Malignant Pleural Mesothelioma

The Puzzling Role of Gene-Environment Interaction

Malignant pleural mesothelioma is a relatively uncommon and yet incurable tumor that is aggressive and highly lethal. After the occurrence of mesothelioma was first reported in 1960 in workers exposed to blue asbestos crocidolite, a huge number of experimental and epidemiologic studies has proved causality between asbestos mineral fibers and mesothelioma, whereas relatively few efforts have been made to understand the mechanisms underlying the pathogenesis of and the susceptibility to this tumor. Yet, in the last 2 decades geographic clusters of mesothelioma have been reported in populations with nonprofessional environmental exposure to asbestos, and other mineral fibers including zeolite fluor-edenite, a new amphibole end-member, which is chemically different from known asbestos types.

According to current knowledge, mesothelioma derives from multipotent mesothelial stem cells, which differentiate into malignant epithelial or mesenchymal elements. However, the mechanisms determining this differentiation as well as the local invasiveness of mesothelioma, despite extensive investigation, still remain poorly understood. Mesotheliomas with a predominantly epithelial growth pattern have a better prognosis than the sarcomatoid mesothelioma and the mixed or biphasic types, consisting of both epithelial and sarcomatous foci. Thus, the phenotype appears to be highly important for the biological behavior of the tumor, but little is known about the mechanisms and genetic determinants of different phenotypes. The mesothelioma occurs in selected individuals among population groups with known exposure to asbestos, either in the workplace or in the community. Interestingly, the evidence of a background incidence of this tumor, along with the description of familial clustering, suggest that the occurrence of asbestos-induced mesothelioma in some individuals, but not in others, may not be a matter of chance and points to the existence of genetic predisposition.

Furthermore, although malignant mesothelioma has received much attention, benign pleural diseases, including pleural plaques, pleural effusion, diffuse pleural thickening, and rounded atelectasis, induced by asbestos and nonasbestos fibers, are also common in clinical practice and often produce difficulties in the differential diagnosis. Hence, an understanding of the genetic profiling of malignant mesothelioma and other asbestos-induced pleural diseases is of pivotal importance and can be viewed from the perspective of how normal mesothelial cells respond to injury, how they transform into malignant cells, and how they proliferate so aggressively.

In this issue of CHEST (see page 1843), Hoang and coworkers explore the expression of matriptase, a trypsin-like protease, in freshly dissected human malignant mesothelioma and cultured mesothelioma cell lines, and find a mean 826-fold overexpression of...

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this enzyme in mesothelioma epithelial cells. Matriptase messenger RNA, which has been detected in tissues rich in epithelial cells, and cancerous breast, ovarian, and colon tissues, but not in cancers of a mesenchymal origin, has been characterized as an extracellular matrix-degrading protease system that may function as an epithelial membrane activator for other proteases and latent growth factors involved in cancer cell growth, invasion, and metastasis. In addition, the article by Hoang and associates describes the up-regulation of insulin-like growth factor (IGF) exon I. According to previous studies, IGF-I acts as an autocrine growth factor stimulus in normal mesothelial and mesothelioma cells, and the production of IGF-I is not only implicated in regulating the carcinogenic process and the growth rate of simian virus 40-induced mesotheliomas, but can also be targeted for carcinogenesis inhibition. Yet IGF-I has been shown to be able to induce the differentiation of mesothelioma cells toward a fibroblast-like morphology. Interestingly, Hoang and coworkers also found an underexpression of IGF binding protein 5, a family of transmembrane ligands whose controversial functional role may be cell type-specific; they speculated that the underexpression of IGF binding protein 5 could act as an inhibitor of IGF-I expression, thus contributing to uncontrolled cell proliferation via an IGF-mediated autocrine growth loop. Taken together, these results represent an interesting advance in that they could explain why mesothelioma is a predominantly local or regional disease, although it grows aggressively, and rapidly invades the pleural spaces and surrounding organs. Yet these results implicate multiple cell-signaling cascades in the process of mesothelial cell proliferation and suggest that a focus on blocking common downstream events or points of convergence of these pathways might be important for the treatment of mesothelioma. A central question remains, however, whether matriptase up-regulation and other gene expression identified in mesothelioma play any direct causative role in mesothelial cell transformation.

