Associations among β-TrCP, an E3 ubiquitin ligase receptor, β-catenin, and NF-κB in colorectal cancer *

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BACKGROUND: The ubiquitin-proteasome pathway is important in regulating protein signaling pathways that are involved in tumorigenesis. β-transducin repeat-containing proteins (β-TrCP) are components of the ubiquitin ligase complex targeting β-catenin and IκBα for proteasomal degradation and are thus a negative regulator of Wnt/β-catenin signaling and a positive regulator of NF-κB signaling. We analyzed expression of β-TrCP in colorectal cancers and its association with types of β-catenin subcellular localization, an indirect measure of activation. **METHODS:** Levels of β-TrCP1 mRNA and protein were measured by quantitative reverse transcription-polymerase chain reaction and immunoblotting, respectively, in samples of tumor and normal tissues from 45 patients with colorectal cancer. Types of β-catenin activation (diffuse or invasion edge) and NF-κB activation were examined by immunohistochemistry. Apoptosis was determined by the terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-biotin nick-end labeling (TUNEL) assay. All statistical tests were two-sided. **RESULTS:** Compared with the β-TrCP1 levels in normal tissues, 25 (56%) of 45 tumors had increased β-TrCP1 mRNA and protein levels. Of the 22 (49%) tumors with β-catenin activation, 12 had the diffuse type (i.e., nuclear accumulation throughout the tumor) and 10 had the invasion edge type (i.e., nuclear accumulation predominantly in the tumor cells that formed the invasion edge). Increased β-TrCP1 levels were statistically significantly associated with β-catenin activation (P =.023) and decreased apoptosis (P =.035). β-TrCP accumulated in the nuclei of tumor cells that contained increased levels of β-TrCP1 mRNA and the active form of NF-κB. Higher levels of β-TrCP1 mRNA were detected in primary tumors of patients who had metastases (0.960 arbitrary units, 95% confidence interval = 0.878 to 1.042) than in the tumors of patients who did not (0.722 arbitrary units, 95% confidence interval = 0.600 to 0.844; P =.016). **CONCLUSION:** In colorectal cancer, increased expression of β-TrCP1 is associated with activation of both β-catenin and NF-κB, suggesting that the integration of these signaling pathways by increased β-TrCP expression may contribute to an inhibition of apoptosis and tumor metastasis.

*References: Ougolkov A, Zhang B, Yamashita K, Bilim V, Mai M, Fuchs SY, Minamoto T. Associations among β-TrCP, an E3 ubiquitin ligase receptor, β-catenin and NF-κB in colorectal cancer. J Natl Cancer Inst 96:1161-1170, 2004.