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Tumorigenesis of Malignant Mesothelioma: The key role of genetics

Introduction

The literature review in this section focuses on several key concepts regarding the genetics and pathways involved in the tumorigenesis of malignant mesothelioma (MM).

With this in mind, approximately 250 articles were analyzed and summarized below but we do not claim that this is an in-depth, exhaustive review, so please consult the bibliography at the end of this text for further information.

Molecular biology of mesothelioma

Malignant mesothelioma (MM) is caused by the abnormal proliferation of tumors in the pleura, pericardium, peritoneum, tunica vaginalis testis or ovarian epithelium (1,2).

Its incidence rate is increasing, and unfortunately the prognosis is often poor (3,4). A number of diverse pathogenetic hypotheses for this disease have been investigated in detail (5-8).

MM is characterized by a long latency period before the appearance of the initial symptoms that can lead to a diagnosis and during this long period, genetic mutations may occur and characterize the neoplastic changes (9-11). The purpose of this literature review is to focus on the genetics and pathogenetic pathways associated with this neoplasm.

Genes

The main chromosomes affected by this neoplasm are: 1, 3, 4, 6, 9, 13 and 14 (12). The genetic abnormalities most commonly associated with malignant pleural mesothelioma (MPM), and which will be analyzed individually, are the following: p16^{INK4a}/p14^{ARF} (13,14), NF2 (15,16), p53 (17-20), PTEN (21-23), BAP-1 (24), LATS2 (25), PI3K/AKT/mTOR (22,26), EGFR (27,28), VEGF (29-31), pRb (32,33), BCL-2 (34-36), hippo (37-39) and Wnt (40,41).

p16^{INK4a}/p14^{ARF}

The p16^{INK4a}/p14^{ARF} gene is also known as CDKN2A/ARF and is located on chromosome 9p21.

This is a very important tumor suppressor gene that codifies for two proteins: p16^{INK4a} and p14^{ARF} (42-43).

Protein p16^{INK4a} inhibits CDK, which inactivates pRb.

Protein p14^{ARF}, on the other hand, regulates the function of p53 and inhibits its degradation by interacting with MDM2 (27,44,45).

These modifications play a fundamental role in regulating the control of the cell cycle; these genetic mutations also appear to be associated with more aggressive tumors and a poorer prognosis (13,14).

These genes in particular are implicated in the development of different types of neoplasia (46-48). Similarly, the same type of genetic mutations may also occur in MPM (13, 50-54). Scientific studies have shown that if this gene is "switched off", cancerogenesis may be "accelerated" due to exposure to asbestos (55-59).

Gene therapy studies are aimed at reactivating the p16^{INK4a}/p14^{ARF} gene to restore the functions that have been lost if the gene is mutated. The studies have shown that reactivating this gene halts the cell cycle of mesothelioma cells, inhibits the phosphorylation of pRb, and decreases cell growth. All these modifications may therefore increase survival, increase the levels of protein p53, and boost cell apoptosis (60-63,12).

Gene therapy aimed at restoring the functions altered by the mutation of this gene has shown promising preliminary results.

NF2

NF2, the abbreviation for the type 2 neurofibromatosis gene, is a genetic trait that follows an autosomal dominant inheritance pattern leading to tumor predisposition syndrome, and is characterized by the development of bilateral vestibular schwannomas on the eighth cranial nerve and other brain tumors, including meningiomas and ependymomas.

This syndrome results from the lack of expression of the NF2 gene, which is a tumor suppressor.

Although known for the above syndrome, this gene is also associated with malignant mesothelioma (64-69).

The lack of protein activity associated with the codification of the mutated gene appears to be associated with a greater possibility of carcinogenesis, as opposed to patients who do not have this genetic mutation, and which is certainly greater for patients who have been exposed to asbestos (22,70). However, the precise functionality of this gene has not yet been fully defined.

Gene therapy associated with this gene involves trying to “over-express” it through the use of viral vectors.

These studies have shown interesting results, such as controlling the cell cycle and proliferation (71-75).

Re-expression of the NF2 gene in patients with MM could certainly be of considerable help in inhibiting cell proliferation and tumor invasion (76).

