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Clinicopathological significance of *PTEN* loss and the phosphoinositide 3-kinase/Akt pathway in sporadic colorectal neoplasms: is *PTEN* loss predictor of local recurrence?

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pAKT;
Colon cancer;
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Abstract

BACKGROUND: *PTEN* is a tumor-suppressor gene located on chromosome 10. Deficient *PTEN* expression leads to activation of the phosphoinositide 3-kinase (PI3K)/Akt (pAkt) signaling pathway, which may contribute to multiple human cancers. The relation between *PTEN* expression and Akt activation is still unclear in colorectal cancers and adenomatous polyps. Moreover, *PTEN* and pAkt expression in relation to demographic, tumoral, and outcome variables remains to be elucidated.

METHODS: *PTEN* and pAkt expression were evaluated in 76 primary colorectal cancers and 25 adenomatous colorectal polyp tissues using immunohistochemical staining on paraffin-embedded sections. *PTEN* and pAkt expression were compared with clinicopathologic features of colorectal cancers. The relationship between *PTEN* and pAkt expression was also investigated.

RESULTS: In colorectal cancers, pAkt expression was found to be significantly higher than polyps ($P = .007$). On the other hand, *PTEN* expression was significantly lower in polyps ($P < .0001$). In colorectal cancer patients, *PTEN* expression showed a negative correlation with young age, female sex, and left-sided (distal) tumors. On multivariate analysis, low *PTEN* expression (*PTEN* loss) was noted as an independent parameter for local recurrence ($P = .024$). There was significant association between pAkt expression and stage ($P = .008$), and preoperative serum carcinoembryonic antigen (CEA) levels ($P = .017$) in colorectal cancers. A negative correlation between *PTEN* and pAkt expression was found in colon cancer patients ($P = .010$), whereas no significiant association was found in adenomatous polyps ($P = .403$). No correlation of *PTEN* expression or pAkt expression was observed in Kaplan-Meier survival statistics and multivariate analyses for disease-free and overall survival.

CONCLUSIONS: The current study suggests that the *PTEN* loss–PI3K/pAkt pathway may play an important role in sporadic colon carcinogenesis and that reduced *PTEN* expression may predict relapse in colorectal cancer patients.

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PTEN (phosphatase and tension homolouge deleted on choromosome 10) is a tumor-suppressor gene located on chromosomal band 10q23.[1] *PTEN* keeps phosphatidylinositol 3-4 biphosphate (PIP2) and phosphatidylinositol 3-4-5 triphosphate (PIP3) in their dephosphorylated forms by inhibiting phosphoinositide 3-kinase (PI3K).[2,3] The enzyme of PI3K is normally inactive in quiescent cells.[4]

PI3K activation induces expression of phosphorylated Akt (pAkt), which is an active form of Akt. Akt is a proto-oncogene and pAkt both promotes cell cycle progression and inhibits apoptosis.[5,6]

The fundamental in vivo role of *PTEN* appears to be the inhibition of PI3K-dependent activation of Akt. Akt activity is normally low in the absence of growth factor stimulation. However, *PTEN*-deficient tumor cell lines and tumors derived from *PTEN*-deficient mice show high levels of Akt phosphorylation.[7,8]

Activated Akt induces expression of anti-apoptotic Bcl-2,[6] inactivates pro-apoptotic Bad,[9] and promotes cell survival by inhibiting-phosphorylating Forkhead transcription factor (FHKR)[10] and by activating-phosphorylating caspase 9.[11] However, in addition to its cell survival role, Akt is also important in regulation of cell cycle entry. Akt inhibits glycogen synthase kinase 3 (GSK3) and prevents GSK3-dependent proteolysis of cyclin D1, thereby enabling accumulation of the latter and cell cycle entry.[12,13] Mammalian target of rapamycin (mTOR) (also known as rapamycin-associated protein (FRAP) and rapamycin and fKBP 12 targets 1 (RAFT-1)) is also activated after Akt phosphorylation, resulting in the phosphorylation of p70S6 kinase and 4E-BP1. Consequently, activated mTOR increases the translation of mRNAs of proteins involved in regulation of cell cycle[14] (Figure 1).

