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Review Article

Malignant Mesothelioma: A Detailed Review of Genetic, Environmental Factors, and Therapeutic Innovations

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Abstract

Malignant mesothelioma is an aggressive cancer predominantly caused by asbestos exposure, yet it also has strong genetic underpinnings. This review provides an in-depth exploration of the genetic factors, such as BAP1 mutations, AQP1 polymorphisms, and other hereditary influences that increase susceptibility to mesothelioma. The role of environmental exposure, particularly to asbestos and erionite, is also examined, highlighting the synergistic effects of genetics and environmental risk factors in disease development.

Recent advances in therapeutic approaches are critically evaluated, including traditional treatments like chemotherapy and innovative therapies such as immunotherapy, gene therapy, and CAR T-cell therapy. Key clinical trials, including the MAPS trial, which combined pemetrexed cisplatin with bevacizumab, showed improved overall survival rates for patients with unresectable pleural mesothelioma. The review also delves into photodynamic therapy and the growing promise of immune checkpoint inhibitors such as nivolumab and ipilimumab, which have demonstrated encouraging results in extending progression-free survival and overall survival. The potential of dendritic cell-based therapies and gene therapy, particularly the intrapleural transfer of interferon-alpha, are explored as novel strategies in mesothelioma management.

Despite the promising advances in treatments, mesothelioma remains challenging to treat effectively. This review emphasizes the importance of continued research into both genetic predispositions and targeted therapies. A combination of personalized medicine, focusing on genetic mutations, and the development of therapies tailored to specific patient profiles could pave the way for more effective and durable treatment outcomes for mesothelioma patients.

Keywords: Mesothelioma; Asbestos; Pleural Mesothelioma; Peritoneal Mesothelioma; BAP1 Gene; Immunotherapy; Chemotherapy; Gene Therapy; Clinical Trials; Targeted Therapy; CAR T-Cell Therapy; Intra Pleural Gene Transfer

Abbreviations

MPM: Malignant Pleural Mesothelioma; BAP1: BRCA1-Associated Protein 1; PD-L1: Programmed Death-Ligand 1; CAR T: Chimeric Antigen Receptor T-cell therapy; PFS: Progression-Free Survival; OS: Overall Survival; CTLA-4: Cytotoxic T-Lymphocyte Antigen 4; PD-1: Programmed Cell Death Protein 1; ICIs: Immune Checkpoint Inhibitors; PDT: Photodynamic Therapy; GWAS: Genome-Wide Association Study; AQP1: Aquaporin 1; EZH2: Enhancer of Zeste Homolog 2; NF2: Neurofibromin 2; VEGF: Vascular Endothelial Growth Factor; PDGFR: Platelet-Derived Growth Factor Receptor; FGFR: Fibroblast Growth Factor Receptor; PARP: Poly (ADP-ribose) polymerase

Introduction

Mesothelioma is an extremely aggressive cancer primarily linked to asbestos exposure, affecting the pleural lining of the lungs and, in rarer instances, the peritoneum and tunica vaginalis [1]. Despite significant advancements in treatment, mesothelioma remains a challenging disease to manage, with a poor prognosis and an average survival of approximately one year [1,2]. Conventional therapies, such as surgery, chemotherapy, and radiotherapy, have yielded limited success [1]. The combination of pemetrexed and cisplatin is the standard Firstline treatment for malignant pleural mesothelioma, but most patients eventually experience disease progression [2]. With median survival after first line treatment at about 14 months, there is an urgent need for more effective therapeutic strategies [2].

Recent research has highlighted the critical role of genetic mutations and molecular pathways in the development and progression of mesothelioma [1,3]. The tumor suppressor gene BAP1 (BRCA1 associated protein 1) has emerged as a key player in mesothelioma, with mutations in BAP1 being strongly associated with tumor development [1,3]. Other significant genetic mutations include alterations in NF2, which is involved in the regulation of the Hippo signaling pathway, and CDKN2A, which is often deleted or mutated in mesothelioma [3]. These genetic mutations not only contribute to the onset of mesothelioma but also have potential implications for targeted therapies.

In addition to genetic factors, the tumor immune microenvironment plays a pivotal role in mesothelioma pathogenesis [3]. The TME is characterized by an inflammatory response to asbestos exposure, involving various immune cells such as macrophages, regulatory T cells, and myeloid derived suppressor cells, which collectively create an immunosuppressive environment [3]. Understanding the interplay between these immune components and tumor cells has opened new avenues for immunotherapy, especially immune checkpoint inhibitors targeting molecules like PD1 and CTLA4 [3]. However, mesothelioma's low tumor mutational burden and limited T cell activation often hinder the effectiveness of immunotherapy [3]. Beyond asbestos, other environmental factors such as radiation and engineered nanomaterials have been linked to mesothelioma, further complicating the disease's etiology [1].

Types of mesotheliomas

Pleural mesothelioma

Pleural mesothelioma is the most prevalent form, accounting for 80% to 90% of all mesothelioma cases [6]. This type originates in the pleura, which is the protective lining surrounding the lungs [4]. The primary cause is asbestos exposure, as inhaled asbestos fibers can become lodged in the pleura, leading to inflammation and tumor formation over time [5].

- Common symptoms include: Chest pain, Coughing, Shortness of breath [5].

Treatment options typically involve a multimodal approach, which may include:

- Surgery (e.g., extra pleural pneumonectomy or pleurectomy/ decortication) Chemotherapy, Radiation therapy [4,5]
- The prognosis for pleural mesothelioma varies, but median survival rates range from 18 months with treatment [5]. Patients receiving multimodal therapy may experience improved outcomes [4].

Peritoneal Mesothelioma

Peritoneal mesothelioma, which accounts for about 10% to 15% of mesothelioma cases, arises in the peritoneum, the lining of the abdominal cavity [6] Like pleural mesothelioma, asbestos exposure is a significant risk factor, as ingested asbestos fibers can lead to tumor development [4].

- **Symptoms often include:** Abdominal pain, Swelling, Weight loss, Ascites (fluid accumulation in the abdomen) [5]

Treatment may involve: Chemotherapy (both systemic and localized), Cytoreductive surgery (CRS), Heated intraperitoneal chemotherapy (HIPEC) [5].

Survival rates for treated patients can vary significantly, with median survival times ranging from 2.5 to 7.5 years depending on the treatment combination [4].

Pericardial mesothelioma

Pericardial mesothelioma occurs in the pericardium, the lining around the heart, and is extremely rare, accounting for less than 1% of mesothelioma cases [6]. Although asbestos exposure is a recognized risk, the specific mechanisms by which this type develops are not well understood due to its rarity [4].

- **Symptoms may include:** Chest pain, Difficulty breathing, Heart palpitations [4].
- **Treatment options include:** Chemotherapy, Surgery (e.g., pericardiectomy) [4].
- The prognosis is generally poor, with median survival rates of around 6 months, but some patients undergoing multimodal therapy may survive longer [5].

Testizular mesothelioma

Testicular mesothelioma is an extremely rare form that affects the lining surrounding the testicles, known as the tunica vaginalis [6]. Like the other types, it has been linked to asbestos exposure, although the exact pathogenesis remains unclear [4].

- **Symptoms often include:** Swelling in the scrotum, Pain, Hydrocele (fluid accumulation) [5]
- **Treatment typically involves:** Radical orchiectomy (removal of the affected testicle), Chemotherapy [4,5].
- The prognosis for treated testicular mesothelioma is relatively better, with a median survival of about 6 years [6].

Mesothelioma by cell type

In addition to classification by location, mesothelioma is also categorized by the type of cells involved, which can significantly influence treatment and prognosis.

Epithelioid mesothelioma

Epithelioid mesothelioma is the most common cell type, comprising approximately 70% of cases [5]. Epithelioid cells typically have a boxy or oval shape and tend to respond more favorably to treatments compared to other cell types [4].

Median survival rates for epithelioid mesothelioma range from 1.5 to 6.5 years, especially for those undergoing multimodal therapy [45].

Grades of epithelioid mesothelioma

- **Low Grade:** Characterized by slower growth and a better prognosis [5].
- **High Grade:** More aggressive and associated with a poorer prognosis [4].

Sarcomatoid mesothelioma

Sarcomatoid mesothelioma makes up about 10% of cases and is characterized by spindle-shaped cells that can be more aggressive [5]. This type is often associated with a poorer prognosis, with median survival rates typically between 8 to 10 months [4,5].

Recent advancements in immunotherapy, particularly the use of immune checkpoint inhibitors, have shown promising results in improving survival for sarcomatoid patients [5].

Grades of sarcomatoid mesothelioma

- **Low Grade:** Less common, but with better outcomes [5]
- **High Grade:** Generally, results in more aggressive disease progression [4].

Biphasic mesothelioma

Biphasic mesothelioma, accounting for about 20% of cases, features both epithelioid and sarcomatoid cells [6]. The prognosis for biphasic mesothelioma varies significantly based on the predominance of cell types; more epithelioid cells generally correlate with better outcomes [4,5].

Grades of biphasic mesothelioma:

- **Low Grade:** Shows a higher proportion of epithelioid cells, leading to a better prognosis [5].

- **High Grade:** More sarcomatoid cells, resulting in an increased risk of aggressive disease [4].

Rare cell types

In addition to the primary cell types, there are rarer subtypes of mesothelioma, which include:

- Adenomatoid [6]. Deciduoid [4]. Desmoplastic [5]. Heterologous [6]. Lymphohistiocytoid [4]. Small cell [5]
- Well, differentiated papillary mesothelioma [6].
- These rare types often exhibit treatment responses like the more common forms but remain less understood due to their infrequent occurrence [4,5].

