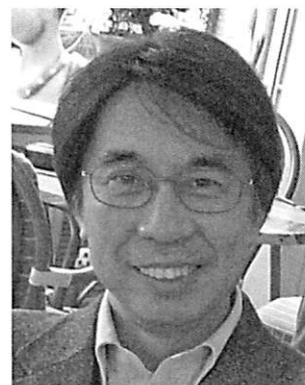


Redox regulation of stem-like cancer cells by CD44

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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 glutathione (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 xenograft 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 conduct 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

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POSITIONS AND HONORS

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| 1987-1988 | Postdoctoral 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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