Genetic and Biologic Evidence that Implicates a Gene in Aggressive Prostate Cancer

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In this issue of the Journal, Duggan et al. (1) report that genetic variation, i.e., a single nucleotide polymorphism (SNP) in the DAB2IP gene, may predict the risk of aggressive prostate cancer. The authors explored 60275 SNPs in 498 case patients and 494 control subjects from the Cancer of the Prostate in Sweden study and 737 case patients and 1105 control subjects with European ancestry from Cancer Genetic Markers of Susceptibility (CGEMS) study. Of the 81 SNPs that were associated with aggressive prostate cancer (P<.05 from allele tests), only seven were statistically significant at P less than .01 in both study groups. These seven SNPs were investigated in a separate confirmation cohort from Johns Hopkins Hospital consisting of 1032 case patients and 571 control subjects, all European Americans. One of the seven SNPs (rs1571801) on chromosome 9q33 was statistically significantly associated with the risk of aggressive prostate cancer after adjusting for multiple testing. This SNP, rs1571801, was further scrutinized in a separate cohort of African Americans (210 case patients and 346 control subjects) recruited at Johns Hopkins Hospital and was found to maintain a statistically significant association with aggressive prostate cancer.

Interestingly, the SNP rs1571801 maps to the DAB2IP gene. The study of Duggan et al. is the first population-based study to link the DAB2IP gene with the risk of aggressive prostate cancer, but the biologic sequelae of this polymorphism are unclear because rs1571801 is located in intron 1, 14 kb upstream of exon 2 in the DAB2IP gene. However, several other findings support the biologic role of this gene in aggressive prostate cancer. DAB2IP was first identified as a DOC-2/DAB2 interactive protein; DOC-2/DAB2 is a tumor suppressor gene associated with ovarian (2,3), prostate (4,5) and mammary cancer (6) as well as choriocarcinoma (7). Decreased expression of DAB2IP is often detected in androgen-independent prostate cancer cell lines but not normal primary cancer cells (8). Analysis of the human DAB2IP gene promoter revealed that it is hypermethylated in androgen-independent prostate cancer cell lines but not in normal epithelial cells. Both DNA methyltransferase inhibitors and histone deacetylase (HDAC) inhibitor can induce expression of the DAB2IP gene (9,10). Similarly, DNA hypermethylation in the DAB2IP gene promoter was observed in several other cancer types (11–14). Moreover, other histone modifications such as histone methylation also play an important role in suppressing DAB2IP gene expression. For example, EZH2, a histone lysine methyltransferase that is often elevated in metastatic prostate cancer (15), can suppress DAB2IP gene expression by recruiting both polycomb repressor complex and HDAC1 to the DAB2IP gene promoter region (16). These data indicate that altered epigenetic modification, particularly DNA methylation and histone modification, play an important role in modulating DAB2IP expression during prostate cancer progression. The regulation of the function of DAB2IP may not be confined to epigenetic modifications, as indicated by a recent report (17) of a patient with acute myeloid leukemia, in whom intron 9 of the MLL gene was translocated to exon 2 of the DAB2IP gene, thereby disrupting the DAB2IP pleckstrin homology domain. The observation of epigenetic or genetic instability raises the possibility that the rs1571801 polymorphism may cause the DAB2IP gene to be more susceptible to genetic alteration or epigenetic regulation in prostate cancer.

Expression of Ras protein has also been assessed in primary and metastatic prostate cancer tumors. Most tumors expressed higher levels of Ras protein than normal prostate tissues (18), and increased c-H-Ras mRNA expression in prostate cancer is associated with the progression of prostate cancer to androgen independence (19). Perhaps surprisingly, prostate cancer specimens from American men have an extremely low rate of mutation in the Ras gene (20). This implies that other effectors may be involved in increasing Ras protein levels in prostate cancer. DAB2IP appears to be a good candidate because it contains an amino acid sequence that is homologous to the GTPase-activating protein (GAP) domain of other RasGAPs that is functionally active based on biochemical and molecular biologic studies (8). In addition to the GAP domain and the pleckstrin homology domain (amino acids 20–70), which has a high affinity for certain phosphoinositides, DAB2IP contains several other functional motifs, such as a C2 domain (amino acids 90–120) involved in binding phospholipids in a calcium-dependent or -independent manner, a proline-rich domain (amino acids 796–805) involved in interacting with proteins that contain a SH3 domain, and a leucine zipper (amino acids 842–861), which mediates dimerization. The C2 domain of DAB2IP can also bind and activate apoptosis-stimulated kinase (ASK1), which is involved in the TNF-α-mediated apoptosis.

In addition to the interaction of C2 domain with ASK1, DAB2IP mutants defective in GAP activity failed to increase ASK1 activity, suggesting that the GAP activity of DAB2IP is required for TNF-α-elicted ASK1 activity (21). Also, the GAP activity of DAB2IP is known to be a negative regulator for Ras-Raf-ERK

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activation critical for cell growth. Thus, DAB2IP appears to be a unique factor in modulating both cell growth and death by inhibiting the Ras-Raf-ERK proliferative pathway and activating ASK1-JNK/p38 apoptotic signaling. Very likely, other functional domains in DAB2IP have different homeostatic functions in prostate epithelium.

In the study of Duggan et al. (1), the criteria for defining aggressive prostate cancer should have been consistent among different study groups, especially given that there is no consensus for defining “aggressive” prostate cancer. Consistent definitions would have reduced the artifact of patient stratification. Even when CGEMS, and the European and African American Johns Hopkins University cohorts were combined, rs1571801 was associated with a moderately increased risk of nonaggressive prostate cancer, suggesting that rs1571801 may have the potential to predict the risk of nonaggressive prostate cancer as well. It also appears that the association of rs1571801 with the risk of both aggressive and nonaggressive cancer in the Johns Hopkins University cohort of African Americans was weaker than in other groups, suggesting different genetic predispositions to prostate cancer among different ethnic groups. Based on the strong evidence for an association between prostate cancer risk and 8q24 polymorphism, a panel of SNPs should be explored prospectively for their association with prostate cancer risk, with consistent patient selection criteria. The results may offer a new tool for assessing prostate cancer risk based on different ethnic origins or geographic location.

References