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Molecular Pathogenesis of Malignant Pleural Mesothelioma

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1. Introduction

Malignant mesothelioma is a rare, highly aggressive cancer which arises from the mesothelial cells which form the lining of the pleural, and less frequently the peritoneal cavities. Malignant pleural mesothelioma (MPM) is an emergent neoplasm, as it was rarely diagnosed prior to the middle of the 20th century. The incidence has risen steadily since 1970, and there are currently an estimated 3000 new cases per year in the United States. The peak incidence of mesothelioma may have occurred in the United States during the past decade, and the peak incidence in much of the developed world is expected to occur in the next 10-20 years. These data are thought to reflect the widespread occupational asbestos exposure in the Western world from the 1940s to the 1970s, as well as the inherent latency period of approximately 30 years between asbestos exposure and disease manifestation which is typical of MPM. Approximately 80% of mesothelioma cases can be directly attributed to asbestos fiber exposure. Additional suspected causes or co-carcinogens include other mineral fibers such as erionite, simian virus 40 (SV40), and radiation (Robinson and Lake 2005). Moreover, a mesothelioma epidemic in Turkey has demonstrated a likely genetic predisposition to mineral fiber carcinogenesis (Carbone, Emri et al. 2007).

Mesothelioma arises from multipotential mesothelial cells which are capable of differentiating into epithelial, sarcomatoid, or biphasic (mixed) neoplasms. There is lack of consensus on a staging system for MPM, however, most patients present with advanced disease. Advanced age, poor performance status, male sex, and sarcomatoid histologic subtype are all poor prognostic factors. Despite modest advances in clinical treatment, the mean overall survival for patients with MPM is approximately 12 months (Ducko and Sugarbaker 2008). There is also lack of consensus regarding treatment of MPM. Suitable surgical candidates with disease limited to one hemithorax may undergo surgical resection via extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D) as part of a multimodality treatment approach. Radiation therapy alone is generally ineffective due to the large volume of primary tumor and its proximity to vital mediastinal structures. However, radiation therapy, particularly intensity-modulated radiation therapy (IMRT), has been demonstrated to reduce local recurrence following resection by EPP (Rice, Stevens et al. 2007). Historically, chemotherapy response rates have been less than 20%. However,

improved response rates of 41% have been demonstrated with the addition of the folate antimetabolite pemetrexed (Vogelzang 2003). Highly selected patients appear to benefit from trimodality therapy consisting of aggressive surgical debulking followed by adjuvant radiation and chemotherapy (Sugarbaker, Flores et al. 1999). Failure of conventional therapies has led to interest in novel treatment approaches including intrapleural administration of immunotherapy and gene therapy, as well as intraoperative adjuncts such as intrapleural chemotherapy and photodynamic therapy (Friedberg, Mick et al. 2011; Vachani, Moon et al. 2011).

Studies of human cell lines and tissues as well as animal models of MPM have demonstrated genetic and epigenetic events which contribute to the multistep process of mineral fiber carcinogenesis. These events include inactivation of tumor suppressor genes, modulation of signal transduction pathways including receptor tyrosine kinases (RTKs), avoidance of apoptosis, and inhibition of the ubiquitin-proteasome degradation pathway. This chapter will focus on the molecular pathogenesis of malignant mesothelioma. Preclinical and clinical trials of targeted therapies such as tyrosine kinase, histone deacetylase, and proteasome inhibitors will be included in the discussion.

2. Etiology of mesothelioma

2.1 Asbestos

The vast majority of cases of mesothelioma can be linked in some fashion to asbestos exposure. Materials utilizing asbestos fibers have been present since ancient times. In fact, the word asbestos is derived from a Greek term meaning inextinguishable or unquenchable, a reference to its fire-resistant properties. It was these heat-resistant and insulating properties which made asbestos a valuable commodity, particularly as the industrial revolution began. In the United States, mining and subsequent use of asbestos increased steadily during the first half of the twentieth century, escalated rapidly following World War II, and peaked in 1973, after which it precipitously declined (Figure 1). Asbestos refers to a group of crystalline-hydrated silicate minerals which occur in one of two forms: serpentine and amphibole. Chrysotile is the only serpentine asbestos, and exists as a long, curly, and pliable fiber most suitable for making fabrics. Amphibole fibers are short, straight, and stiff, and have been used to make pipes and tiles. The major commercial amphiboles are amosite, crocidolite, and anthophyllite. Mixtures of chrysotile and amphiboles were used to produce an array of roofing, insulation, and fire-proofing materials. Evidence exists that all asbestos fiber types may demonstrate pulmonary toxicity in a dose-dependent fashion. Moreover, all fiber types possess carcinogenic potential, however, exposure to amphibole fibers is more likely to cause mesothelioma than chrysotile fibers (Cugell and Kamp 2004).

