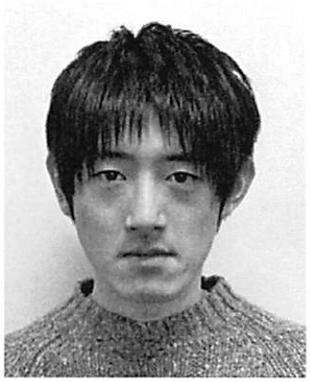
Undifferentiated state induced by Rb inactivation associated with metabolic reprogramming and inflammation



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In the majority of cancer types, inactivation of retinoblastoma tumor suppressor product (pRb) is frequently found during their progression. To address the role of Rb in tumor progression, we established a mouse model in which Rb-deficiency in varied genetic backgrounds generates calcitonin-producing cell (C-cell)-derived tumors of different malignancies. Rb-deficiency in Ink4a, Arf, Suv39h1 or p53 null background directly induced highly malignant C-cell adenocarcinoma. Only p53 null C-cell adenocarcinoma, however, lost the expression of neuroendocrine lineage markers such as calcitonin and Ascl1, and cells derived from these tumors exhibited particularly high sphere-forming activity. In addition, Rb depletion in $p53^{-/-}$ mouse-derived fibrosarcoma cells induced significantly higher sphere-forming and cancer-initiating activity without affecting cell proliferation rate in 2D culture condition. These findings indicate that Rb inactivation in p53 null background may contribute to the acquisition of "cancer stemness".

We succeeded in the enrichment of cell populations with high sphere-forming activity from Rb-depleted $p53^{-/-}$ mouse-derived fibrosarcoma cells. DNA microarray and RNA- sequence analysis revealed that these cells exhibited signatures of inflammatory conditions (e.g., increased expression of IL-1a and IL-6, and activation of STAT3 pathway) and glycolytic shift of cellular metabolism (e.g., upregulation of GLUT family expression and glucose consumption). Our model may contribute to elucidating the mechanisms that underlie the stem cell-like behaviors seen in cancer cells in the context of Rb and p53 inactivation.

EDUCATIONS AND POSITIONS

2004	Nagoya University School of Agricultural Sciences, Japan
2006	Kyoto University Graduate School of Medicine, Japan (M.S.)
2010	Ph.D. from Kyoto University, Japan
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