Stages of mesothelioma

Staging is a critical aspect of cancer diagnosis, providing valuable information about the extent of the disease and guiding treatment decisions. Mesothelioma staging typically relies on the International Mesothelioma Interest Group (IMIG) system or the TNM system, which evaluates Tumor size (T), Node involvement (N), and Metastasis (M) [4,5].

Stage I: Early Localized Disease

- At this initial stage, mesothelioma is localized and has not spread beyond the pleura or peritoneum [5]

- **Pleural Mesothelioma:** The cancer is confined to one side of the pleura and may have affected the lung or chest wall [6].

- **Peritoneal Mesothelioma:** The tumor is limited to one area of the peritoneum [4].

Stage II: Localized Disease with Regional Spread

- In Stage II, the cancer remains localized but may have spread to nearby tissues or lymph nodes [5]
- **Pleural Mesothelioma:** The tumor may extend to the chest wall or diaphragm [4]
- **Peritoneal Mesothelioma:** Cancer may involve multiple areas of the peritoneum but is still confined to the abdomen [5].

Stage III: Advanced Localized Disease, Stage III indicates a more advanced disease, with the cancer spreading to nearby organs and lymph nodes [4,5]

- **Pleural Mesothelioma:** Tumors may invade the chest wall, mediastinum, or regional lymph nodes [6]
- **Peritoneal Mesothelioma:** Cancer has spread throughout the abdomen and may involve organs such as the intestines [4].

Stage IV: Metastatic Disease, Stage IV mesothelioma represents the most advanced stage, where the cancer has metastasized to distant organs, such as the liver, bones, or brain [4,5].

- Pleural Mesothelioma: Widespread involvement of both pleural layers and distant spread is common [6].

- Peritoneal Mesothelioma: Cancer has spread beyond the abdomen and may affect other body systems [5].

- Treatment Planning: Staging helps healthcare providers determine the most effective treatment option [4].

- Prognosis: It gives patients an understanding of their prognosis and potential survival outcomes [5].

- Clinical Trials: Staging is often a requirement for eligibility in clinical trials investigating new treatment options [4].

Market size

Global market overview

The global mesothelioma treatment market was valued at approximately $276.6 million in 2020, and it is projected to grow at a compound annual growth rate (CAGR) of 7.5% from 2021 to 2028, reaching $468 million by 2028 [27,28]. This growth is driven by increasing awareness of asbestos-related diseases, rising incidence rates of mesothelioma, and advancements in novel therapies, particularly immunotherapies and gene therapies [28]. The market is segmented regionally, with North America holding the largest share, accounting for around 43% of the global market, valued at $120 million in 2020 [27,29]. Europe followed with 29%

of the global market, valued at $80 million, while the Asia-Pacific region, although smaller, is expected to grow the fastest, with a CAGR of 8.2% [30].

In North America, the presence of advanced healthcare infrastructure, high incidence of mesothelioma due to prolonged asbestos exposure, and ongoing clinical trials have led to significant market dominance [29]. The region's market is projected to grow at a CAGR of 7.8%, reaching $185 million by 2028 [27]. In Europe, countries such as Germany, France, and the United Kingdom have been at the forefront of mesothelioma research, supported by government funding and research initiatives aimed at asbestos-related diseases [30]. The European market is forecasted to reach $135 million by 2028, driven by the increasing adoption of advanced therapies [30].

The Asia-Pacific region, though currently smaller, is anticipated to exhibit the highest growth rate due to increasing awareness of mesothelioma and improvements in healthcare infrastructure in countries like China, Japan, and India [27,30]. The Asia-Pacific market is expected to reach $90 million by 2028, with key drivers including rising healthcare expenditure and increased asbestos exposure in certain regions [27,30].

Market segmentation by treatment type

The mesothelioma treatment market is segmented into chemotherapy, immunotherapy, gene therapy, and radiation therapy. Chemotherapy remains the most widely used treatment, with drugs like Pemetrexed [Alimta] and Cisplatin forming the standard of care [31]. In 2020, the chemotherapy segment accounted for 47% of the market, with a total value of $130 million [31]. Although chemotherapy has been the cornerstone of mesothelioma treatment for decades, its market share is projected to decline gradually as newer, more targeted therapies such as immunotherapy gain prominence [31].

Immunotherapy has emerged as a significant growth driver in the mesothelioma treatment landscape [32]. In 2020, the immunotherapy market was valued at $58 million, and it is projected to grow at a CAGR of 12.5%, reaching $150 million by 2028 [32,33]. This growth is primarily attributed to the increasing use of checkpoint inhibitors like Nivolumab (Opdivo) and Pembrolizumab (Keytruda), which have shown promising results in clinical trials for patients with advanced stage mesothelioma [32,33]. The expanding use of these drugs in clinical practice is expected to significantly reshape the treatment landscape, with immunotherapy anticipated to capture a larger market share in the coming years [32,33].

Gene therapy is another emerging treatment modality, particularly for patients with specific genetic mutations such as BAP1 and CDKN2A [31]. In 2021, the gene therapy segment was valued at $25 million, and it is expected to grow at a CAGR of 9.2%, reaching $58 million by 2030 [31]. Gene therapy, although still in its early stages, has the potential to revolutionize mesothelioma treatment by targeting the underlying genetic mutations that drive the disease [31]. As more gene therapies progress through clinical trials and receive regulatory approval, this segment is expected to expand rapidly [31].

Regional market analysis

The North American market for mesothelioma treatments was valued at $120 million in 2020, accounting for approximately 43% of the global market [27,29]. This dominance is due to high mesothelioma incidence rates, advanced healthcare systems, and strong research funding [29]. The United States alone contributed 75% of this market share [29]. The North American market is expected to grow at a CAGR of 7.8%, reaching $185 million by 2028 [27].

In Europe, the mesothelioma treatment market was valued at $80 million in 2020, making up around 29% of the global market [30]. Germany, France, and the United Kingdom are key contributors, with increased investment in mesothelioma research and treatment development [30]. The European market is forecasted to grow at a CAGR of 6.8%, reaching $135 million by 2028 [30].

The Asia-Pacific region was valued at $45 million in 2020 and is projected to grow at the fastest rate, with a CAGR of 8.2%, reaching $90 million by 2028 [27,30]. This growth is driven by rising healthcare awareness, particularly in countries like China, Japan, and India, where increasing asbestos exposure is contributing to a higher incidence of mesothelioma [27,30].

Future market trends

Immunotherapy is expected to play a significant role in shaping the future of the mesothelioma treatment market [32]. In 2020, the immunotherapy segment was valued at $58 million, and it is projected to grow at a CAGR of 12.5%, reaching $150 million by 2028 [32,33]. Drugs like Nivolumab (Opdivo) and Pembrolizumab (Keytruda) are gaining regulatory approval and are anticipated to drive significant market growth [32]. By 2028, immunotherapy is projected to account for 20% of the global mesothelioma treatment market [32].

Gene therapy, while still emerging, is another key trend. In 2021, the gene therapy segment was valued at $25 million and is expected to grow at a CAGR of 9.2%, reaching $58 million by 2030 [31]. Gene therapies targeting BAP1, and other mutations offer a targeted approach to mesothelioma treatment and are projected to see increasing uptake as more clinical trials demonstrate their efficacy [31,34].

The rise of personalized medicine is also a notable trend, with treatments tailored to individual patients' genetic profiles expected to become more prevalent [35]. By 2030, personalized therapies are projected to account for nearly 40% of the mesothelioma treatment market [35,34].

Key market drivers and restraints

The growth of the mesothelioma treatment market is being driven by several key factors. One of the primary drivers is the increasing incidence of mesothelioma, largely due to continued exposure to asbestos in various industries, particularly in developing regions [36]. Globally, over 3,000 new cases of mesothelioma are diagnosed annually, with the highest rates observed in countries with significant historical asbestos use [36]. The rising awareness of mesothelioma, combined with government initiatives aimed at reducing asbestos exposure, is expected to further drive the demand for treatments [36].

Another major driver is the advancement of novel therapies, particularly in the fields of immunotherapy and gene therapy [36]. Checkpoint inhibitors, such as Pembrolizumab (Keytruda) and Nivolumab (Opdivo), have shown promising results in clinical trials and are becoming increasingly adopted in standard treatment protocols [32]. The success of these therapies is expected to increase their market share, contributing significantly to the overall growth of the mesothelioma treatment market [36]. Moreover, the development of gene therapies targeting specific genetic mutations like BAP1 has the potential to revolutionize treatment, offering targeted approaches that can improve patient outcomes [31]. As these therapies continue to receive regulatory approval, they are expected to drive significant market expansion [31].

Despite these positive developments, there are several restraints that are limiting the market's growth potential. One of the primary challenges is the high cost of treatment, particularly for advanced therapies such as immunotherapy [36]. For example, Pembrolizumab and Nivolumab can cost upwards of $150,000 per year, making them inaccessible to a significant portion of the global population [36]. This high cost is a major barrier to widespread adoption, especially in lower income regions [36].

Additionally, the long latency period of mesothelioma, which can range from 20 to 50 years, presents another challenge [36]. This long latency period makes early detection difficult, leading to late-stage diagnoses that are harder to treat effectively [36]. As a result, many patients do not benefit from advanced therapies, further restraining market growth [36]. Moreover, the limited availability of advanced treatments in developing regions, where healthcare infrastructure is less developed, restricts access to cutting-edge therapies such as gene therapy [36].

Environmental factors of mesothelioma

The main cause of mesothelioma is exposure to asbestos, a group of naturally occurring fibrous minerals that were extensively used in construction, manufacturing, and other industries throughout the 20th century [7]. The latency period between asbestos exposure and the development of mesothelioma can be as long as 20 to 50 years, which complicates early diagnosis and often results in poor prognosis for patients [7].

