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The pathogenesis of mesothelioma ^{*}, ^{**}

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Abstract

About 80% of malignant mesotheliomas (MM) in the Western World develop in individuals with higher than background exposure to asbestos. Only a fraction of those exposed to asbestos develop mesothelioma, indicating that additional factors play a role. Simian virus 40 (SV40), a DNA tumor virus that preferentially causes mesothelioma in hamsters, has been detected in several human mesotheliomas. The expression of the SV40 large tumor antigen in mesothelioma cells, and not in nearby stromal cells, and the capacity of antisense T-antigen treatment to arrest mesothelioma cell growth in vitro suggest that SV40 contributes to tumor development. The capacity of T-antigen to bind and inhibit cellular p53 and retinoblastoma (Rb)-family proteins in mesothelioma, together with the very high susceptibility of human mesothelial cells to SV40-mediated transformation in vitro, supports a causative role of SV40 in the pathogenesis of mesothelioma. Asbestos appears to increase SV40-mediated transformation of human mesothelial cells in vitro, suggesting that asbestos and SV40 may be cocarcinogens. p53 mutations are rarely found in mesothelioma; p16, p14ARF, and NF2 mutations/losses are frequent. Recent studies revealed the existence of a genetic factor that predisposes affected individuals to mesothelioma in the villages of Karain and Tuzkoy, in Anatolia, Turkey. Erionite, a type of zeolite, may be a cofactor in these same villages, where 50% of deaths are caused by mesothelioma. Mesothelioma appears to have a complex etiology in which environmental carcinogens (asbestos and erionite), ionizing radiation, viruses, and genetic factors act alone or in concert to cause malignancy. *Semin Oncol* 29:2-17. Copyright © 2002 by W.B. Saunders Company.

Section snippets

Benign mesotheliomas

Multicystic mesothelioma, also called multilocular peritoneal inclusion cyst, is a benign mesothelial lesion, characteristically formed by multiple cysts arranged in grape-like clusters. Adenomatoid mesotheliomas are benign mesothelial lesions of the genital system. Mesothelioma of the atrioventricular node is neither a mesothelioma nor a tumor. This lesion represents congenital heterotopia of the endodermal sinus in the atrioventricular node. Well-differentiated papillary mesothelioma is found ...

Asbestos

Prior to the 1950s, MM were extremely rare. The first documented case of mesothelioma, according to current diagnostic criteria, was published in 1947.² In fact, some authors even questioned whether mesotheliomas existed at all because using current methodologies and reviewing 47,000 autopsies performed at the Massachusetts General Hospital from 1896 until 1947 they did not find any evidence of mesothelioma.³ From 1947 until 1990, about 100 mesotheliomas were recorded at autopsy at the...

Simian virus 40

(SV40) is a DNA tumor virus capable of inducing mesotheliomas, as well as other tumors, in hamsters and of transforming human cells in vitro.^{4, 21, 22} The SV40 genome is a double-stranded circular DNA molecule containing 5243 base pairs that can be divided into two regions, early and late, according to the order in which they are transcribed. The early region encodes three proteins, large T-antigen (Tag), small t-antigen (tag), and 17kT, and it is responsible for the transforming ability of the ...

Asbestos

Experimental models demonstrating asbestos carcinogenicity have been established in several animals.²⁹ In 1969, Wagner and Berry injected 96 rats intrapleurally with amosite, crocidolite, and chrysotile asbestos and found that mesotheliomas developed in 38, 61, and 55 rats, respectively.³⁰ Therefore, in contrast to the data in humans, in animals, all types of asbestos can induce tumors without notable differences. It was determined that the likelihood of mesothelioma development in rats was...

Asbestos exposure

It is generally agreed that background exposure (ie, most people who live in industrial areas or in large cities contain some asbestos fibers in their lungs) does not constitute a health risk, and that mesothelioma and other diseases are associated with higher than background levels of exposure. However, measuring higher than background levels of exposure is a difficult task prone to errors. Some studies rely on history of exposure, while others look to the amount of asbestos fibers found in...

Asbestos and human mesothelioma

In a mortality study of 1,225 deaths among 7,317 men who worked in crocidolite or amosite mines in South Africa, there were 30 mesotheliomas.¹⁰ Twenty of these were in crocidolite miners (in 423 deaths, 4.7%), four were in amosite miners (in 648 deaths, 0.6%), and six in miners with mixed exposure (in 154 deaths, 3.9%).¹⁰ Among crocidolite-associated mesotheliomas, six developed in individuals exposed from 12 to 95 months, six in miners exposed for 96 to 191 months, and eight in miners exposed...

SV40 and human mesothelioma

The discovery that SV40 caused the development of mesotheliomas in hamsters led to polymerase chain reaction (PCR) analysis of human mesothelioma specimens for the presence of the virus. Altogether, 29 of 48 (60%) mesothelioma samples contained SV40 sequences. SV40 Tag expression was also detected by both immunohistochemistry and immunoprecipitation experiments.⁴¹ These results were confirmed by an independent multilaboratory study organized by the International Mesothelioma Interest Group,⁴²...

Radiation and human mesothelioma

There have been several case reports in which mesothelioma developed in patients who had received radiation to the thorax or to the abdomen, or who had received Thorotrast intravascularly.⁵⁵ Mesothelioma in these patients developed after an interval of 7 to 36 years. In many of these cases, the possibility that asbestos or other factors had contributed

to mesothelioma could not be entirely ruled out. However, at least for those mesotheliomas which developed in young adults who had received...

Genetics and human mesothelioma

In the villages of Karain (population ~600) and Tuzkoy (population ~1,400) in Cappadocia, a region in Central Anatolia, Turkey, characterized by volcanic tuffs and natural caves, 50% or more of deaths are caused by malignant mesothelioma. These two villages, like most others in the region, were built with stones mined from the nearby natural caves. When Dr Y.I. Barish found a very high incidence of mesothelioma in Karain,⁵⁸ scientists looked for asbestos, which in the 1970s was the only known...

Genetic alterations in mesothelioma

Whatever the cause, genetics, asbestos, SV40, or radiation, mesothelial cells eventually accumulate a number of genetic alterations and become malignant. Human mesothelioma cells are characterized by many different genetic abnormalities and separating those that play a causative role during the establishment of the transformed phenotype and tumor progression from those that do not has not been possible to date, particularly since data on early lesions are not available.

Karyotypic studies and...

Conclusions

Most mesotheliomas in the Western World are caused by exposure to asbestos. Certain types of asbestos, especially crocidolite asbestos, appear more carcinogenic than others (crysotile). SV40 in the United States and in parts of Europe, and genetic predisposition in the villages of Karain and Tuzkoy, have recently been linked to mesothelioma. Rare cases of mesothelioma have been associated with radiation exposure. Whether these factors act independently or interact in causing mesothelioma is...

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