Recently, microarray technology has been successfully applied in a number of studies to identify specific gene expression changes in mesothelioma compared with normal mesothelial cells. These studies have identified the expression of a variety of genes that could explain many of the biological characteristics exhibited by mesotheliomas.

Abnormal karyotypes are common in mesothelioma cell lines, and abnormalities in chromosome 6 have been frequently described. The present evidence suggests that chromosome arm 6q harbors at least three tumor suppressor genes involved in the pathogenesis of mesothelioma. By doing simple segregation analysis of the occurrence of mesothelioma among nuclear families (parents and children) in Cappadocia, Turkey, an autosomal-dominant pattern of inheritance was postulated. More recently, by using gene expression-profiling data that had been previously collected from 17 mesothelioma patients with different overall survival times, Gordon and colleagues have been able to define two outcome-related groups of patients and to evaluate an expression ratio-based outcome predictor model. This approach could allow the preoperative identification of patients with widely divergent prognoses and could enhance the allocation of therapeutic resources.

Although experimental and circumstantial evidence clearly indicate that a number of genes may influence the malignant transformation of human mesothelial cells and the biological behavior of mesothelioma, we know relatively little about the way genes expressed by mesothelioma cells interact with each other or how this interaction is influenced by environmental risk factors. Similarly to other complex disorders, malignant pleural mesothelioma does not follow a clear Mendelian mode of inheritance, and it is likely to involve several low-penetrance genes, each with only weak-to-moderate effects. Thus, identification of these genes has proven difficult so far. Two main approaches to identify disease genes in complex disorders are the positional candidate and the functional candidate gene approach. The first approach is based on the choice of candidate genes according to their chromosomal position, whereas the other approach is to choose candidates based on a gene’s function and how that gene might fit into disease pathophysiology. Both of these approaches have limitations, but, most often, investigators rely on the retrospective case-control study design, which appears to be powerful enough to study the relationship between genetic susceptibility and environmental risk factors, to determine whether a candidate gene is associated with a disease.

In conclusion, our knowledge of gene expression in mesothelioma is still fragmentary, and a systematic approach to the nomination of a candidate susceptibility gene for mesothelioma is still lacking. However, due to the complexity of the gene-environment interaction, the study of this susceptibility could be better approached by combining genetic and epidiomologic analyses. This seems particularly important if one takes into account that not only are patients with malignant mesothelioma induced by asbestos and nonasbestos fibers commonly seen in clinical practice, but also those patients with benign pleural diseases. Unfortunately, this is further complicated by the long latency period between the exposure and the occurrence of mesothelioma, and by the complex
relationships among the time since first exposure, fiber concentration, duration of exposure, and risk of disease. This makes the use of the prospective cohort study design unpractical. Notwithstanding, mesothelioma and perhaps other asbestos-related pleural disorders are disease states in which environmental exposure and genetic susceptibility are strikingly important. Until now, malignant mesothelioma has been considered to be an invariably fatal tumor of the pleural and peritoneal cavities, the pathogenesis of which is not clearly understood and the gene expression profile of which is far from complete. Identifying the genetic signaling pathways of mesothelioma could help in understanding susceptibility and carcinogenesis, aiding diagnosis and prognostic evaluation, or designing new therapeutic strategies that are aimed at improving the treatment of this disease. Thus, it is believed that the interaction between genetic predisposition and environmental exposure to mineral fibers deserves further investigation.

In recent years, the evidence linking mesothelioma to asbestos exposure has prompted the setup of costly asbestos removal programs. Owing to the widespread use of end-products containing asbestos or other potentially harmful mineral fibers and the length of the postexposure period, the incidence of this tumor is expected to rise during the next 2 or 3 decades.

