Cancer Stem Cell:
Characteristics and Therapeutic Implication

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医学教育図書棟3階 第2講義室

　　Stem-like cancer cells, so called cancer stem cells (CSCs), are a subset of tumor cells that are responsible for initiating and maintaining the disease. In the clinical point of view, one of the most important characteristics of CSCs is their resistance to various therapeutic interventions. However, the underlying mechanisms of the resistance remain unclear.

　　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 (*Cancer Cell* 2011). 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 (*Cancer Res* 2012; *Clin Cancer Res* 2012). Therefore, ablation of CD44 reduced GSH levels and increased ROS levels, leading to suppression of tumor growth and metastasis in both transgenic and xenograft tumor models (*Nat Commun* 2012; *Cancer Res* 2013). 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 currently conducting a clinical trial using an xCT inhibitor for advanced gastric cancer patients.

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