Phosphatase Protein Homologue to Tensin Expression and Phosphatidylinositol-3 Phosphate Kinase Mutations in Colorectal Cancer

To the Editor:

Phosphatidylinositol-3 phosphate kinase (PI3K) and phosphatase protein homologue to tensin (PTEN) are involved in cell signaling by catalyzing opposite reactions in the balance of phosphatidylinositol-3,4,5,-trisphosphate and are deregulated in many tumors. Recently, Saal et al. (1) reported that these two proteins are altered in a consistent fraction of breast cancers and, more importantly, that *PIK3CA* mutations and PTEN loss seem mutually exclusive. These results prompted us to verify a possible correlation between *PI3K* mutations and PTEN protein deregulation also in colorectal cancer, where both of them have been shown to play a relevant role (2, 3).

By screening of 60 colorectal cancers from patients submitted to radical surgery at the National Cancer Institute of Milan, Italy, from 1998 to 2000 (4), we found 12 cases (20%) carrying *PIK3CA* mutations. These results are in keeping with the literature (2). The same cohort, along with 28 colorectal cancers randomly selected from those lacking *PIK3CA* mutations, were then analyzed for PTEN protein expression by immunohistochemistry as previously described (1). In our panel, PTEN protein expression was detected mainly at the cytoplasmic level, although occasional nuclear positivity was present. Tumors having reduced or no immunostaining in at least 50% of cells compared with the internal control were considered PTEN negative.

All the cases (12 of 12 = 100%) carrying *PIK3CA* mutations were PTEN positive (see Supplemental Data). On the contrary, among tumors without *PIK3CA* mutation, only 14 cases (14 of 28 = 50%) showed PTEN immunodecoration. This difference is statistically significant (P = 0.001728, two-sided Fisher's exact test). Interestingly, seven cases were completely PTEN immunonegative (see Supplemental Data). We also observed a trend toward PTEN protein reduction in mucinous colorectal cancers, compared with well-differentiated tumors. No association between PIK3CA and PTEN deregulation and those occurring in the markers mainly involved in colorectal carcinogenesis (APC, K-Ras, DCC, and TP53; ref. 4) was observed.

Our results point out that PTEN and PIK3CA are altered in a consistent number of colorectal cancers and that *PIK3CA* mutations and PTEN protein deregulation are mutually exclusive. Moreover, because other members of the PI3K pathway (PDPK1, AKT2, and PAK4) have been recently found to be altered in human tumors carrying *PIK3CA* wild-type gene (5), we could assume that colorectal cancers carrying normal expression of PTEN protein and *PIK3CA* wild-type gene might present a mutation in one of these genes. Our data, therefore, support the notion that the PTEN/PI3K/AKT pathway could represent an attractive target for pharmacologic interventions in this type of tumors.

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