BAP-1

Several clinical studies have sought to understand how there appears to be a genetic predisposition to MPM in certain localities. BAP-1 was found among the genes that were mutated and thus deemed to be involved in this disease (77-79).

Recent studies have also shown that BAP-1 is a tumor suppressor located on chromosome 3p21, which appears to play a role in regulating the cell cycle and responding to DNA damage (80-81).

This genetic mutation was found in patients with MM, especially the squamous histotype rather than the epithelial histotype (82-84).

This pathologic genetic modification seems to be particularly associated with a poorer prognosis (85-86), as well as the development of neoplasia (87).

Gene therapy is being investigated not only to find an effective treatment for patients with a genetic alteration of this gene, but also to eventually prevent MM in subjects with a mutated BAP-1 gene.

LATS2

The Large Tumor Suppressor (LATS) was the first tumor marker identified in *Drosophila* (88).

In humans, this gene is located in a region of chromosome 13 (13q11-12) and is often mutated in tumors (89-90).

Two forms of LATS have been identified: LATS1 and LATS2. LATS2 in particular is a centrosomal protein which appears to be involved in mitotic subdivision (91), regulating the inhibition of the growth of Hippo (37) and activating p53 (92-93).

This gene has been studied in MM, particularly in cell lines characterized by a deletion of chromosome 13q11-12. Comparative genomic hybridization techniques were used for these analyses, subsequently confirmed by PCR.

These studies have shown the presence of genetic mutations of LATS2 in MM cells (25). According to these studies, LATS2 appears to play a role in cell proliferation and survival. However, further studies are needed to confirm whether this gene actually plays a causal role in the development of MM.

DNA methylation

Studies investigating DNA methylation in MM have shown promising results.

They have shown that the methylation profile can be a differentiating factor between the physiological pleura and their pathological mutations, especially those that are characteristic of mesothelioma (94).

Some studies maintain that the methylation profile could even be considered a diagnostic marker that can be used to identify primitive and secondary pleural tumors (95).

Other studies investigated the relationship between patient outcomes and their methylation status and have observed interesting differences in survival associated this genetic mutation (96).

Other studies have also analyzed diagnosis and an eventual epigenetic therapeutic approach (15,97).

MicroRNA

miRNA expression is another important mechanism in the development of tumors, which supports their ability to control different biological processes.

For this reason, many researchers have focused their attention on the profile of miRNA to verify if there are any discrepancies/associations between these various genetic expressions and the pleura (98-103).

Other genes

A component of the Hippo cascade, the salvador gene (SAV) was discovered in the *Drosophila* 81349 and is considered one of the gene suppressors altered in different neoplastic forms (16, 104-105). Deletion of the chromosome 14q22 was recently demonstrated in approximately 5% of mesothelioma cell lines; however, the actual role of this gene in the pathogenesis of this disease is still being studied (25).

Deletion of the β -catenin (CTNNB1) gene in MM cell lines was discovered in approximately 10% of cases (106). CTNNB1 appears to be a cell growth stimulation factor in different tumor forms (107), although further studies are needed in this case too to clarify their pathogenetic role.

Recent studies have suggested that the Hedgehog signal pathway is activated in MM cell lines (108). This pathway in fact appears to be regulated by 13 genes in cancer pathogenesis. However, only three of these genes were mutated in MM cell lines: PTCH1, SMO and SUFU (108-110).

The circadian rhythm is regulated by different genes and proteins that involve different processes: sleep, body temperature, hormones, the immune response and many others (111). Various studies have demonstrated a possible correlation between changes in the circadian rhythm and the development of cancer (112-113).

Studies are investigating different genes with respect to MM, including the following: the clock genes PER (period), CRY (cryptochrome) BMAL1 (aryl hydrocarbonreceptor nuclear translocator-like) (114- 116).

Conclusions

Genetic mutations associated with MM are being studied, with many already identified and many others being defined.

All these studies are aimed at increasing our knowledge about the genetics of MM, to understand how genetic mutations are associated with this disease.

Defining their pathogenetic role and cause would open up new avenues of research and certainly to potential experimental therapeutic strategies aimed at restoring the correct genetics whenever possible, which appear to be distorted in this disease.

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