The pulmonary hazards of asbestos exposure, including asbestosis and bronchogenic carcinoma, were recognized and published by physicians in the early twentieth century. However, the link between asbestos exposure and mesothelioma was not established until 1960, when Wagner reported 33 cases of pleural mesothelioma occurring in a relatively short time period in an area of South Africa where crocidolite was mined (Wagner, Sleggs et al. 1960). In 1964, Selikoff and colleagues reported on the link between asbestos exposure and thoracic neoplasia (bronchogenic carcinoma and mesothelioma) in New York-area

insulation workers in a variety of industries, including shipbuilding (Selikoff, Churg et al. 1964). Subsequently, this group reported mesothelioma as the cause of 10 of 307 consecutive deaths among these same workers, concluding that mesothelioma was indeed a complication of relatively light and intermittent (occupational) exposure to asbestos, including chrysotile, which was the dominant fiber in American industry at the time (Selikoff, Churg et al. 1965).

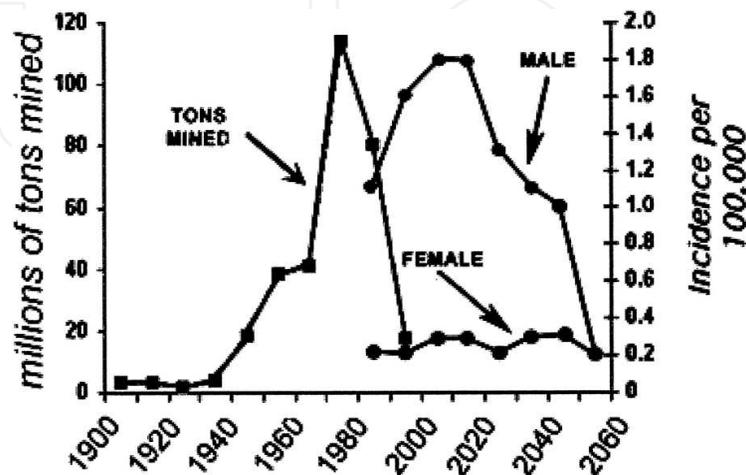


Fig. 1. Asbestos production and mesothelioma incidence: asbestos production in the United States in the last century and mesothelioma incidence from 1980 projected to 2055.

Reprinted from Cugell, D. W. and D. W. Kamp (2004). "Asbestos and the pleura: a review." *Chest* **125**(3): 1103-1117, with permission.

While smoking cigarettes has been proven to increase the likelihood of developing bronchogenic carcinoma in individuals exposed to asbestos, mesothelioma is not associated with smoking. It is also interesting that while most cases of mesothelioma are associated with asbestos exposure, only a small minority (approximately 5%) of exposed individuals develop mesothelioma (Gazdar and Carbone 2003). Asbestos exposure induces benign manifestations such as pleural effusion or plaques in some individuals, while causing malignant mesothelioma in others. Obviously, other etiologic factors, including genetics, play a role in mesothelioma pathogenesis.

2.2 SV40

SV40 is a polyoma virus of monkey origin which has been identified in a number of human tumors. SV40 contributes to the transformation of human cells by perturbing several intracellular pathways, including disabling the p53 and retinoblastoma (Rb) tumor suppressor pathways. In the 1960s, SV40 was found to be a contaminant in poliovirus vaccines which were prepared in primary cultures of rhesus monkey kidney cells. Contaminated vaccines were administered to children and adults in many countries including the United States. In fact, in the U.S. prior to 1963, approximately 90% of children and 60% of adults received at least one contaminated vaccination. The prevalence of SV40 infections in humans is not known. However, indirect evidence of widespread distribution of SV40 throughout the human population exists in that SV40-positive tumors have been detected throughout the world except in countries that reportedly did not use SV40-contaminated vaccine (Gazdar, Butel et al. 2002).

The human tumors most frequently found to have SV40 sequences are brain and bone tumors, lymphoma, and malignant mesothelioma. SV40 is also a potent oncogenic virus in rodents, and a similar spectrum of tumors is induced in hamsters following viral inoculation. In fact, the incidence of mesothelioma is 100% in hamsters following intrapleural inoculation. Human mesothelial cells contain high endogenous levels of p53 and are unusually susceptible to SV40-mediated transformation, with asbestos acting as a co-carcinogen. Despite powerful evidence regarding the biologic effects of SV40 in mesothelial cells, considerable skepticism exists within the scientific community regarding a causal relationship between the presence of SV40 viral sequences and development of mesothelioma (Gazdar and Carbone 2003).

