone curative intent gastrectomy at the Yonsei Cancer Center (N = 497; GSE13861 and GSE84437) was analyzed for molecular characterization of SEM-type GC tumor. Whole transcriptome RNA sequencing, chromatin immunoprecipitation sequencing, and transposase-accessible chromatin using sequencing analysis were performed to investigate the mechanism under the metabolic plasticity of SEM-type GC cells *in vitro*. Patient-derived organoids were used to test the efficacy of treatment regimen via single-nucleus transcriptome analysis.

SEM-type GC exhibited distinct metabolic profile characterized by high glutaminase(GLS) level. However, SEM-type GC cells were resistant to glutaminolysis inhibition and survived under glutamine starvation via up-regulating 3‑phosphoglycerate dehydrogenase(PHGDH)-mediated mitochondrial folate cycle pathway to produce NADPH as ROS scavenger for survival. The metabolic plasticity stems from globally open chromatin structure of SEM-type GC cells, and ATF4/CEBPB were identified as the main transcription drivers of PHGDH-driven salvage pathway. Single-nucleus transcriptome analysis of patient-derived SEM-type GC organoid has revealed intratumoral heterogeneity, and stemness-high subpopulations were GLS-high and resistant to GLS inhibition along with ATF4/CEBPB activation. Co-inhibition of GLS and PHGDH, however, successfully eliminated stemness-high cancer cells in patient-derived organoids

This study provides detailed molecular mechanisms behind the metabolic plasticity of stemness-high gastric cancer cells at every level from chromatin architecture to transcription drivers and the importance of ROS scavenging activity, which may lead to novel therapeutic strategy to chemo-resistant gastric cancer patients, as verified in the patient-derived cancer organoid.