Although asbestos use has been heavily regulated in many countries, environmental exposure continues to be a significant issue [8]. Naturally occurring asbestos is present in some areas, and people can be exposed to asbestos fibers without occupational contact, simply by living near asbestos mines or factories that produce asbestos-containing materials [8]. Additionally, fibers from asbestos-containing products used in homes, such as insulation or cement, can become airborne when disturbed, leading to prolonged exposure [8].

Environmental exposure to asbestos has become an increasingly important focus for public health research, as occupational exposure has declined due to regulations [8]. This review will explore the relationship between environmental factors, particularly non-occupational asbestos exposure, and the incidence of mesothelioma, drawing from various case studies and epidemiological research [7,8].

Types of environmental asbestos exposure

Occupational and non-occupational exposure

Asbestos exposure is a well-documented cause of mesothelioma, particularly among individuals who worked in industries such as mining, construction, shipbuilding, and manufacturing [9]. Workers in these fields frequently encountered asbestos fibers, which, when inhaled, led to the development of mesothelioma after a long latency period [9]. Occupational exposure has been widely studied and remains a major cause of mesothelioma in many regions [9].

However, non-occupational exposure has also emerged as a significant risk factor. In some areas, asbestos occurs naturally in rocks and soil, and local populations are exposed to fibers through environmental contact [10]. For example, in Turkey, the use of asbestos-laden white soil in construction and everyday activities has resulted in numerous cases of mesothelioma, even among individuals who never worked in asbestos-related industries [10]. This environmental exposure, particularly in rural areas, shows that non-occupational sources can be just as dangerous as direct occupational exposure [10].

Para-occupational exposure (Take-Home)

Para-occupational exposure, also known as take-home exposure, occurs when asbestos workers inadvertently carry asbestos fibers home on their clothing or tools [11]. Studies have shown that family members of workers are at increased risk of mesothelioma due to secondary exposure to these fibers [11]. Handling contaminated clothing, such as shaking out or washing work clothes, can release asbestos fibers into the home environment, posing a serious health risk [11]. Research suggests that even small amounts of asbestos brought into the home can result in significant exposure over time [11].

Environmental exposure from asbestos-containing materials

Asbestos-containing materials (ACMs) have been widely used in industries such as construction, manufacturing, and shipbuilding. These materials include insulation, cement, and other building products that, when disturbed, can release asbestos fibers into the environment [8]. In homes or buildings where asbestos-containing materials are present, renovation or demolition activities can cause asbestos fibers to become airborne, posing significant health risks to occupants [8].

One prominent case of asbestos contamination occurred in Libby, Montana, where vermiculite mining led to widespread asbestos exposure [12]. Vermiculite from the mine was contaminated with tremolite asbestos, and both workers and residents of the area were exposed to asbestos fibers through the air, leading to numerous cases of mesothelioma [12]. This example highlights how industrial processes involving asbestos can contaminate entire communities, not just workers [12].

Additionally, asbestos cement factories have been identified as significant sources of environmental asbestos exposure [9]. In areas surrounding these factories, local populations are at risk due to asbestos fibers being released during the production process [9]. These exposures can occur even if individuals have no direct involvement with the factory, as fibers can travel through the air or be present in dust that settles in residential areas [9].

Asbestos-containing products in residential and commercial buildings also pose a risk to inhabitants when these materials degrade or are disturbed [8]. Insulation, roofing, and other construction materials that contain asbestos can release fibers over time, particularly if they are damaged or improperly handled during maintenance [8]. This ongoing contribute from everyday materials contributes significantly to the number of mesothelioma cases worldwide [8].

Naturally occurring asbestos (NOA)

Naturally occurring asbestos (NOA) refers to asbestos that is found in rocks and soil and is released into the environment through natural weathering or human activities such as construction or mining [13]. NOA is particularly prevalent in certain geographic areas, such as parts of California, where asbestos-bearing rocks are widespread [13]. People living in these regions may be exposed to

asbestos fibers through everyday activities like gardening, driving on unpaved roads, or even during natural events like landslides [13].

A case-control study conducted in California found that individuals living near areas with naturally occurring asbestos had a significantly higher risk of developing mesothelioma [13]. The study demonstrated that mesothelioma risk decreased with increasing distance from asbestos deposits, showing a clear link between proximity to NOA and the likelihood of developing the disease [13]. Similar findings have been reported in regions of Turkey, where villagers have long been exposed to asbestos fibers in the soil, used for construction purposes [10].

In addition to human activities, natural processes like erosion and weathering can release asbestos fibers from NOA into the air [8]. These fibers can be inhaled by individuals living nearby, contributing to long-term environmental exposure. Even though many regions have identified the presence of NOA, few public health measures have been taken to limit exposure, particularly in rural or less industrialized areas [8]. As a result, NOA remains an important yet under-researched factor in the incidence of mesothelioma [8].

Health impact and epidemiological studies

Epidemiological studies have shown a strong link between asbestos exposure and the development of mesothelioma, particularly in populations exposed through industrial activities or environmental contamination [14]. One such study conducted in Cairo found that the risk of mesothelioma was higher among people living in areas with high environmental asbestos exposure compared to those with no history of exposure [14]. This highlights the critical role of asbestos in both occupational and non-occupational settings as a cause of mesothelioma [14].

In Italy, spatial analyses of mesothelioma cases have revealed clusters of the disease in regions where asbestos cement factories operated [15]. These clusters demonstrated a higher incidence of mesothelioma among local populations, suggesting that both occupational exposure in factories and environmental exposure in surrounding areas contributed to the elevated rates [15]. The study also found that non-asbestos industries, such as metal engineering and textiles, contributed to some cases due to incidental exposure to asbestos fibers [15].

In the United States, data from the National Mesothelioma Virtual Bank [NMVB] cohort have provided insight into the survival rates of mesothelioma patients [16]. Factors such as age, gender, and treatment type were found to influence survival, with younger patients and those receiving combined surgical and chemotherapy treatments showing better outcomes [16]. However, despite advances in treatment, mesothelioma remains a highly fatal disease, with survival rates remaining low over the years [16].

Studies on asbestos exposure have consistently demonstrated a long latency period between initial exposure and the onset of mesothelioma [9]. This latency can range from 20 to 50 years, making it difficult to detect and prevent the disease in populations that were exposed decades ago [9]. As a result, many countries continue to see new cases of mesothelioma despite bans and regulations on asbestos use [9].

Public health implications and future directions

Public health efforts to limit asbestos exposure have significantly reduced occupational exposure in many countries, yet the issue of environmental asbestos exposure remains a critical challenge [8]. Regulations have banned the use of asbestos in many industries, but asbestos-containing materials still exist in older buildings and infrastructure, posing ongoing risks [8]. Efforts to remove or contain asbestos in these environments are essential to prevent further exposure [8].

In regions with naturally occurring asbestos, like parts of California, public health strategies must focus on raising awareness and minimizing activities that disturb asbestos-bearing rocks and soils [13]. Local governments can implement policies that limit construction in high-risk areas, promote safer land-use practices, and provide clear guidelines on dealing with asbestos contamination [13]. For example, monitoring and zoning laws could prevent residential development in areas with significant NOA deposits [13].

Ongoing research into the health effects of asbestos exposure is crucial, particularly as new cases of mesothelioma continue to emerge due to the long latency period of the disease [7]. Scientists are also exploring the role of genetic susceptibility in mesothelioma development, which could lead to targeted prevention strategies for high-risk populations [7]. Identifying genetic factors that

increase vulnerability to asbestos exposure could allow for earlier detection and improved treatment options [7].

Furthermore, the development of better treatment protocols is essential, as mesothelioma remains a highly fatal disease with limited effective therapies [16]. Advances in surgical techniques, chemotherapy, and experimental treatments like immunotherapy offer hope, but these interventions are still in the early stages of development [16]. As research progresses, a combination of preventive measures and more effective treatments will be vital in reducing mesothelioma mortality [16].

Genetic factors of mesothelioma

Although asbestos exposure is the leading cause, genetic factors also play an important role in the development of mesothelioma [17]. Research has identified several genetic mutations that can increase an individual's susceptibility to mesothelioma, even with lower levels of asbestos exposure [17].

One of the most significant genetic mutations associated with mesothelioma is in the BAP1 gene (BRCA1-associated protein 1), which functions as a tumor suppressor [17]. BAP1 mutations are common in both sporadic and familial cases of mesothelioma, making it one of the key genetic factors in the disease's development [17,18]. Mutations in other tumor suppressor genes, such as CDKN2A and TP53, also contribute to mesothelioma by disrupting normal cell cycle control and DNA repair mechanisms [19,20].

In addition to genetic mutations, epigenetic modifications such as DNA methylation and miRNA dysregulation have been implicated in mesothelioma [21]. These epigenetic changes can alter gene expression without changing the DNA sequence, contributing to tumor progression [22]. Understanding both the genetic and epigenetic factors involved in mesothelioma is crucial for identifying high-risk individuals and developing targeted therapies [17,21].

Key genetic mutations in mesothelioma

BAP1 (BRCA1-Associated Protein 1) mutation

The BAP1 gene is one of the most studied genetic mutations associated with mesothelioma. BAP1 functions as a tumor suppressor by regulating cell growth, differentiation, and DNA repair [17]. Mutations in BAP1 impair its ability to repair damaged DNA, leading to increased cancer risk [17]. These mutations are found in both familial and sporadic cases of mesothelioma, with individuals carrying BAP1 mutations showing a higher susceptibility to asbestos exposure [17,18]. In addition, studies suggest that BAP1 mutations are linked to less aggressive tumor behavior and better survival outcomes [22]. The interaction between BAP1 and other pathways, such as HIF-1α regulation, further supports its role in mesothelioma development [22].

