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

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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 E_2 (PGE_2) and *IL6* (Interleukin-6) in tumor cells such as colon cancer cells. The *PTGS2*/PGE_2 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-interspersed nucleotide element-1 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 α 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.