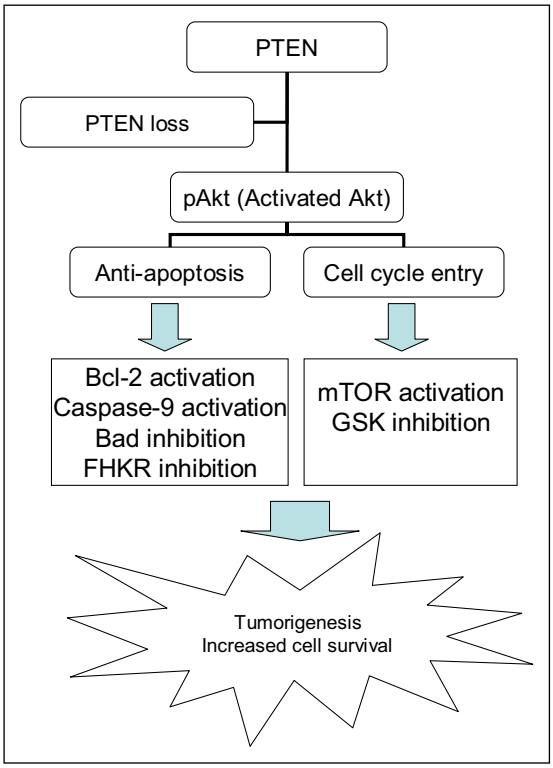

Figure 1 Steps leading to tumorigenesis and increased cell survival from *PTEN* loss.

Akt-1, Akt-2, and Akt-3 are 3 isoforms of Akt and their amino acid structures show 80% homology.[15] Fuctional deficits of *PTEN* appear to activate the PI3K pathway, which results in tumor development, especially in patients with gastric, thyroid, glioblastoma multiforme, breast, prostate, non-small lung, and endometrium cancers.[16–21] On the other hand, germ-line mutations of *PTEN* cause rare autosomal-dominant inherited cancer syndromes like Cowden disease and Bannayan-Rivel-Ruvalcaba syndrome.[20]

Although activation of PI3K/Akt supports the malignant transformation in colon cells,[22–24] the importance of the *PTEN*–PI3K/Akt pathway and correlations with clinicopathologic variables still remain controversial for sporadic colorectal cancers.

The aims of the current study were to establish *PTEN* and pAkt expression in relation to demographic, tumoral, and outcome variables, and to determine whether there was any association between *PTEN* expression and Akt activation in colorectal tumors and adenomatous polyps.

Materials and Methods

Patients

Seventy-six primary operable colorectal adenocarcinoma and 25 adenomatous polyp tissues with corresponding normal mucosa were evaluated in this study. Seventy-six colorectal cancer patients underwent primary surgery in the Department of Surgery at Baskent University, Adana Research and Teaching Centre between 1998 and 2005. For all cancer patients, data recorded included age, sex, tumor size, and histological grade, coincidental existence of lymph node metastasis, stage, lymphatic invasion, preoperative serum carcinoembryonic antigen (CEA) levels and localization of tumor. Follow-up data on local recurrence, liver metastasis, and survival were also recorded retrospectively.

No patient had received chemotherapy and/or radiotherapy before surgery. The mean age of patients was 62.4 years (range 34–85 years); the group consisted of 45 men (59.2%) and 31 women (40.8%). The mean follow-up time was 24.1 months.

Thirteen of 25 adenomatous polyp tissues were obtained from operated colon cancer patients' specimens as synchronous polyps. The remaining 12 polyps were found in only-polyp patients during colonoscopy.

This study was performed in accordance with the Ethics Code for Human Experimentation, Baskent University School of Medicine (KA05/215).