CDKN2A and cell cycle control

The CDKN2A gene encodes two important tumor suppressor proteins, p16INK4a and p14ARF, both of which regulate cell cycle progression [19]. Mutations or deletions in CDKN2A result in loss of control over the cell cycle, leading to uncontrolled cell proliferation, a hallmark of cancer [19]. In mesothelioma, CDKN2A mutations are often associated with resistance to certain therapies, such as EZH2 inhibitors, which makes it a significant target for future treatments [19].

TP53 and other tumor suppressor genes

TP53 is another critical tumor suppressor gene that plays a central role in controlling the cell cycle, DNA repair, and apoptosis [20]. Mutations in TP53 are common in various cancers, including mesothelioma, and contribute to the progression of the disease by allowing damaged cells to proliferate unchecked [20]. In addition to TP53, other tumor suppressor genes like SETDB1 have been implicated in mesothelioma development [20]. These mutations disrupt cellular pathways that normally prevent tumor growth, further driving mesothelioma progression [20].

SPARC gene and tumor progression

The SPARC gene (Secreted Protein, Acidic, and Rich in Cysteine) is involved in cell-ECM (extracellular matrix) interactions and plays a significant role in tumor progression [23]. In mesothelioma, SPARC is often overexpressed, promoting tumor invasiveness and poor prognosis [23]. The SPARC protein contributes to the desmoplastic reaction, a dense fibrous tissue surrounding the tumor, which supports tumor cell survival and resistance to therapy [23]. Studies suggest that SPARC could serve as a biomarker for mesothelioma prognosis, as its elevated levels are associated with shorter survival [23].

Genome-wide association studies (GWAS) and polymorphisms

GWAS data

Genome-wide association studies (GWAS) have identified several single nucleotide polymorphisms (SNPs) associated with increased susceptibility to mesothelioma [24]. These studies analyze genetic variations across large populations to pinpoint specific alleles linked to the disease. For example, a GWAS identified polymorphisms in regions of chromosome 9p21 that are associated with higher mesothelioma risk [24]. This region includes the CDKN2A gene, which is already known to play a critical role in tumor suppression [24]. By identifying such polymorphisms, GWAS provides new insights into genetic predispositions for mesothelioma that go beyond major mutations [24].

AQP1 polymorphisms

Aquaporin 1 (AQP1) is a water channel protein that has been studied for its role in fluid transport across cell membranes [25]. Recent research has shown that polymorphisms in the AQP1 gene are associated with an increased risk of developing mesothelioma [25]. In particular, the AQP1 rs1049305 polymorphism has been linked to mesothelioma risk, showing significant associations with disease susceptibility [25]. Furthermore, AQP1 polymorphisms have been identified as potential biomarkers for predicting responses to cisplatin-based chemotherapy [25]. Patients with specific AQP1 variants showed different levels of treatment toxicity, indicating that these polymorphisms could help personalize treatment options [25].

Inherited Genetic Mutations and Predispositions

Inherited mutations can significantly increase the risk of developing mesothelioma, even in individuals with minimal asbestos exposure [18]. These mutations are often passed down in families, creating a hereditary predisposition to cancer. One of the most prominent genes associated with hereditary mesothelioma is BAP1 [18,26].

Hereditary cancer syndromes

The BAP1 tumor predisposition syndrome is characterized by inherited mutations in the BAP1 gene, which greatly increases the risk of mesothelioma, uveal melanoma, and other cancers [26]. Families carrying BAP1 mutations tend to develop mesothelioma even at lower levels of asbestos exposure [18]. Additionally, the MITF gene, another key player in hereditary cancer syndromes, has been linked to mesothelioma development [26]. These findings highlight the importance of genetic screening in individuals with a family history of mesothelioma or related cancers [26].

Other inherited mutations

In addition to BAP1, other genetic mutations have been identified in families with a predisposition to mesothelioma [18]. For instance, mutations in BRCA1 and BRCA2, which are commonly associated with breast and ovarian cancers, have also been found in mesothelioma patients [18]. Similarly, germline mutations in TP53, the gene responsible for Li-Fraumeni syndrome, can increase mesothelioma risk [18]. These inherited mutations underscore the genetic complexity of mesothelioma and suggest that genetic counseling and testing should be considered for high-risk families [18].

Epigenetic regulation in mesothelioma

Epigenetic modifications, unlike genetic mutations, do not alter the DNA sequence but can still significantly affect gene expression and contribute to mesothelioma development [21]. These changes include DNA methylation, histone modifications, and the regulation of gene expression by microRNAs (miRNAs) [21].

miRNAs and gene silencing

MicroRNAs (miRNAs) are small non-coding RNA molecules that play a critical role in regulating gene expression by binding to messenger RNAs (mRNAs) and preventing them from being translated into proteins [21]. In mesothelioma, several miRNAs have been found to be dysregulated, contributing to the silencing of tumor suppressor genes [21]. For example, miR-126 and miR-145 are significantly downregulated in mesothelioma, leading to the uncontrolled proliferation of tumor cells [21]. Studies have shown that restoring normal levels of these miRNAs can inhibit tumor growth, making them potential therapeutic targets [21].

Epigenetic modifications and their impact on gene expression

In addition to miRNA dysregulation, epigenetic modifications such as DNA methylation and histone acetylation play a significant role in mesothelioma [22]. DNA methylation often leads to the silencing of tumor suppressor genes, such as CDKN2A and BAP1, which are critical in preventing cancerous growth [22]. Similarly, alterations in histone acetylation can affect the chromatin

structure, making it more difficult for tumor suppressor genes to be expressed [22]. These epigenetic changes contribute to the aggressive nature of mesothelioma and offer new opportunities for targeted therapies [22].

Treatments

Chemotherapy and chemoresistance

Pemetrexed and cisplatin remain the cornerstone of first-line chemotherapy for treating malignant pleural mesothelioma [37]. Despite their widespread use, resistance often develops due to factors like the low mutation burden of mesothelioma tumors and the loss of tumor suppressor genes such as BAP1 and NF2, limiting long-term efficacy [37].

The challenge of chemoresistance is further compounded by the activation of pathways such as NF-kB, which helps cancer cells evade the cytotoxic effects of chemotherapy [42]. Additionally, chemotherapy induces a senescence-associated secretory phenotype, which modifies the tumor microenvironment, promoting resistance [42].

Efforts to improve outcomes include schedule-dependent strategies [38]. For instance, pretreatment with pemetrexed 48 hours prior to administering cisplatin has shown to enhance the overall efficacy of chemotherapy by increasing DNA damage and inducing cell cycle arrest at the G2/M phase, contributing to improved long-term control of the disease [38].

For patients who experience disease progression after first-line treatment, vinorelbine and gemcitabine are commonly used as second- and third-line options [39]. However, these therapies provide limited benefits, with low response rates (approximately 2%) and primarily lead to stable disease rather than significant tumor shrinkage [39]. Moreover, their use is associated with significant toxicity, as nearly 46% of patients experience grade 3–4 toxicities [39].

Further advancements in chemotherapy involve exploring capecitabine as a treatment option [40]. When used in combination with cisplatin, chemotherapy-induced upregulation of cytidine deaminase sensitizes mesothelioma cells to capecitabine, improving therapeutic response through a schedule-dependent approach [40]. This combination therapy presents a promising avenue for overcoming chemoresistance in certain patient populations [40].

Immunotherapy

Immune-checkpoint inhibitors have become a significant advancement in the treatment of malignant pleural mesothelioma [42]. The use of PD-1 and CTLA-4 inhibitors in combination therapies has shown promising results, particularly for patients with non-epithelioid mesothelioma [42]. For instance, patients with sarcomatoid or biphasic histologies have demonstrated better responses to dual ICI therapy [42].

Nivolumab and ipilimumab have been approved as first-line treatment options for unresectable MPM, with the FDA approval based on a study showing a median overall survival of 18.1 months compared to 14.1 months for chemotherapy [43]. This dual regimen has significantly changed the landscape for patients who cannot undergo surgery [43].

Moreover, studies highlight that PD-L1 expression and tumor mutational burden are crucial in determining responses to ICIs [37]. High PD-L1 expression correlates with a better progression-free survival in some patients [37]. However, many mesothelioma cases, particularly epithelioid histologies, show low PD-L1 expression, making it challenging to achieve substantial therapeutic responses with single-agent immunotherapy [37].

One significant development is the use of mesothelin-targeted CAR T-cell therapy in combination with pembrolizumab, which has shown prolonged survival in patients with mesothelioma [44]. This approach focuses on regional delivery of CAR T cells directly to the pleural cavity, enhancing immune response while minimizing systemic side effects [44].

In terms of second-line treatments, studies comparing immunotherapy vs. chemotherapy show that ICIs may not always outperform chemotherapy in terms of overall survival [43]. Some studies suggest chemotherapy offers a slight benefit in progression-free survival, though immunotherapy can still provide durable responses in certain subgroups [43].

CAR T-cell therapy

CAR T-cell therapy is a cutting-edge immunotherapy that modifies a patient's own T-cells to specifically target and attack

cancer cells [50]. In mesothelioma, this therapy focuses on mesothelin, a protein that is highly expressed in most mesothelioma tumors [50]. The process involves extracting the patient's T-cells and genetically engineering them to express chimeric antigen receptors (CARs) [50]. These receptors are designed to recognize mesothelin on the surface of mesothelioma cells [50]. Once reintroduced into the patient's body, the CAR T-cells seek out mesothelin-expressing tumor cells and initiate a direct immune attack [50]. These modified T-cells not only kill cancer cells but can also stimulate a broader immune response, enhancing the body's ability to fight the tumor [50].

