Tumor Nuclear YAP1 Expression Status and Molecular Characteristics in relation to Immune Response to Colorectal Carcinoma

Jennifer Borowsky, Chunxia Du, Keisuke Kosumi, Tsuyoshi Hamada, Teppei Morikawa, Annacarolina da Silva, Katsuhiko Nosho, Jonathan A Nowak, Reiko Nishihara, Jochen K Lennerz, Marios Giannakis, Andrew T Chan, Jeffrey A Meyerhardt, Charles S Fuchs, Shuji Ogino, Department of Oncologic Pathology, Dana-Faber Cancer Institute, Boston, MA, 2Department of Pathology, Center for Integrated Diagnostics, 3Clinical and Translational Epidemiology Unit, 4Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, 5School of Medicine, University of Queensland, Brisbane, Australia, 6Conjoint Gastroenterology Laboratory, Queensland Institute of Medical Research Berghofer, Brisbane, Australia, 7Department of Oncologic Pathology, 8Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, 9Department of Pathology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, 10Department of Gastroenterology, Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine, Sapporo, Hokkaido, Japan, 11Program in MRI Molecular Pathological Epidemiology, Department of Pathology, 12Department of Medicine, 13Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 14Department of Nutrition, 15Department of Epidemiology, 16Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, 17Broad Institute of MIT and Harvard, Boston, MA, 18Yale Cancer Center, New Haven, CT, 19Department of Medicine, Yale School of Medicine, New Haven, CT, 20Smilow Cancer Hospital, New Haven, CT

The YAP1 protein is considered as a transcriptional co-activator, and nuclear YAP1 can combine with TEAD (TEA domain transcription factors) to promote proliferation of colorectal cancer cells. Experimental evidence suggests that the YAP1 protein may increase production of PTGS2 (cyclooxygenase-2) and inflammatory mediators including prostaglandin E2 (PGE2) and IL6 (Interleukin-6) in tumor cells such as colon cancer cells. The PTGS2/PGE2 pathway and IL6 play a pivotal role in recruiting myeloid-derived suppressor cells into the tumor microenvironment, thereby inhibiting anti-tumor immune response. Therefore, we hypothesized that tumor nuclear YAP1 expression level might be inversely associated with immune response to colorectal cancer.

Using 682 rectal and colon carcinoma cases in the Nurses’ Health Study and Health Professionals Follow-up Study, we examined tumor nuclear YAP1 expression by immunohistochemistry. Multivariable logistic regression models were used to assess the association of nuclear YAP1 expression (negative, low, or high) with histopathologic lymphocytic reaction patterns, and densities of CD3+ cells, CD8+ cells, CD45RO+ (PTPRC+) cells, or FOXP3+ cells, adjusting for potential confounders, including microsatellite instability status, CpG island methylator phenotype status, long-interpersed nucleotide element-I methylation level, and KRAS, BRAF and PIK3CA mutations.

Nuclear YAP1 expression level was inversely associated with CD3+ cell density (for a unit increase in tertile categories of CD3+ cell density as an outcome: multivariable-adjusted odds ratio, 0.47; 95% confidence interval, 0.33 to 0.67; P_trend < 0.0001), and CD8+ cell density (for a unit increase in tertile categories of CD8+ cells as an outcome: multivariable-adjusted odds ratio, 0.49; 95% confidence interval, 0.34 to 0.71; P_trend = 0.0001). The expression of nuclear YAP1 was not significantly associated with histopathologic lymphocytic reaction patterns, or the density of CD45RO+ cells or FOXP3+ cells (with the adjusted level of 0.006 for multiple hypothesis testing).

In summary, tumor nuclear YAP1 expression level is inversely associated with the densities of CD3+ cells and CD8+ cells in colorectal carcinoma tissue. Our findings support an important role of YAP1 in regulating anti-tumor immune response to colorectal cancer.