2.3 Genetic predisposition: The cappadocia epidemic

In 1978, an unprecedented epidemic of mesothelioma was discovered in three villages located in Cappadocia, Turkey. Mesothelioma accounts for >50% of all deaths in these villages. Mineralogic studies of the volcanic rock in these villages demonstrated the presence of a fibrous mineral called erionite which shares some physical properties with crocidolite. Curiously, large erionite deposits are present in other parts of the world, including the western United States, but had never been associated with development of mesothelioma in these regions. The mesothelioma epidemic in Cappadocia was initially linked solely to exposure to erionite contained in the stones used to build houses in the region. However, construction and examination of careful pedigrees demonstrated that mesothelioma occurred in certain families but not in others. Studies have confirmed that the cause of the mesothelioma epidemic in Cappadocia is genetic predisposition to erionite-induced carcinogenesis which is transmitted in an autosomal dominant fashion (Carbone, Emri et al. 2007).

3. Molecular pathogenesis of mesothelioma

The mechanisms whereby inhaled asbestos fibers induce pleural disease, including mesothelioma, are diverse and likely multifactorial. The traditional explanation includes migration of fibers from the airway, through the visceral pleura, and eventual uptake from the parietal pleura. Alternative routes of fiber translocation to the parietal pleura include lymphatic and hematogenous dissemination (Cugell and Kamp 2004). There are several features of asbestos fibers which contribute to their carcinogenicity, including chemical composition, fiber length and form, and their biopersistence. Local responses to these characteristics include frustrated phagocytosis of fibers, generation of reactive oxygen and nitrogen species which may be genotoxic, initiation of inflammatory mechanisms, stimulation of growth factors and their receptors, and initiation of signal transduction pathways which stimulate proliferation and avoidance of apoptosis (Godleski 2004).

3.1 Chromosomal alterations

Allele loss, with subsequent loss of heterozygosity (LOH) at tumor suppressor loci, is a common occurrence in oncogenesis. Mutations and deletions of the p53 and pRb tumor suppressor pathways are prominent features in many human malignancies; however, p53 and pRb remain genetically intact in most mesotheliomas (Lee, Raz et al. 2007). Gene copy

number alterations are present in mesothelioma. Common chromosomal regions of allele loss include 1p, 3p21, 6q, 9p21, 15q11-15, and 22q (Zucali, Ceresoli et al. 2011). Homozygous deletion of the 9p21 region is frequently present in mesothelioma cell lines and tumor specimens. Loss of 9p21 results in loss of the INK4a/ARF locus, which encodes two distinct proteins, p16INK4a and p14ARF, translated from alternatively spliced mRNA. p16INK4a inhibits the cyclin-dependent kinase (CDK)-mediated inactivation of pRb. p14ARF stabilizes p53 through its actions on Mdm2. As the INK4a/ARF locus plays an important role in the activity of both the p53 and pRb tumor suppressor pathways (Figure 2), a single mutational event may lead to the functional loss of both of these two key regulatory pathways (Lee, Raz et al. 2007).

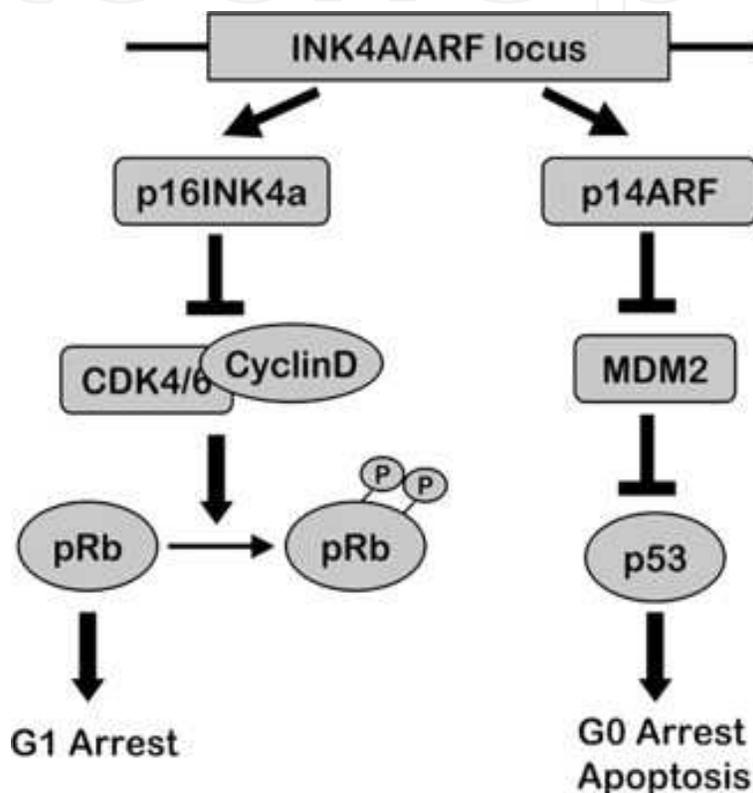


Fig. 2. The role of the INK4A/ARF locus in the regulation of the pRb and p53 tumor suppressor pathways. Reprinted from Lee, A. Y., D. J. Raz, et al. (2007). "Update on the molecular biology of malignant mesothelioma." *Cancer* 109(8): 1454-1461, with permission.

