Is TIG1 a New Tumor Suppressor in Prostate Cancer?

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Carcinogenesis is a multistep process during which normal cells undergo a series of genetic and phenotypic changes that lead to immortalization, transformation, acquisition of tumorigenic properties, and eventually to metastatic propensity. Carcinogenesis involves the inactivation or inhibition of genes that function as tumor suppressors and the activation of genes that function as oncogenes (1). Changes in the expression and function of a variety of genes result from deletions, mutations, or epigenetic activation or silencing of transcription, and the changes in protein levels that follow or result from post-transcriptional modifications can lead to altered growth, differentiation, and apoptosis rates. Identification of the molecules and mechanisms involved in carcinogenesis holds promise for improved diagnosis and prognosis and for targeted approaches to cancer prevention and therapy.

The advent of novel molecular analyses, such as differential display (2) and serial analysis of gene expression (SAGE) (3), and high throughput techniques, such as complementary DNA (cDNA) microarray (4) and proteomics (5), have facilitated the characterization of genes and proteins that are differentially expressed between normal and malignant cells. However, although many of the numerous differentially expressed genes may be indirectly associated with carcinogenesis, only a few differentially expressed genes are linked causally to the carcinogenesis process. Direct implication of an individual gene or protein in a particular step of carcinogenesis requires its functional characterization in the context of cell proliferation, differentiation, and tumorigenicity.

In this issue of the Journal, Jing et al. (6) report the identification of a gene whose decreased expression may contribute to the development and progression of prostate cancer. The gene has been identified with the use of a novel selective subtractive differential gene display as one of several genes that are expressed in benign prostate cell lines but not in malignant prostate cancer cell lines. The gene was found to be identical to the gene retinoic acid receptor responder (tazarotene induced) 1 (RARRES1), which had been discovered originally as tazarotene-treated skin in raft cultures and its increased expression in psoriatic lesions after tazarotene treatment (7,8). The TIG1 gene encodes a protein of 228 amino acids. The predicted amino acid sequence suggests a trans-membrane protein with a short N-terminal intracellular region, a single membrane-spanning hydrophobic region, and a large, extracellular C-terminal region. The latter region includes a glycosylation site and a hyaluronate-binding site (6,7). Jing et al. (6) speculate that TIG1 may function as a cell adhesion molecule (CAM). It is interesting to note that other adhesion molecules have also been implicated in prostate cancer progression. For example, the trans-membrane protein CD44, which also can bind hyaluronic acid, exhibits tumor suppressor-like properties (10).

The results of experiments in which TIG1 was transfected into a malignant prostate cancer cell line, which did not express this gene constitutively, demonstrated that restoration of its expression did not alter the in vitro growth rate; however, restoring TIG1 expression resulted in a 75% decrease in the ability of the cells to invade through an extracellular matrix in vitro and a 58% decrease in the average tumor weight after 32 days of in vivo subcutaneous growth in nude mice, without any decrease in tumor incidence. These findings suggest that TIG1 is a tumor suppressor gene whose diminished expression is an early event in hyperplastic/neoplastic transformation and may be involved in the malignant progression of prostate cancer (6).

Jing et al. (6) have shown that TIG1 is expressed in many normal tissues besides prostate and have suggested that it would be interesting to examine TIG1 expression in cancers that develop in these other tissues. Indeed, a couple of years ago, we detected loss of TIG1 mRNA expression in three of six head and neck squamous carcinoma cell (HNSCC) lines and in three of five non-small-cell lung cancer (NSCLC) cell lines (9), supporting the notion that TIG1 may function as a tumor suppressor in a variety of other cancers.

The only previous reports on TIG1 described its isolation as a gene that is expressed differentially between untreated and retinoid-treated skin in raft cultures and its increased expression in psoriatic lesions after tazarotene treatment (7,8). The TIG1 gene encodes a protein of 228 amino acids. The predicted amino acid sequence suggests a trans-membrane protein with a short N-terminal intracellular region, a single membrane-spanning hydrophobic region, and a large, extracellular C-terminal region. The latter region includes a glycosylation site and a hyaluronate-binding site (6,7). Jing et al. (6) speculate that TIG1 may function as a cell adhesion molecule (CAM). It is interesting to note that other adhesion molecules have also been implicated in prostate cancer progression. For example, the trans-membrane protein CD44, which also can bind hyaluronic acid, exhibits tumor suppressor-like properties (10).

Another CAM isoform I (C-CAM1), which does not bind hyaluronate, was shown to play a critical role in prostate cancer initiation and progression. Like TIG1, C-CAM1 expression is lost early in the development of prostate cancer, and its reintroduction into prostate cancer cells via an adenoviral vector reversed their cancerous growth in therapeutic studies (11,12). It was suggested that besides the
C-CAM1 molecule itself, drugs that increase C-CAM1 expression are promising agents for prostate cancer treatment (12).

To reactivate TIG1 expression in prostate cancer cells, it is important to determine the mechanism of its silencing. Jing et al. (6) localized the TIG1 gene to the short arm of chromosome 3, between 3p12 and 3p13. This region exhibits loss of heterozygosity in many types of cancer. A loss of one TIG1 allele may lead to partial loss of function due to haploinsufficiency (6). Further suppression of TIG1 expression may be due to loss of both alleles, mutation of the remaining allele, or methylation of its promoter. In an attempt to activate TIG1 expression, we treated cancer cells with tazarotene or all-trans-retinoic acid and found that these and other retinoids increased TIG1 mRNA in two of six HNSCC lines and in three of five NSCLC cell lines (9). It remains to be determined whether retinoids can induce TIG1 mRNA in some of the prostate cancer cell lines.

Many putative tumor suppressor genes are silenced by methylation (12). Recently, by using the methylated CpG island amplification coupled with representational difference analysis (13), TIG1 was identified as a gene whose promoter is methylated in leukemia cells (Issa JP: personal communication). TIG1 methylation and expression status were then examined in human lung, head and neck, skin, breast, and leukemia cell lines. TIG1 promoter hypermethylation was found in 17 (68%) of 25 cell lines examined. There was a strong association between the loss of TIG1 mRNA expression, as measured by reverse transcription–polymerase chain reaction, and the methylation status of its promoter. Treatment of some cell lines by the demethylating agent 5′-aza-2′-deoxycytidine restored expression to nearly normal levels (14). Thus, it is likely that silencing of the TIG1 gene may also be found in BPH and prostate cancer. TIG1 hypermethylation may prevent TIG1 induction by retinoic acid and loss of retinoic acid responsiveness in some neoplastic cells, including prostate cancer cells.

Despite the findings described above, it is not yet clear that TIG1 is a bona fide tumor suppressor gene. Although TIG1 fulfills some of the criteria expected from a tumor suppressor, it failed to block tumor formation when expressed in prostate cancer cells. It merely decreased the growth of the tumors. An ultimate test for tumor suppressor function may require gene deletion in mice as suggested by Baylin and Herman (15).

REFERENCES