

Commentary

Asbestos and mesothelioma: Genetic lessons from a tragedy

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Malignant mesothelioma is an uncommon tumor of mesothelial surfaces of the pleural and peritoneal cavities that is remarkable for its association in the vast majority of cases with asbestos fibers (1). Transport of the fibers to these surfaces can lead to mesothelial proliferation, and, after many years, to malignant mesotheliomas. Among cigarette smokers who are exposed to asbestos there is a synergistically high incidence of lung cancer, but not a significantly higher incidence of mesothelioma than among exposed subjects who do not smoke (2). Tobacco smoke evidently supplies some carcinogens to the respiratory tract that do not reach mesothelial surfaces. This difference contributes to the lower incidence, and longer latent period, of mesothelioma relative to lung cancer among those exposed to asbestos.

Each of these tumors reveals elevated frequencies of certain cytogenetic aberrations that are regarded as clues to critical genetic events in the formation of many tumors. One event that is common to some cases of the two tumors involves loss of material from chromosome 9p (3). For mesothelioma this is associated with loss and/or mutation of the *CDKN2* (*p16*) gene, which is a regulator of phosphorylation of the protein product, p105, of the retinoblastoma tumor suppressor gene (*RBI*) (4). Unphosphorylated p105 can inhibit passage from G₁ to S phase of the cell cycle, whereas phosphorylated p105 is permissive (5–7). Interference with control of the G₁-to-S transition by p105 is a familiar story in cancer. Thus in some cancers, as in small cell carcinoma of the lung, it is accomplished by mutation of *RBI*, but in other cancers by loss of p16 or by mutation of still other genes. This loss of control can be overcome, at least to some extent, by activation of the *TP53* gene and its product, p53, so it is not surprising that many tumors have sustained mutations in this gene too. For small cell carcinoma of the lung, virtually every tumor harbors mutations of both *RBI* and *TP53* (8). This is not true for most cancers, but many have functionally equivalent mutations. In mesothelioma *RBI* mutations either do not occur or are very rare, but *CDKN2* mutation can produce such an equivalent effect. Mutations of *TP53* are found in some mesotheliomas (9), but in others there are mutations of

genes that interfere with *TP53* or its activation. For example, the Wilms tumor gene, *WT1*, is normally expressed in mesothelium and has been found to be mutant in some mesotheliomas (10). It is of interest that WT1 protein can form a complex with p53 (11) and that it can down-regulate the cyclin/CDK complexes that interact with the protein products of *RBI* and *TP53* (12). It may yet prove to be the case that most mesotheliomas, indeed even most cancers, are defective in the controls mediated by these two genes.

Another recurrent theme of genetic loss in mesothelioma is monosomy 22 (3). Monosomy is a striking abnormality, but discerning its genetic meaning is difficult because so many genes are lost with a whole chromosome. One of these is the neurofibromatosis type 2 (*NF2*) gene, a tumor suppressor gene whose mutation in the germ-line produces neurofibromatosis type 2 (13, 14). Sekido *et al.* (15) recently reported mutations in some cell lines but in only one primary tumor. This discrepancy between primary tumors and cell lines, which is common for the *CDKN2* gene (16), could be explained by admixture of normal cells and tumor cells or by irrelevant mutation arising in culture. In this issue of this journal, Bianchi *et al.* (17) report that single-strand conformation analysis of cDNA revealed *NF2* mutations in 8 of 15 cell lines and in 6 matching tumors. A 40% incidence is clearly significant, and the true percentage could be still higher, since some kinds of mutation could be missed. The mutations included deletions, insertions, and a nonsense mutation, all of which predict truncation of the protein product of *NF2*. The genomic DNA of two cell lines did not show the changes predicted from the cDNA abnormalities. One of these contained in-frame deletion of exon 10 in the cDNA, which may have resulted from aberrant splicing. How these *NF2* mutations contribute to oncogenesis of mesothelioma, or indeed of any tumor, is not clear. The protein product of the gene, called merlin (14) or schwannomin (13), belongs to a family of proteins that link cytoskeletal elements to the plasma membrane of the cell. Presumably the protein plays a role in signal transduction, but its ultimate gene target is unknown.

The *NF2* gene was discovered by positional cloning, following the mapping of

the hereditary disease neurofibromatosis type 2 (*NF2*) to chromosome 22q (13, 14). *NF2* predisposes primarily to acoustic neuromas, which are schwannomas of the eighth cranial nerve, but also to neurofibromas and meningiomas. It does not predispose to mesothelioma or to any of the common carcinomas, although the gene is widely expressed. Somatic mutations of *NF2* have been found in some carcinomas, but they are not found in carcinomas of the lung (15). Why tumors occur at these preferred sites, and in mesothelial cells, which are not derived from the neural crest, is not clear. Is there any significance to the fact that pia-arachnoid/nerve sheath tissues and mesothelium are covering tissues of the organs of the craniospinal and body cavities, respectively?

We are left wondering why mesothelioma is not a feature of the hereditary disease *NF2*. This situation has been observed for several of the hereditary cancers that are caused by tumor suppressor genes. Thus *RBI* and *TP53* are both mutant in nonhereditary small cell carcinoma of the lung, yet that tumor is not a feature of either hereditary retinoblastoma or the Li-Fraumeni syndrome, in many of which cases *TP53* is mutant in the germ line (18). In both of these hereditary conditions, the characteristic tumors (notably retinoblastoma for the former, bone and soft tissue sarcomas for both, and breast cancer for the latter) arise in tissues whose stem cells proliferate physiologically during fetal life or adolescence (19). In typical renewal tissues, like epithelial linings and mesothelium, it seems that some pathological condition must stimulate such proliferation. In the colon, for example, this may be germ-line mutation of the adenomatous polyposis coli (*APC*) gene or the presence of chronic ulcerative colitis. Asbestos fibers seem to provide this stimulus to the mesothelium and lung. Thus, in a rat model system, asbestos acted like a tumor promoter in combination with a carcinogen (20). Although asbestos does not appear to operate as a mutagen, it can interact with the mitotic spindle to cause missegregation of chromosomes and aneuploidy, including monosomy (21). A scenario for asbestos-induced mesothelioma might therefore begin with stimulation of stem cell proliferation by some epigenetic means, followed by progressive

accumulation, over many years, of spontaneously occurring mutations and asbestos-induced chromosomal missegregation. For NF2 in particular, one copy of this tumor suppressor gene would be mutated and the other lost by monosomy.

It often happens that a naturally occurring product can be both useful and harmful to humans. Such has been the case with asbestos. We are still suffering from the widespread use of this substance in the shipbuilding industry during World War II. In the absence of asbestos, mesothelioma is so rare that it might never be studied. However, investigation of the association between a specific exposure and an uncommon tumor is now teaching us about carcinogenesis. Some genetic changes seen in mesothelioma are common to many tumors, while at least one other, loss of the normal *NF2* tumor suppressor gene, is limited to a few tumors. However, this gene may operate in a signal transduction pathway from cell membrane to nucleus that is disturbed at other points in other tumors. Finally, the agent itself, asbestos, may have an epigenetic effect that is equivalent to that produced elsewhere by genetic change.

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