3.2 Bcl-XL and resistance to apoptosis

Conventional chemotherapeutic agents and radiation therapy have been shown to exert their cytotoxic effects by inducing apoptosis via the mitochondrial (intrinsic) pathway (Figure 3). Alterations in expression levels of genes and proteins that regulate this pathway of programmed cell death occur frequently in tumor cells. These alterations favor inappropriate cell survival via increased expression of anti-apoptotic proteins. This in turn may lead to resistance to chemotherapeutics and radiation, as these therapies utilize apoptosis as a final common death pathway (Mow, Blajeski et al. 2001). Apoptotic resistance is therefore not only a hallmark of cancer but also a key mechanism of treatment failure (Hanahan and Weinberg 2011).

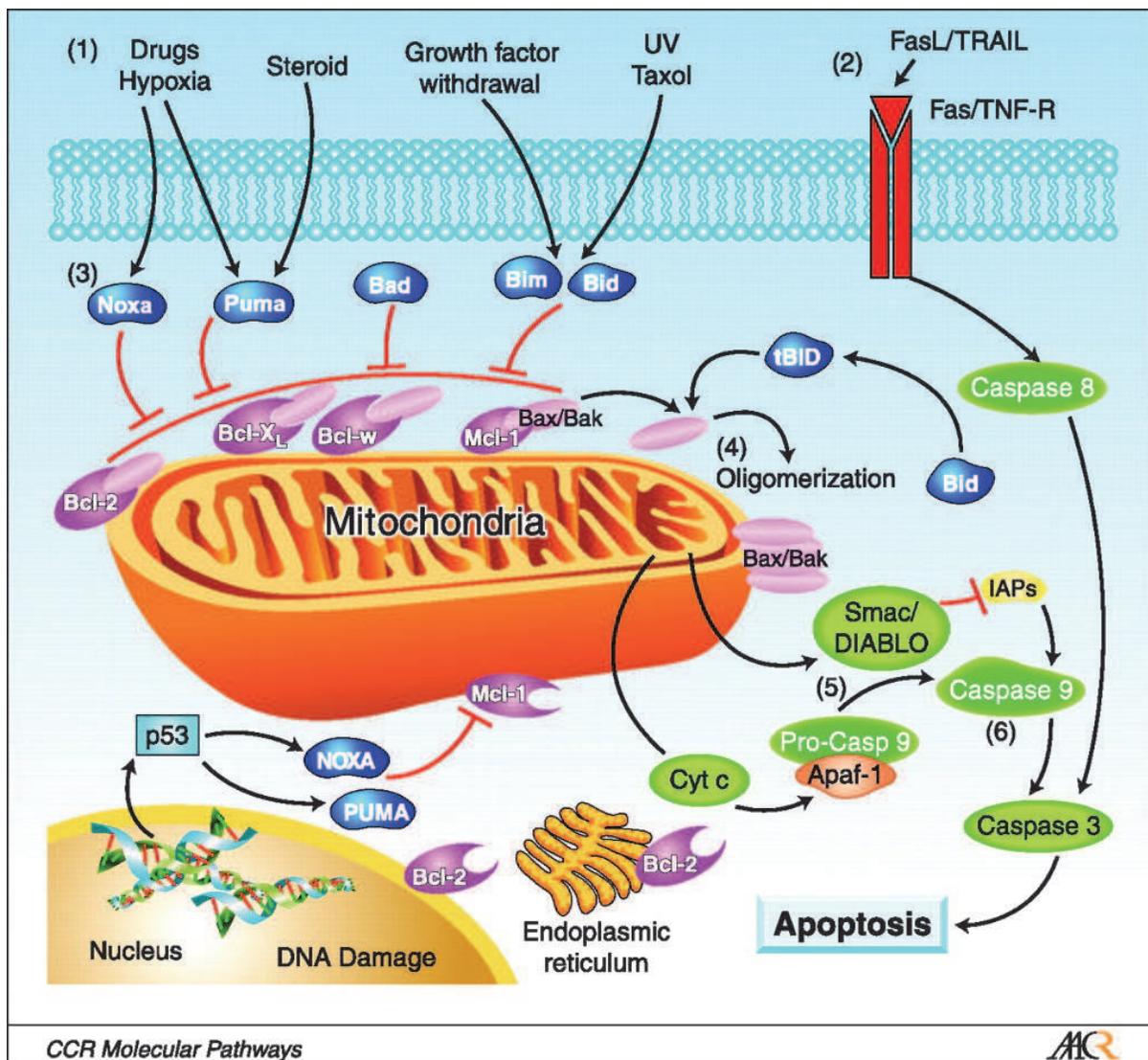


Fig. 3. The apoptotic pathway to cell death from the perspective of the Bcl-2 family of proteins. 1, The intrinsic pathway is initiated by various signals, principally extracellular stimuli. 2, The extrinsic pathway is activated by Fas ligand or TRAIL, subsequently activating caspase-8. Caspase-8 transforms Bid into truncated Bid. In addition, caspase-8 initiates a cascade of caspase activation. 3, BH3-only proteins (Bim, Bid, Bad, Noxa, Puma) engage with anti-apoptotic Bcl-2 family proteins to relieve their inhibition of Bax and Bak to activate them. 4, Next, Bax and Bak are oligomerized and activated, leading to mitochondrial outer membrane permeabilization. 5, Once mitochondrial membranes are permeabilized, cytochrome c and/or Smac/DIABLO is released into the cytoplasm, wherein they combine with an adaptor molecule, apoptosis protease-activating factor 1, and an inactive initiator caspase, procaspase-9, within a multiprotein complex called the apoptosome. Smac/DIABLO inhibits inhibitors of apoptosis proteins to activate caspase-9. 6, Caspase-9 activates caspase-3, which is the initiation step for the cascade of caspase activation. Intrinsic and extrinsic pathways converge on caspase-3. Bcl-2 family proteins are also found on the endoplasmic reticulum and the perinuclear membrane in hematopoietic cells, but they are predominantly localized to mitochondria. Reprinted from Kang M H , Reynolds C P Clin Cancer Res 2009;15:1126-1132, with permission.

