Redox regulation of stem-like cancer cells by CD44

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CD44 has been identified as one of the cell surface markers associated with cancer stem cells (CSCs) in several types of epithelial tumor. However, function-based evidence to support the role of CD44 in CSCs has been lacking. We have recently found that expression of CD44, in particular variant forms of CD44 (CD44v), contributes to the defense against reactive oxygen species (ROS) by promoting the synthesis of reduced gluathione (GSH), a primary intracellular antioxidant. CD44v interacts with and stabilizes xCT, a subunit of a glutamate-cystine transporter, and thereby promotes the uptake of cystine for GSH synthesis. Furthermore, we found that expression of CD44 enhances the glycolytic phenotype of p53-deficient cancer cells, and promotes metabolic flux to pentose phosphate pathway (PPP) and thereby increases GSH levels. Therefore, ablation of CD44 reduced GSH levels and increased ROS levels, leading to suppression of tumor growth in a transgenic mouse model of gastric cancer and xenographt models. Our findings reveal a novel function for CD44v in protection of CSCs from high levels of ROS in the tumor microenvironment. Based on these preclinical findings, we are planning to conduce a clinical trial using an xCT inhibitor for advanced gastric cancer patients.

We also found that orthotopic transplantation of $CD44v^+$ population in breast cancer 4T1 cells, but not that of $CD44v^-$, in mice resulted in efficient lung metastasis accompanied by expansion of stem-like cancer cells. Such metastasis was dependent on the ability of the cells to reduce ROS through up-regulation of cystine transporter xCT. Therefore, therapies targeted to the CD44v/xCT axis are expected to perturb the ROS-resistance of disseminating stem-like cancer cells and might be a novel strategy for the prevention of metastasis.

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EDUCATIONS/TRAINING

1981	Kobe University School of Medicine, Japan (MD)
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POSITIONS AND HONORS

1987-1988	Postdoctocal Fellow, Brain Tumor Research Center, University of California, San Francisco, USA
1988-1994	Assistant Professor, Department of Neuro-Oncology, The University of Texas, M. D. Anderson Cancer Center, Houston, TX, USA
1994-2006	Professor, Department of Tumor Genetics and Biology, Kumamoto University School of Medicine, Kumamoto, Japan
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2008	The 6th Special Research Award, Sagawa Foundation for Promotion of Cancer Research

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