A New Tumor Suppressor Gene: Invasion, Metastasis, and Angiogenesis as Potential Key Targets

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A tumor suppressor gene is generally defined as a gene whose loss of function promotes the replication of a transformed cell. Because the loss of function yields a malignant phenotype, and in most cases deletion or inactivation of both alleles is required (1), most tumor suppressor genes have been identified through linkage analyses in cancer families or through genome-wide analyses of loss of heterozygosity (LOH) that is frequent in tumors of a specific type. Many genes whose products influence cell growth in vitro fail this test, which makes identifying a new tumor suppressor gene perhaps one of the most daunting tasks in molecular biology. Solid in vitro evidence and supporting clinical data are required before a candidate gene can be defined as a tumor suppressor. Tsai et al. (2) present a comprehensive study that strongly supports the identification of a heat shock protein family member as a new tumor suppressor gene. Using microarray analyses to compare invasive and non-invasive non–small-cell lung cancers (NSCLCs) (3), they identified DNAJB4, the DnaJ-like heat shock protein (HLJ1), as a putative tumor suppressor gene that fulfills crucial criteria: reintroduction of HLJ1 expression inhibits lung cancer cell proliferation and anchorage-independent growth in vitro and xenograft tumorigenesis in vivo. Furthermore, they observed reduced expression and LOH of HLJ1 in most of the human NSCLC samples tested.

Tumor suppressor genes for NSCLC are eagerly sought for both our understanding of lung cancer biology and the need of a prognostic marker. The extensive basic and translational studies of another suppressor, fragile histidine triad (FHIT) (4), testify to the importance of these markers in the field. Despite the fact that metastasis remains the critical problem for lung cancer patients and that angiogenesis is closely linked with outcome in NSCLC (5), the potential anti-invasive and anti-angiogenic properties of FHIT have yet to be thoroughly investigated. Tsai et al. report that higher the potential anti-invasive and anti-angiogenic properties of FHIT

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The example of EGFR1 mutations that show different frequencies between white and Asiatic patients (9,12) imposes some caution when extending the findings of Tsai et al. to the general population. LOH encompassing chromosome 1p is, however, apparently not limited to Asian NSCLC patients. A more general acclamation of HLJ1 as a tumor suppressor might be achieved if the gene lies within the critical LOH regions in other tumors that also exhibit LOH in chromosome 1p.

A notable aspect of this work is the data indicating HLJ1 in the suppression of metastasis. Going beyond classic control of cell proliferation, this study shows that HLJ1 also inhibits migration and invasion in vitro. Accordingly, the microarray analysis of HLJ1’s downstream effects revealed several genes associated with invasion and metastasis. In the widely accepted multistep carcinogenesis model, the metastatic phenotype is thought to be acquired through additional mutations in the tumor cells. If we consider these additional mutations to be strictly limited to metastasis, however, one would not expect them to give a selective growth advantage to a cell within the primary tumor. Thus, the few cells that occasionally acquire mutations that prime them for metastasis seem inadequate for the formation of distant colonies, because the metastatic process is inherently inefficient. As a solution to this paradox, Bernards and Weinstein (13) suggest that oncogenes that are responsible for cellular transformation also determine its ability to develop metastases. Data from comparative genome hybridization of single disseminated breast cancer cells also challenge the dogma predicting the location of precursors of metastasis in the most advanced clones within the primary tumor (14). Although metastasis-promoting genes can also transform cells, specific metastasis suppressor genes do not always affect tumorigenicity (15). Metastasis is a process that relies on gain of transforming oncogene function as well as loss of specific
suppressor gene function. The DNAJ homologue(s) could once again play a double role. Local loss of their expression could promote cell proliferation in the primary tumor and increase the probability to survive anoikis (detachment-induced apoptosis). In extravasated cells, loss of expression could promote tethering to endothelial cells in potential target tissues and burrowing across basement membranes to sustain proliferation at the new location. As we proposed earlier, many steps of carcinogenesis could already be accomplished in small tumors before they are detected, and the actual metastatic dissemination could occur during the long period of asymptomatic primary tumor growth, after it is facilitated by tumor-induced alterations of the microenvironment (16).

One of the key microenvironment alterations favoring malignancy is the angiogenic switch (17). Control of angiogenesis is becoming recognized as a major function of tumor suppressor genes. Tumor suppressor genes can act through the influence of tumor cells on the microenvironment, as it has been shown for the von Hippel-Lindau (VHL) tumor suppressor gene (18), through an altered response of endothelial cells to proangiogenic factors produced by tumors harboring an inactive inactivating form of the gene, as for the neurofibromatosis type I gene (NF1) (19), or through the control of antiangiogenic factors, as seen for SMAD4/DPC4 (deleted in pancreatic carcinoma locus 4) (20) and nucleolar protein 7 (NOL7) (21). Tumor suppressor genes may also be direct regulators of angiogenesis, as it has been shown for the phosphatase and tensin homologue of chromosome 10 (PTEN) (22) and MASPIN (23). Interestingly, another serine proteinase inhibitor, serpin B1, is among the genes induced by HLJ1 in NSCLC cells. By acting through STAT1, HLJ1 also induces several genes of the interferon pathway. Interestingly, interferons are inhibitors of angiogenesis (24, 25) and their retroviral delivery can block tumor angiogenesis (26). Consistent with this finding, we found that the antioxidant N-acetyl-cysteine, a molecule proposed for lung cancer chemoprevention (27) that also shows anti-invasive and antiangiogenic activity (28), strongly induces DNAJB9, a homologue of HLJ1 belonging to the same subfamily of DNAJ like heat shock proteins (29). Similarly, other antioxidant angiopreventive drugs also activate transcription of genes encoding proteins of the same subfamily (our unpublished observations). Together with the data suggesting repression of invasion (2), this effect indicates a possible role for HLJ1 in tumor angiogenesis, although HLJ1 and its downstream genes are absent from the metastasis signature proposed by Ramaswamy and colleagues (30). The article by Tsai et al. will further stimulate scrutiny of the DNAJ protein family and put cancer invasion, angiogenesis, and metastasis back on the list of functions inhibited by onc-suppressor genes in lung and perhaps other organs.

References