The Bcl-2 family consists of 23-25 genes coding for proteins that, in conjunction with other constituents of programmed cell death pathways, regulate apoptotic homeostasis. The longer splice product of the *bcl-x* gene (located on the short arm of chromosome 20, 20pter-p12.1), Bcl-XL, is an important anti-apoptotic member of the family and is over-expressed in several solid tumors including malignant mesothelioma (Cao, Littlejohn et al. 2009). The physiological role of anti-apoptotic proteins is to prevent apoptosis by inhibiting release of soluble mitochondrial intermembrane proteins such as cytochrome c and DIABLO into the cytoplasm. The release of these proteins leads to caspase activation. Interactions of the various members of the Bcl-2 family have been revealed to be more complex than originally thought, but the role of BAX/BAK as effectors of mitochondrial membrane permeability remains central. The exact mechanism by which BAX/BAK affects membrane permeability is not completely understood, but it is known to involve membrane incorporation of these proteins, as well as autodimerization and interaction with VDAC proteins (Kim, Rafiuddin-Shah et al. 2006; Youle and Strasser 2008). Anti-apoptotic proteins such as BCL-XL act by sequestration of BAX/BAK “activator” proteins tBID, BIM and PUMA. This activity is antagonized by the interaction of “inactivator” proteins such as BIK, NOXA, and BAD with Bcl-XL. When challenged with pro-apoptotic stimuli in a wide variety of human tumor cell lines, Bcl-XL is at least as potent as Bcl-2 in prevention of apoptosis. In systems where Bcl-2 and Bcl-XL have been alternatively and co-over-expressed, Bcl-XL is more important to prevention of apoptosis. (Huang, Cory et al. 1997). Although there is significant homology between Bcl-2 and Bcl-XL, Bcl-XL has proved to be uniquely important in human disease, and has been the focus of our studies in mesothelioma, in which Bcl-2 is not typically overexpressed. Our laboratory has demonstrated the therapeutic potential of Bcl-XL down-regulation and functional inhibition both in vitro and in pre-clinical models of mesothelioma. In combination therapies, these models have proven successful in helping to overcome resistance to conventional chemotherapy.