One of the advantages of CAR T-cell therapy is its specificity: it targets mesothelin, which is largely absent from healthy tissues, reducing the risk of damage to normal cells [50]. Moreover, preclinical studies have shown that when CAR T-cells are delivered directly into the pleural cavity, they can infiltrate the tumor more effectively, allowing for a more localized and powerful response [50].

Despite its promise, challenges remain in treating solid tumors like mesothelioma [50]. The tumor microenvironment often suppresses immune activity, limiting the effectiveness of CAR T-cells [50]. To address this, researchers are developing strategies to enhance CAR T-cell function, such as modifying the T-cells to resist immunosuppression and ensuring they can persist longer in the body, increasing their impact over time [50]. This makes CAR T-cell therapy an exciting, emerging approach for treating mesothelioma, especially in cases where conventional treatments like chemotherapy and surgery have limited success [50].

Targeted therapies

In malignant pleural mesothelioma, targeted therapies focus on specific molecular pathways, including vascular endothelial growth factor, platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor [42,45]. Bevacizumab, an anti-VEGF antibody, has been shown to improve overall survival when combined with chemotherapy [45]. The MAPS trial reported a median OS of 18.8 months with bevacizumab plus cisplatin and pemetrexed, compared to 16.1 months with chemotherapy alone, making this one of the most promising treatments [42,45]. However, increased cardiovascular toxicities are a concern, limiting its broader application [37,45].

PDGFR inhibitors, such as imatinib, have also been explored, but with limited success [45]. In a phase II trial, imatinib as a monotherapy resulted in a median OS of only 5.7 months [42,45]. Combination strategies with gemcitabine have shown synergistic effects in preclinical studies, but these have yet to translate into significant clinical outcomes [45]. Similarly, FGFR inhibitors like nintedanib, which target VEGFR, PDGFR, and FGFR, showed improvements in progression-free survival in early trials but ultimately failed in phase III [42,45].

A more novel approach involves mesothelin-targeted therapies [37]. Chimeric antigen receptor T-cell therapy, targeting mesothelin, has shown potential in extending survival when combined with immune checkpoint inhibitors like pembrolizumab [42,44]. This approach has led to durable disease control in early trials [37,44].

PARP inhibitors, such as rucaparib and Olaparib, are being studied for their effects on BAP1-mutant mesotheliomas, given their role in DNA damage repair [42,45]. The MiST 1 trial reported a disease control rate of 58% with rucaparib, showing promise for this subset of patients [37,42]. Although PARP inhibitors have shown mixed results overall, they represent a promising therapy for select patients with BAP1 mutations [42,45].

Surgical approaches

Surgical interventions in malignant pleural mesothelioma aim for macroscopic complete resection, which is a critical component of multimodality treatment [37,46]. The two primary surgical procedures are extra pleural pneumonectomy and pleurectomy/decortication (P/D) [37,46]. EPP involves the removal of the affected lung, part of the diaphragm, and pleura, offering a radical approach to respect the tumor, but it is associated with significant morbidity and mortality [37]. Recent guidelines, such as those from the European Respiratory Society and European Society of Thoracic Surgeons, now favor P/D over EPP due to its lung-sparing nature [46]. Studies suggest that P/D provides similar oncological outcomes with reduced postoperative complications and improved quality of life [37,46]. For instance, P/D is associated with a 30-day mortality rate of 2.9%, compared to 6.8% for EPP [46].

The Mesothelioma and Radical Surgery trial also provided evidence supporting the shift towards P/D, concluding that lung-sparing surgeries result in better overall outcomes and

fewer complications [37,46]. In comparison, P/D offers survival benefits with fewer severe postoperative complications, including decreased instances of cardiopulmonary morbidity [46].

However, P/D is not without its limitations. Though it improves QoL, some argue that EPP may provide more radical tumor resection in advanced cases [37]. The choice between these procedures depends on factors such as the extent of tumor invasion, patient performance status, and the expertise of the surgical team [37]. postoperative adjuvant therapies—including chemotherapy, radiotherapy, and emerging treatments like immunotherapy—have been shown to improve outcomes, particularly in patients undergoing P/D [37]. The integration of these therapies into MMT has extended the median survival rates from 12 months (surgery alone) to 20+ months when combined with adjuvant treatments [37,46].

Radiotherapy

Radiotherapy plays an important, albeit complex, role in the treatment of malignant pleural mesothelioma [47] [48]. Traditionally, its use has been limited due to concerns about toxicity to surrounding organs, including the lungs, heart, and spinal cord [48]. However, with advancements in radiotherapy techniques, its potential role in both curative and palliative settings is expanding [48]. Radiotherapy is often used in a multimodal approach, particularly in conjunction with surgery and chemotherapy. Hemi thoracic radiotherapy is sometimes used following extra pleural pneumonectomy to reduce local recurrence [47,48]. Studies suggest that this combination may improve local control of the disease, but its impact on overall survival remains modest [47] [48]. For example, one study showed that post-surgery hemi thoracic radiotherapy extended median survival to 23 months, particularly in patients with epithelial subtypes [48]. More recently, advanced radiotherapy techniques like intensity-modulated radiotherapy, stereotactic body radiation therapy, and proton therapy have allowed for more precise targeting of tumor tissues while sparing nearby organs [48]. These techniques are often used when surgery is not an option, providing palliative relief and improving quality of life for patients [48]. In palliative care, radiotherapy is frequently employed to manage pain and thoracic tumor progression, with newer studies showing significant pain relief for about 47% of patients [48]. despite these advances, randomized controlled trials have not consistently demonstrated significant improvements in overall survival when radiotherapy is used alone [47]. For instance, no study has definitively proven that radiotherapy significantly enhances survival when compared to other modalities such as chemotherapy [47]. Moreover, radiotherapy is rarely recommended as a standalone therapy in the treatment of MPM [47].

There is also controversy regarding prophylactic radiotherapy to prevent malignant seeding after surgical procedures. While older studies suggested a benefit, more recent trials have found no substantial differences between patients receiving immediate prophylactic radiotherapy and those under observation [48].

Intrapleural gene transfer therapy

Intrapleural gene transfer therapy is an emerging treatment designed to deliver therapeutic genes directly into the pleural space, offering a targeted approach to treating malignant pleural mesothelioma [49]. This method focuses on stimulating local immune responses, while minimizing systemic side effects [49].

One promising application involves the use of interferon-alpha (IFN-alpha), introduced via adenoviral vectors. IFN-alpha enhances the activity of T-cells, NK cells, and other immune cells, leading to a localized anti-tumor response [49]. This local immune activation is particularly important for mesothelioma, where traditional systemic therapies may not penetrate the tumor microenvironment effectively [49].

A clinical trial evaluating IFN-alpha intrapleural gene transfer has demonstrated its safety, with minimal systemic toxicity [49]. Common side effects included fever, pleuritic chest pain, and transient liver enzyme elevations, all of which were manageable [49]. Preliminary findings showed encouraging improvements in progression-free survival and potential long-term immune memory formation [49].

However, challenges persist in optimizing the delivery system and ensuring consistent gene expression throughout the pleural cavity [49]. While more research is needed to validate its efficacy, intrapleural gene transfer holds potential as part of multimodal treatment, especially when combined with other immunotherapies such as checkpoint inhibitors [49].

Multimodal treatment

The integration of surgery, chemotherapy, and immunotherapy has emerged as an effective multimodal approach for treating

malignant pleural mesothelioma [41]. Data from recent studies indicate that patients receiving surgery combined with immunotherapy and chemotherapy (siCT) exhibit the longest overall survival (OS) compared to those treated with fewer modalities [41]. For example, patients treated with siCT demonstrated a median survival of 22.6 months, significantly higher than those receiving chemotherapy alone (11.7 months) [41].

the combination of surgery and immunotherapy was particularly beneficial for patients with non-epithelioid subtypes, where the survival benefit of immunotherapy was pronounced [41]. Specifically, patients with sarcomatoid subtypes who received immunotherapy had a 12-month survival rate of 76.2%, compared to only 13.6% among those not receiving immunotherapy [41].

However, while the benefits of combining surgery, immunotherapy, and chemotherapy are clear, there remains variability in survival outcomes depending on the timing of the therapies and the patient's health condition [41]. Further research and clinical trials are needed to optimize the sequencing and combination of these therapies [41].

Clinical trails

Chemotherapy: Pemetrexed-Cisplatin with or without Bevacizumab

The MAPS trial (Mesothelioma Avastin Plus Pemetrexed and Cisplatin) was a Phase II/III randomized trial designed to evaluate the efficacy of adding bevacizumab to the standard chemotherapy regimen of pemetrexed and cisplatin for patients with malignant pleural mesothelioma [51]. The trial enrolled 448 patients, divided into two groups: one group received pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) every 21 days for 6 cycles, while the other group received the same chemotherapy regimen combined with bevacizumab (15 mg/kg) [51].

The primary endpoint was overall survival, with secondary endpoints focusing on progression-free survival, disease control rates, and adverse events [51]. The trial showed that patients receiving the bevacizumab combination had a significantly longer median overall survival of 18.8 months, compared to 16.1 months in the chemotherapy-only group [51]. Furthermore, disease control rates (which include partial responses and stable disease) were improved in the bevacizumab group, indicating better tumor control [51].

In terms of safety, the addition of bevacizumab resulted in increased rates of hypertension and thromboembolic events, but these were manageable and did not outweigh the survival benefits [51]. The trial concluded that the combination of pemetrexed, cisplatin, and bevacizumab should be considered a new standard of care for patients with unresectable malignant pleural mesothelioma [51].