In conclusion, the news provided in the report by Hoang and coworkers is interesting. Pleural mesothelioma is a devastating malignancy with a median survival time of 6 to 18 months after diagnosis that likely develops in susceptible individuals because of the interaction between a number of genes with low penetrance, and environmental exposure to mineral fibers and other risk factors. Under these circumstances, the determination of individual genetic variants may have low predictivity, and dissecting the genetic and environmental influences is highly challenging. However, genetic studies of mesothelioma may be relevant for several reasons. First, familial clustering of cases convincingly demonstrates that a genetic susceptibility to mesothelioma exists even if familial clustering of the disease in many instances has been shown to be associated with the sharing of a common asbestos exposure. Thus, advances in the genetic profile represent important steps forward in the targeted use of genetic tests in healthy subjects to predict the future risk of disease. Additionally, short survival time and resistance to conventional therapy are typical of mesothelioma, and findings like those reported here by Hoang and coworkers provide further background for the future development of novel therapeutic strategies.

The understanding of the genetic profiling of malignant mesothelioma, and the correlation of genetic variants and environmental risk factors with the development and biological characteristics of this tumor might eventually give us a more complete picture of this puzzling disorder, and hopefully will lead to important health gains.

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α₁-Antitrypsin Deficiency
More Than a Protease Imbalance?

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oes the protease-antiprotease concept need an update? The novel observation provided by the work from Mulgrew and colleagues in this issue of CHEST (see page 1948) suggests that the process is likely much more complex than originally conceived 4 decades ago. More about that later.

In 1963, Laurell and Eriksson demonstrated the connection between a deficiency of α₁-antitrypsin and the fact that three of the first five individuals identified had unmistakable evidence of pulmonary emphysema. The recognition that the main function of α₁-antitrypsin is to inhibit proteases (most specifically neutrophil elastase and protease 3), and the demonstration that these enzymes when instilled into the lung produce pulmonary emphysema, led to the genesis of this hypothesis. It has now been almost 2 decades since α₁-antitrypsin infusions have been used clinically in an attempt to counterbalance the protease burden. Yet, to date there are only limited data to suggest that this treatment has impacted the natural history of α₁-antitrypsin deficiency-associated emphysema. The largest comparison to date, the Alpha-1-Antitrypsin Deficiency Registry, which analyzed 927 subjects, failed to demonstrate an effect of augmentation therapy on FEV₁ rate of decline. Is the concept of an imbalance between enzyme and inhibitor too simplistic? Why doesn’t augmentation therapy have a more dramatic effect on the progression of a disease that is the most classic example of the protease anti-protease hypothesis? These questions certainly raise a number of interesting possibilities.

Perhaps, α₁-antitrypsin augmentation is started too late and the initial proteolytic insult sets a process in motion that is only partly suppressed by treatment. A computer model of the elastin-centered lung structure suggests that this is a real possibility. Suki et al. demonstrate that elastin breakdown may beget elastin breakdown. Mechanical strain on previously injured matrix may induce further strand breakage. Since the lung is constructed in a network that depends on the sum of the parts for its structure, loss of individual support structures may put additional stress on remaining supports that ultimately leads to further destruction. The collapse of the World Trade Center towers comes to mind. Therefore, perhaps augmentation treatment needs to be in place before any matrix is destroyed. However, given the average cost of approximately $50,000/yr, this hypothesis is not likely to be tested soon. Furthermore, prospective studies demonstrate that despite the high frequency of the PiZ allele in the world population, the incidence of clinically significant emphysema is surprisingly low. So treating everyone would likely mean treating a majority that does not need it.

Why then doesn’t everyone respond in the same way to the presumed protease imbalance? Additional risk factors are undoubtedly playing a role. For example, cigarette smoking shortens the life expectancy of an individual with α₁-antitrypsin deficiency by almost 20 years. But individual smokers have huge variances in the severity of disease despite what appear to be similar exposures to tobacco. Additional inherited predispositions are likely to be present. Family genetic studies currently underway may answer the gene-environment question in the near future.

Furthermore, the pathophysiology of α₁-antitrypsin diseases is clearly not all due to protease excess. Panniculitis is a case in point. α₁-Antitrypsin may be an anti-inflammatory agent, and its deficiency may predispose to inflammation. However, the mechanisms of its anti-inflammatory effect are not understood. We documented that α₁-antitrypsin can prevent antineutrophil cytoplasmic antibodies (ANCA) from activating the release of the neutrophil che-