Increased expression of pro-apoptotic members of the Bcl-2 family should favor programmed cell death in the presence of an appropriate stimulus. In fact, transduction of mesothelioma cell lines with an adenoviral vector containing the pro-apoptotic protein BAK induces decreased cellular viability and increased apoptosis in vitro (Pataer, Smythe et al. 2001). Antisense oligonucleotide (ASO) therapy directed at Bcl-XL mRNA has been shown to chemosensitize a number of tumor cell types, including mesothelioma. ASOs directed at Bcl-XL mRNA were utilized in vitro to down-regulate Bcl-XL protein expression, decrease viability, and engender apoptosis in human mesothelioma cell lines (Smythe, Mohuiddin et al. 2002). Furthermore, exposure of human mesothelioma cells to Bcl-XL ASOs in vitro was demonstrated to sensitize them to the conventional chemotherapeutic agent cisplatin in a synergistic manner (Ozvaran, Cao et al. 2004). Finally, the combination of Bcl-XL ASO and cisplatin was demonstrated to reduce the growth of established flank tumor xenografts in mice as well as extend survival in an orthotopic xenograft mouse model of mesothelioma (Littlejohn, Cao et al. 2008). Similar results have been obtained utilizing small interfering RNA (siRNA)-induced inhibition of Bcl-XL rather than antisense oligonucleotides.

Pharmacological agents that neutralize the functions of anti-apoptotic Bcl-2 family proteins have emerged as a promising new class of anti-cancer agents. These direct inhibitors of Bcl-XL function have a number of theoretical advantages over ASO and

siRNA-based approaches, including facilitation of systemic delivery and cross reactivity with other anti-apoptotic members. 2-methoxy antimycin A3 is a small molecular ligand which inhibits binding of pro-apoptotic family members such as BAK by occupying the binding cleft of Bcl-XL and Bcl-2. Treatment of mesothelioma cell lines with 2-methoxy antimycin A3 results in apoptotic cell death without altering Bcl-2 family protein expression. Furthermore, co-administration of 2-methoxy antimycin A3 and cisplatin results in synergistic inhibition of tumor growth in an *in vivo* mesothelioma tumor model (Cao, Rodarte et al. 2007). Pharmacologic inhibitors of antiapoptotic Bcl-2 family members continue to undergo further refinement and have shown promise in a number of tumor types, including mesothelioma.

3.3 Histone Deacetylase Inhibitors (HDACi)

Histones are a family of proteins that serve as structural and regulatory components of chromatin. The fundamental complex of chromatin is the nucleosome, which consists of 146 base pairs of DNA wrapped around an octamer of histone subunits (Marks, Miller et al. 2003). Histone acetylation, regulated by histone acetyltransferases (HAT) and histone deacetylases (HDAC), affects the relative condensation of chromatin. In short, when histones are acetylated, chromatin is decondensed, and DNA is available for transcription. Histone deacetylases facilitate chromatin condensation, preventing transcription of genes which include tumor suppressors (Zucali, Ceresoli et al. 2011). In addition to effects on histone proteins and the structure of chromatin, histone deacetylase inhibitors (HDACi) also modulate the acetylation of nonhistone proteins such as transcription factors. This ultimately leads to a number of biologic effects such as promotion of apoptosis, cell cycle inhibition, and inhibition of angiogenesis (Paik and Krug 2010).

Sodium butyrate is a histone deacetylase inhibitor known to alter Bcl-2 family gene expression in a variety of tumor types. Exposure of mesothelioma cell lines to sodium butyrate leads to decreased mRNA transcription and protein expression of Bcl-XL as well as induction of apoptosis (Cao, Mohiuddin et al. 2001). In a subsequent study, cellular death and apoptosis of mesothelioma cell lines were augmented by the combination of sodium butyrate with proapoptotic gene therapy, namely adenoviral transfer of the proapoptotic Bcl-2 family members BAX and BAK (Mohiuddin, Cao et al. 2001). Similar *in vitro* effects have been demonstrated in mesothelioma utilizing the HDACi suberoylanilide hydroxamic acid (SAHA, Vorinostat). Others have demonstrated a synergistic response between HDACi and combination chemotherapy in mesothelioma. Treatment with valproic acid, another known HDACi, in combination with pemetrexed and cisplatin led to complete suppression of epithelioid mesothelioma growth in a mouse xenograft model (Vandermeers, Hubert et al. 2009).

An increasing amount of preclinical data demonstrating the utility of histone deacetylase inhibition *in vitro* and in mouse xenograft models has led to early phase clinical trials in patients with mesothelioma. Based on compelling evidence from two phase I trials involving mesothelioma patients who received Vorinostat, a multicenter, randomized, placebo-controlled phase III trial of Vorinostat in patients with advanced mesothelioma has been initiated. Patients who have progressed or relapsed following treatment with pemetrexed and platinum therapy are randomized 1:1 to receive Vorinostat or placebo. This study is ongoing (Paik and Krug 2010).