Immunotherapy: Nivolumab and ipilimumab

The Peritoneal Mesothelioma Immunotherapy Trial evaluated the combination of nivolumab and ipilimumab in patients with peritoneal mesothelioma [52]. The trial enrolled 30 patients, with 20 receiving the combination therapy alongside surgery, and the remaining 10 undergoing surgery alone [52]. Patients receiving the combination therapy exhibited a median progression-free survival of 11.3 months, compared to 7.9 months in the surgery-only group [52]. 40% of patients who received nivolumab and ipilimumab experienced partial tumor regression, while 35% achieved stable disease [52]. The therapy was well-tolerated, with no reported grade 3 or 4 toxicities, suggesting its safety as an adjunct treatment for peritoneal mesothelioma [52].

CAR T-Cell Therapy: Mesothelin-Targeted Therapy (Mesothelin CAR T-Cell Trial)

The Mesothelin CAR T-Cell Trial assessed the safety and efficacy of mesothelin-targeted CAR T-cell therapy in patients with pleural mesothelioma [53]. The study enrolled 21 patients, with 6 patients experiencing partial tumor regression, while 9 patients had stable disease [53]. The median overall survival for all patients was 17.4 months, with a subset of patients surviving beyond 24 months [53]. However, the trial noted T-cell exhaustion as a significant limiting factor, which reduced the therapy's long-term efficacy [53]. The study highlighted the need for future advancements in CAR T-cell therapy to maintain T-cell activity over time [53].

Photodynamic Therapy: Intrapleural PDT (PDT with Extended Pleurectomy Study)

The PDT with Extended Pleurectomy Study investigated the use of intrapleural photodynamic therapy combined with surgery in patients with pleural mesothelioma [54]. The study enrolled 45 patients, evaluating the combination of PDT with extended pleurectomy/decortication (eP/D) [54]. Patients treated with PDT had a median progression-free survival (PFS) of 15.6 months,

compared to 9.5 months for those who only received surgery [54]. Additionally, the median overall survival for the PDT group was 31.7 months, significantly longer than the surgery-only group [54]. The treatment was well-tolerated, with minor side effects such as skin sensitivity, and no severe adverse events were reported [54]. The results indicate that PDT, when combined with surgery, can significantly improve long-term outcomes for mesothelioma patients [54].

BAP1 mutation and genetic therapy (BAP1 Mutation Study)

The BAP1 Mutation Study examined the prevalence of BAP1 germline and somatic mutations in patients with mesothelioma, uveal melanoma, and other cancers [55]. The study enrolled 196 patients, collecting tumor and germline DNA samples for analysis [55]. Results indicated a high prevalence of BAP1 mutations in mesothelioma patients, suggesting a potential genetic predisposition to the disease [55]. The findings from this study have provided valuable insights into targeted therapy development, especially for individuals with hereditary cancer risks [55].

Dendritic Cell Immunotherapy: MesoPher (DENIM Trial)

The DENIM Trial evaluated the use of dendritic cell immunotherapy (MesoPher) as a maintenance treatment after chemotherapy in patients with mesothelioma [56]. A total of 176 patients were randomized into two groups: one group received MesoPher, and the other received best supportive care [56]. The primary endpoint was overall survival. Patients treated with MesoPher had a median OS of 18.8 months, compared to 14.1 months in the best supportive care group [56]. The therapy was well-tolerated, with no severe toxicities reported, making it a promising maintenance treatment option for extending survival in mesothelioma patients [56].

Gene Therapy: Intrapleural Interferon-Alpha (Interferon Gene Therapy Study)

The Interferon Gene Therapy Study explored the use of adenoviral-mediated interferon-alpha gene transfer for patients with pleural mesothelioma [49]. The study involved 13 patients, each receiving intrapleural gene therapy via a catheter [49]. Patients received two doses of the therapy, spaced four days apart, with radiographic evaluations on Day 64 and again at six months [49]. Of these patients, two achieved stable disease, maintaining this state for up to six months, while others showed minimal response or disease progression [49]. The treatment was well-tolerated, with mild side effects such as fever and pleuritic chest pain, and no severe toxicities were observed [49]. Though no significant tumor shrinkage was reported, the study demonstrated the potential for gene therapy in local tumor control [49].

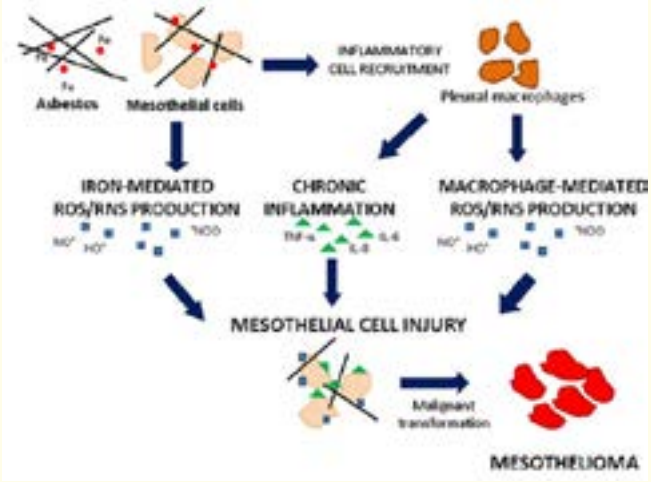

Figure 1: Mesothelioma Mechanism of Tumor Formation [57].

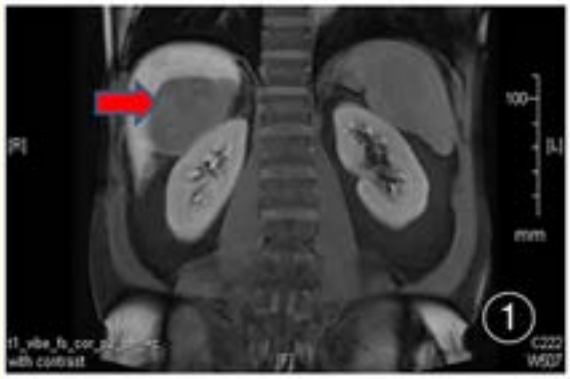

Figure 2: PET/CT shows multiple nodular and lump-like abnormal signal lesions under the liver surface, the larger one is in the space between the liver and the right kidney, about 85 mm × 57 mm in size [58].

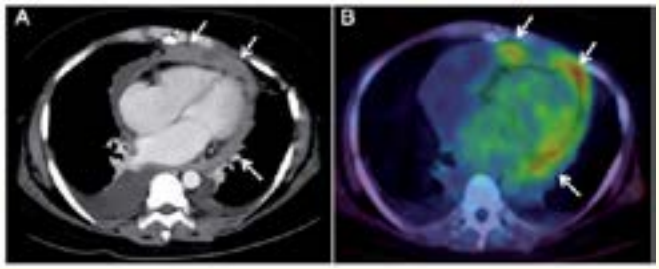

Figure 3: A. Chest computed tomography revealed an irregular, thickened pericardium with diffuse enhancement (arrows), loculated large amounts of pericardial effusion and bilateral pleural effusions. (B) Fluorodeoxyglucose (FDG) positron emission tomography imaging demonstrated intrapericardial FDG accumulation (arrows) with a standardized uptake value of 6.0 [59].

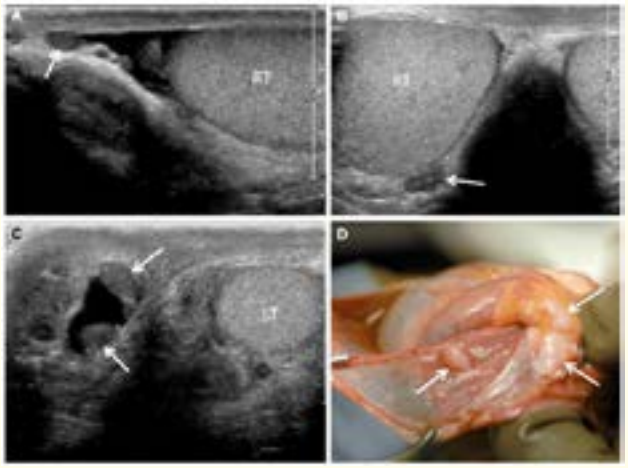

Figure 4: Mesothelioma of uncertain malignant potential in a 58-year-old man with a palpable mass. (A) Sagittal image of the right testis (RT)showing a small amount of fluid in the tunica vaginalis and a small solid nodule (arrow) at the upper part of the cavity. (B), Axial view showing another nodule, which was not surrounded by fluid (arrow). (C) Axial image below the lower pole of the testis showing 2 additional nodules with a small quantity of fluid (arrows). (D) Surgical specimen showing the nodules on the surface of the tunica vaginalis. LT indicates left testis [60].

Figure 5: Comparison of Eight-Hour TWA Airborne Chrysotile Concentrations (TEM) for Loading and 30-Minute Shake-Out and Bystander Measurements [11].

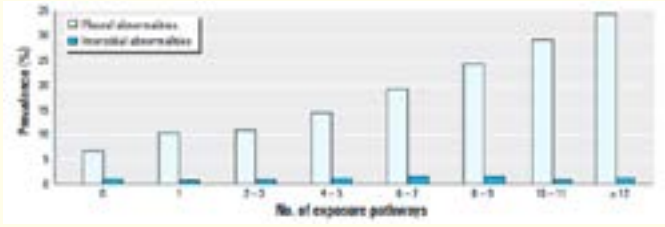

Figure 6: Prevalence of abnormalities by number of exposure pathways [12].

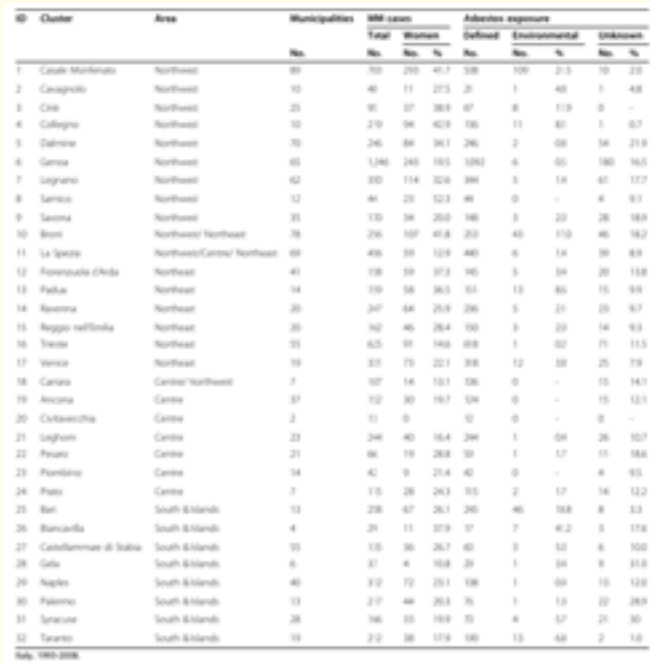

Figure 7: Identified clusters of malignant mesothelioma cases by territorial area, number of municipalities included, number of cases (total, female) and modality of asbestos exposure (defined, environmental and unknown) [14].

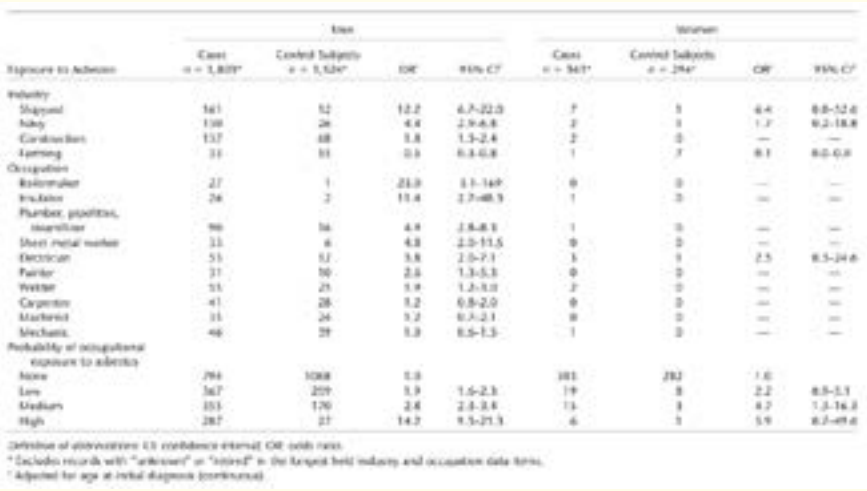

Figure 8: Age adjusted odds ratio and their 95% CI for longest held industries or occupations with 25 cases or more by sex, California 1998-1997, based on a subject of 2146 mesothelioma cases and 1818 control subjects with pancreatic cancer [13].

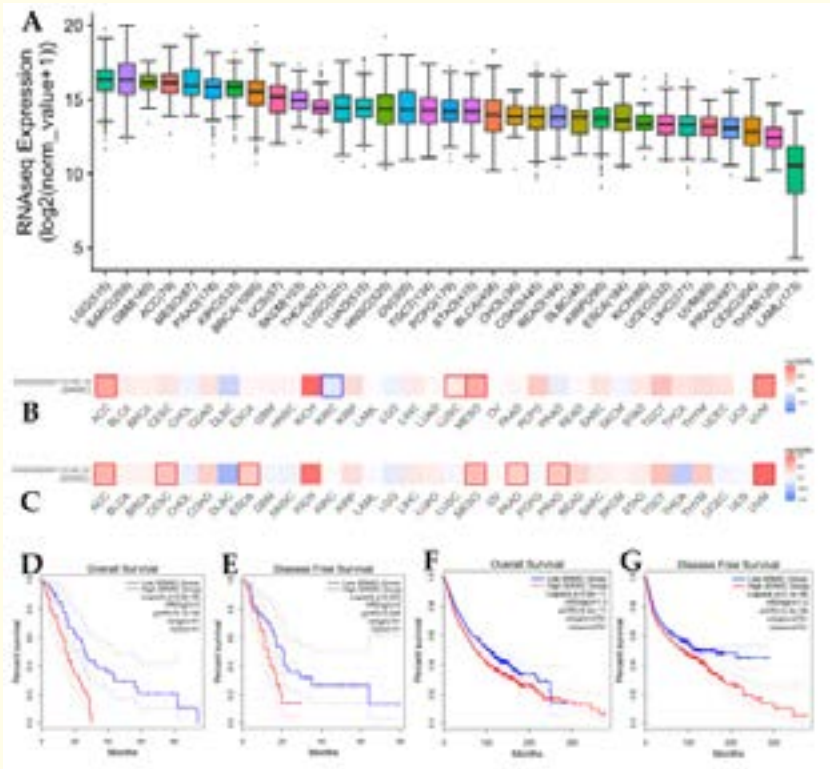

Figure 9: SPARC gene expression and its association with survival in the MESO cohort and pancancer. (A) SPARC gene expression in the pancancer TCGA database; (B,C) survival maps showing that SPARC gene expression is associated with overall survival (OS) and disease-free survival (DFS) in pancancer; (D,E) SPARC gene expression associated with OS and DFS in the MESO cohort; (F,G) SPARC gene expression associated with OS and DFS in pancancer [23].

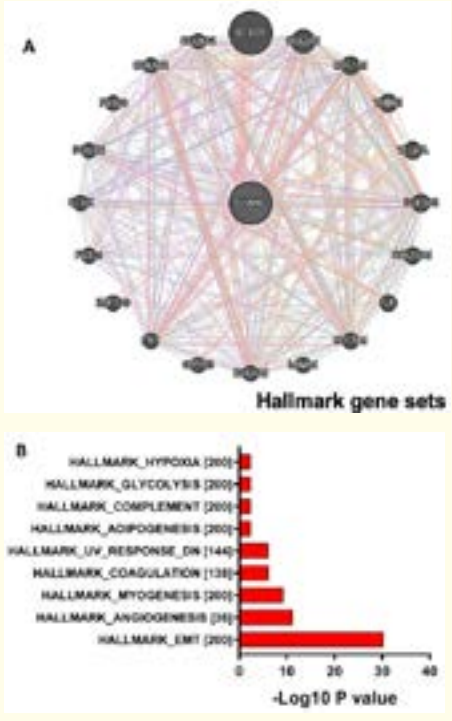

Figure 10: Networks in which the SPARC gene is involved, as determined by GeneMANIA. (A) All networks, including physical interactions, co-expression, predicted, co-localization, genetic interactions, pathways, and shared protein domains, are analyzed based on the published literature. https://genemania.org/search/homo-sapiens/sparc accessed on 1 May 2022; (B) Hallmark gene sets of SPARC-centered networks determined by gene set enrichment analysis (GSEA) [23].

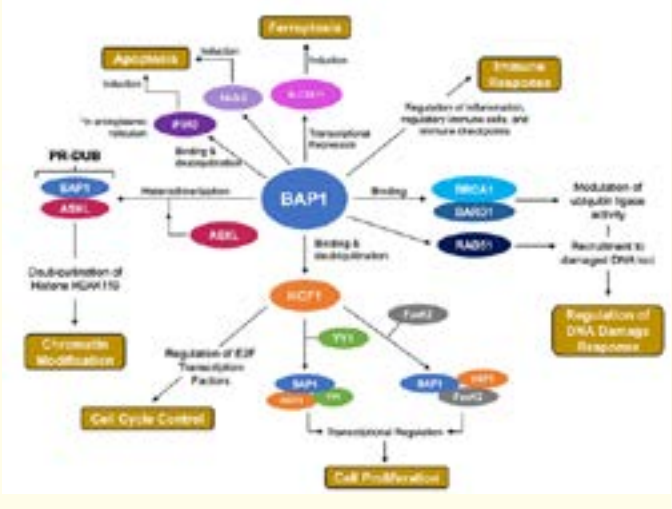

Figure 11: BAP1 regulates the DNA damage repair pathway through interactions with BRCA1, BARD1, and RAD51. BAP1 interacts with host-cell control factor 1 (HCF1) in several processes involved in cell-cycle control and cell proliferation. BAP1 binds to ASXL to form the PR-DUB complex, responsible for regulation of chromatin through Histone H2A deubiquitination. BAP1 is associated in a number of regulated cell death pathways including apoptosis and ferroptosis. BAP1 is implicated in immune regulation [17].

	Patients with Germline *BAP1* Alterations (Total, N=215)		Median Age of Onset (years)	
Tumor Type	No. of tumors of specific class, N	% of patients with tumor of specific class	Tumors with Germline *BAP1* Mutations	Sporadic Tumors
Uveal melanoma	60	28%	59	62
Malignant mesothelioma	48	22%	46	78
Cutaneous melanoma	38	18%	43	61
Renal cell carcinoma	20	9%	51	64
Basal cell carcinoma	14	7%	41	75
BAP1-inactivated melanocytic tumor (BIMT)	40	75%	31	28

Figure 12: Tumors Commonly Associated with BAP1 Germline Alterations (BAP1-Tumor Predisposition Syndrome (BAP1-TPDS). Of the total 215 patients with BAP1-TPDS, 53 underwent the necessary total body skin examination to diagnose BIMT; of these, 40 patients (75%) had a positive diagnosis for one or more BIMTs [17].