3.4 Receptor Tyrosine Kinases (RTKs)

Peptide growth factors are important in maintaining tumor cell viability, particularly in the face of apoptotic stimuli. These growth factors are well known to induce intracellular signal transduction pathways such as the phosphoinositide-3 (PI-3) kinase and mitogen-activated protein (MAP) kinase pathways through their interaction with specific cell surface transmembrane receptor tyrosine kinases (RTKs). Several growth factors and their receptors have been shown to play a significant role in the oncogenesis, progression, and resistance to therapy of malignant mesothelioma. Among them, Epidermal Growth Factor (EGF), Hepatocyte Growth Factor (HGF), Vascular Endothelial Growth Factor (VEGF), and Insulin-like Growth Factor (IGF) have been shown to be targets for therapy based on promising preclinical data (Villanova, Procopio et al. 2008).

3.4.1 Epidermal Growth Factor (EGF)

One of the most thoroughly studied targets in cancer therapeutics is the epidermal growth factor receptor (EGFR) and its ligand, EGF. EGFR is well known to be overexpressed in many human cancers, among them colon, breast, lung, and upper aerodigestive tract malignancies. In 1990, Dazzi and colleagues found that 68% of mesothelioma specimens stained positively for EGFR by means of immunohistochemistry and that EGFR positivity was more common in the epithelial subtype (Dazzi, Hasleton et al. 1990). In studying the immunohistochemical expression of EGFR and its ligand, transforming growth factor- α (TGF- α), Cai and associates found that 76% of mesotheliomas expressed TGF- α , whereas 45% expressed EGFR, indicating the possibility of an EGFR autocrine loop (Cai, Roggli et al. 2004). EGFR expression has also been linked to asbestos exposure in tissue culture. SV40-transformed human mesothelial cells exposed to asbestos fibers in vitro overexpress EGFR compared with control cells and EGFR expression is related to increasing fiber length of crocidolite asbestos (Pache, Janssen et al. 1998). Similar results have been obtained in vivo in rat pleural mesothelial cells (Faux, Houghton et al. 2001). A preclinical study using gefitinib (Iressa), an orally-bioavailable EGFR kinase inhibitor, demonstrated growth inhibition and G1 cell-cycle arrest in four mesothelioma cell lines (Janne, Taffaro et al. 2002). EGFR kinase inhibition led to apoptotic cell death via downregulation of PI-3 kinase/Akt signaling in mesothelioma in vitro (Rascoe, Cao et al. 2005). Finally, gefitinib was noted to potentiate the radiation response of mesothelioma xenografts in nude mice, with many animals demonstrating complete regression with no tumor regrowth (She, Lee et al. 2003).

Based on the aforementioned preclinical data, pharmacologic inhibition of EGFR was thought to be a promising strategy in mesothelioma therapy. Moreover, the identification of activating mutations in the kinase domain of EGFR as a biomarker of response to tyrosine kinase inhibitor therapy in non-small cell lung cancer (NSCLC) patients was equally promising (Lynch, Bell et al. 2004) (Paez, Janne et al. 2004). While activating mutations of EGFR have been reported in patients with malignant peritoneal mesothelioma (Foster, Gatalica et al. 2008; Foster, Radhakrishna et al. 2010), no such activating mutations of EGFR have been discovered in patients with pleural mesothelioma, and the results of EGFR inhibitors in phase II clinical trials have been disappointing (Velcheti, Kasai et al. 2009). The Cancer and Leukemia Group B (CALGB) 30101 phase II trial enrolled 43 chemotherapy-naïve patients to receive 500 mg gefitinib (Iressa) daily. 3-month progression free survival was 40%, which was not different than historical controls, and the authors concluded that

single-agent gefitinib was not active in malignant mesothelioma. 97% of the patients in CALGB 30101 who had EGFR expression scored by immunohistochemistry were found to have high expression (Govindan, Kratzke et al. 2005). A Southwest Oncology Group (SWOG) phase II trial enrolled 63 chemotherapy-naïve patients to receive erlotinib (Tarceva). Despite high EGFR expression in 75% of participants, only 42% of patients had stable measurable disease, and the median progression-free survival of 2 months was significantly lower than that observed with standard first-line chemotherapy (Garland, Rankin et al. 2007).

Phosphatase and tensin analog (PTEN) is a tumor suppressor gene which has been localized to chromosome 10q23. Loss of heterozygosity at 10q23 has been demonstrated in a number of tumor types, including mesothelioma. In a large tissue array study of clinical mesothelioma samples, 62% demonstrated absent PTEN expression while 14% demonstrated weak expression. Examination of clinical data from this cohort revealed that loss of PTEN expression was an independent predictor of poor survival in mesothelioma patients (Opitz, Soltermann et al. 2008). Our laboratory has previously demonstrated that adenoviral gene transfer and forced overexpression of PTEN engenders apoptosis in mesothelioma by Akt hypophosphorylation and decreased Akt kinase activity (Mohiuddin, Cao et al. 2002). It has been hypothesized that loss of PTEN and resultant constitutive Akt activation may explain the resistance seen with EGFR tyrosine kinase inhibitors, as they act upstream of PTEN (Agarwal, Lind et al. 2011).