Characteristic		N (%)
Chemotherapy type	Gemcitabine and cisplatin	132 (68.0)
	Pemetrexed and cisplatin	62 (32.0)
Chemotherapy response*	Complete response (CR)	6 (3.2)
	Partial response (PR)	61 (32.8)
	Stable disease (SD)	92 (49.5)
	Progressive disease (PD)	27 (14.5)
Progression of disease*	No	20 (10.5)
	Yes	171 (89.5)
Death	No	58 (29.9)
	Yes	136 (70.1)
PFS	Median (25%–75%) (month)	7.8 (5.3–13.8)
OS	Median (25%–75%) (month)	18.1 (9.4–28.7)
Follow-up from the start of chemotherapy	Median (25%–75%) (month)	49.2 (18.9–75.5)
CRP	Median (25%–75%)	20.5 (9–58)
LDH	Median (25%–75%)	2.67 (2.26–3.11)
Pain*	No	79 (41.4)
	Yes	112 (58.6)
Weight loss*	No	68 (35.8)
	Yes	122 (64.2)

Figure 13: Clinical characteristics of MM patients treated with cisplatin-based chemotherapy (N = 194) [25].

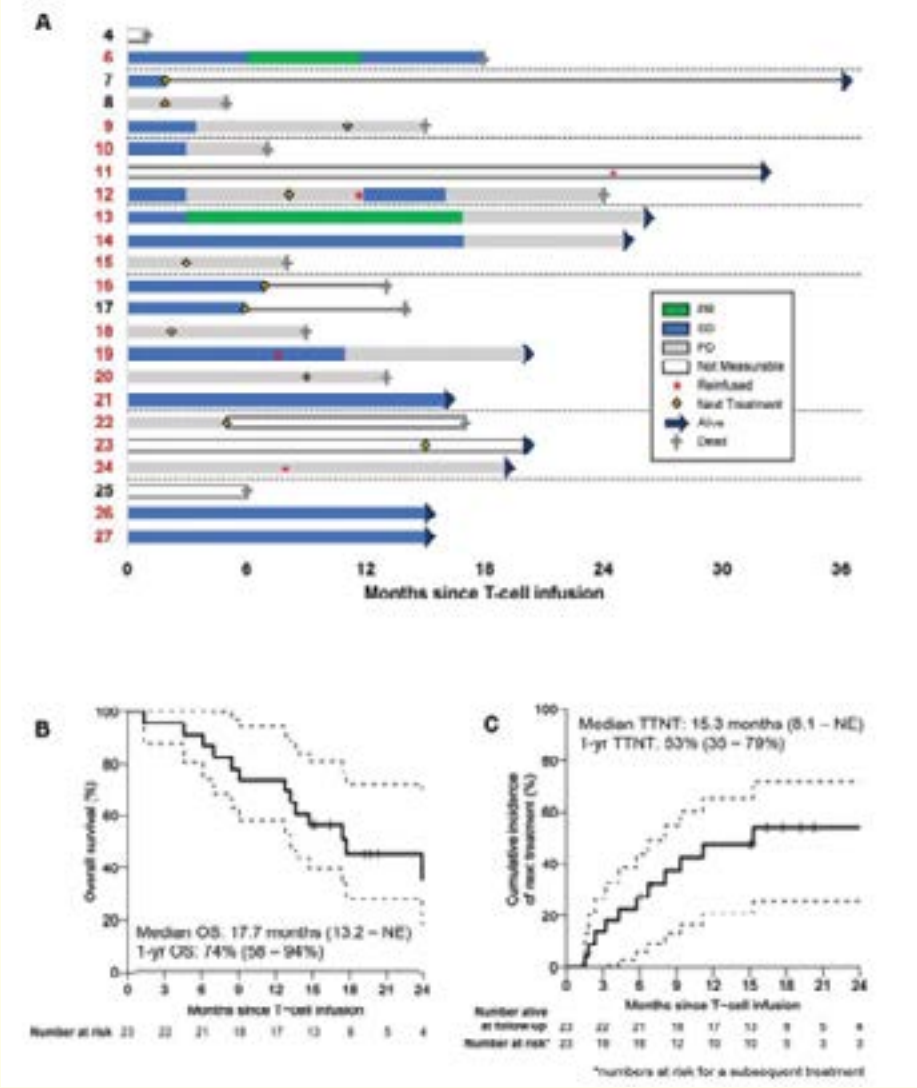

Figure 14: Outcomes of patients with MPM (n = 23). A, Therapy responses in patients with MPM (3 did not have measurable disease, 1 had no subsequent scan available) or disease stabilization or progression until next treatment during a period (0 to 36 months), as monitored by mRECIST on CT scan, are shown—PR (green), SD (blue), and PD (gray) are represented in relation to time in months. Solid line indicates survival post-next treatment. Patients who received combination immunotherapy are represented in red type. B, The Kaplan-Meier curve reports overall survival (OS) of patients with malignant pleural mesothelioma after CAR T-cell infusion (median survival, 17.7 months [95% confidence interval, 13.2 months to not estimable {NE}]). C, The time-to-next-treatment (TTNT) curve shows the proportion of patients receiving next treatment over time (median time to next treatment, 15.3 months [95% confidence interval, 8.1 months to NE] [44].

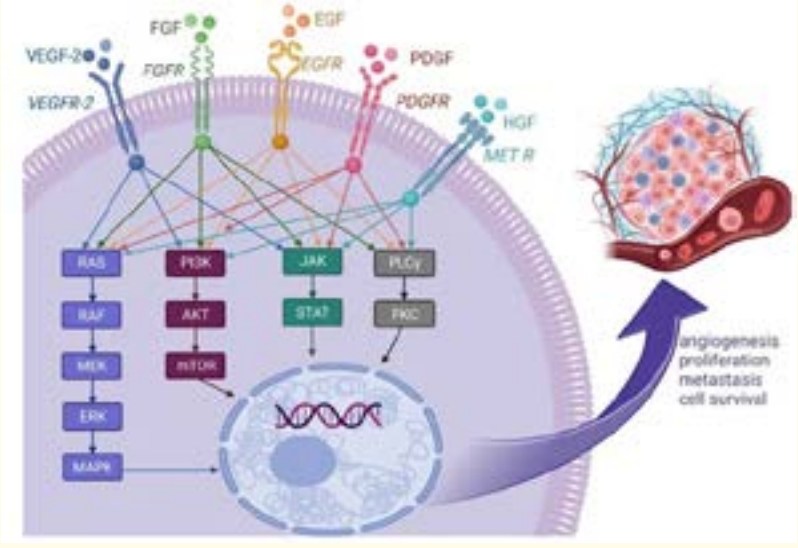

Figure 15: Upregulation of growth factors that activate the tyrosinase kinase receptors in MPM cells leads to the initiation of several pathways, which in turn modify gene transcription in the nucleus and provide cancer cells with many features increasing their aggressiveness. VEGF(R): vascular endothelial growth factor (receptor); PDGF(R): platelet-derived growth factor (receptor); EGF(R): epidermal growth factor (receptor); FGF(R): fibroblast growth factor (receptor); HGF hepatocyte growth factor; MET R: hepatocyte growth factor receptor; RAF: Rapidly Accelerated Fibrosarcoma; MEK: mitogen-activated kinase/ERK kinase; ERK: extracellular regulated kinase; MAPK: mitogen-activated protein kinase; PI3K: type I phosphoinositide 3-kinase; AKT: Protein kinase B; mTOR: mammalian target of rapamycin; JAK: Janus kinase; STAT: signal transducer and activator of transcription; PLCγ: phospholipase Cγ; PKC: protein kinase C [45].

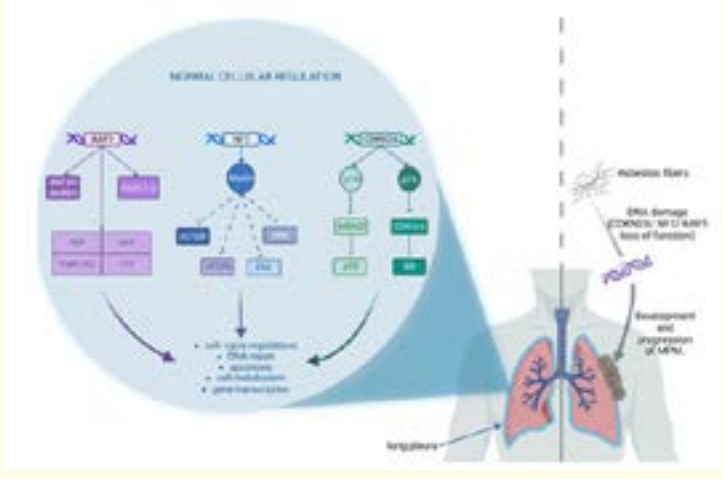

Figure 16: Three major genomic regulations in cells that are mostly suppressed in malignant pleural mesothelioma (MPM) induced by asbestos exposure. CDKN2A: Cyclin-Dependent Kinase Inhibitor 2; CDK4/6: cyclin-dependent kinases 4/6; RB: retinoblastoma protein; MDM2: Mouse double minute 2 homolog; NF2: neurofibromatosis 2; Merlin: Moesin ezrin radixin-like protein; ERK: extracellular signal-regulated kinase; FAK: Focal adhesion kinase; VEGFA: Vascular Endothelial Growth Factor A; mTOR: Mammalian target of rapamycin; BAP1: BRCA1—Associated protein1; ASXL1/2: Additional Sex Combs-Like 1/2; BRCA1: Breast cancer type 1 susceptibility protein; BARD1: BRCA1-associated RING domain protein 1; OGT: Protein O-GlcNAc transferase; HCF: Host cell factor; YY1: Yin Yang 1; FoxK1/K2: forkhead transcription factors [16].

Conclusion

This review clearly showed the importance of continued research into the genetic predispositions and therapies for Malignant Mesothelioma. Furthermore, a combination of personalized medicine, focusing on genetic mutations, and the development of therapies tailored to specific patient profiles will pave the way for more effective and durable treatment outcomes for mesothelioma patients.

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Conflict of Interest

Authors declare that there is no conflict of interest.

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