3.4.2 Hepatocyte Growth Factor (HGF)

Hepatocyte Growth Factor (HGF) is a multifunctional growth factor known to induce cellular growth and proliferation, motility, and morphogenesis. HGF induces these biological functions through binding to its transmembrane tyrosine kinase receptor, c-Met (Zucali, Ceresoli et al. 2011). c-Met is overexpressed and activated in a majority of cases of mesothelioma when compared to normal tissues. In addition, the circulating serum levels of HGF are two-fold greater in mesothelioma patients as compared with healthy control patients. Upon HGF stimulation and c-Met phosphorylation, the PI-3 kinase and MAP kinase signal transduction pathways are activated in mesothelioma cell lines. Moreover, c-Met small interfering RNA (siRNA) and a pharmacologic c-Met inhibitor (SU11274) are effective in inhibiting cell growth and migration of these same cell lines (Jagadeeswaran, Ma et al. 2006).

An association between c-Met and Bcl-XL levels in malignant tissues has been established. In mesothelioma, the HGF/cMet axis appears to upregulate Bcl-XL expression at the transcriptional level. Specifically, via activation of MAP kinases, members of the ETS family of transcription factors are phosphorylated. This leads to nuclear importation of the factors ETS-2 and PU.1, both of which increase Bcl-XL promoter activity in mesothelioma. Conversely, the transcriptional repressor, Tel, is phosphorylated and exported from the nucleus to the cytoplasm (Cao, Littlejohn et al. 2009).

3.4.3 Vascular Endothelial Growth Factor (VEGF)

Vascular endothelial growth factor is an essential regulatory component of physiologic angiogenesis. Furthermore, its role in tumor pathogenesis, growth, and metastasis are well

documented, and VEGF is overexpressed in most human malignancies. The effects of VEGF are mediated through binding to two tyrosine kinase receptors: VEGFR-1, or Flt-1 (fms-like tyrosine kinase-1), and VEGFR-2, or KDR/Flk-1 (kinase-insert domain receptor/fetal liver kinase-1) (Villanova, Procopio et al. 2008).

Mesothelioma patients have higher serum levels of VEGF than normal controls and, in fact, have higher VEGF levels than other solid tumor patients (Linder, Linder et al. 1998). VEGF and its two receptors are expressed in mesothelioma cell lines, biopsy specimens, and pleural effusions. VEGF levels in the pleural effusions of mesothelioma patients were 7-fold higher than levels in effusions in patients with non-malignant disease. Moreover, linear regression analysis has demonstrated an inverse correlation between serum VEGF levels and survival in mesothelioma patients (Strizzi, Catalano et al. 2001).

A number of angiogenesis inhibitors directed at VEGF and its receptors have been developed. The anti-VEGF monoclonal antibody bevacizumab (Avastin) has demonstrated modest survival benefit and is approved for use in metastatic colorectal carcinoma and non-small cell lung cancer. Unfortunately, despite the aforementioned promising preclinical data, a phase II trial combining cisplatin and gemcitabine with and without bevacizumab in unresectable, chemotherapy-naïve mesothelioma patients yielded no differences in progression-free or overall survival (Karrison, Kindler et al. 2007). A similar trial comparing bevacizumab and placebo in patients receiving current first-line chemotherapy (cisplatin/pemetrexed) is ongoing. Studies investigating several small molecule pharmacologic inhibitors of VEGF receptor tyrosine kinases have demonstrated only modest activity to date (Kelly, Sharon et al. 2011).

3.4.4 Insulin-like Growth Factors (IGF)

Insulin-like growth factors represent a family of peptides produced by various tissues throughout the body. IGFs possess growth stimulatory activities similar to insulin and may work in an autocrine, paracrine, or endocrine fashion. As such, IGF has been reported to be an important growth factor in many tumor types. Both normal mesothelial and mesothelioma cell lines express IGF-1 and IGF-1R mRNA, indicating the possibility of an autocrine loop (Lee, Raz et al. 2007). An IGF-1 receptor antisense expression vector led to a decrease in proliferation and tumorigenicity in a hamster mesothelioma cell line (Pass, Mew et al. 1996). We observed increased IGF-1R expression in mesothelioma cell lines relative to a transformed mesothelial line as well as decreased cellular viability and apoptosis in a sarcomatous-type mesothelioma line following IGF-1R inhibition (Rascoe, Cao et al. 2005). Others have demonstrated dose-dependent growth repression, inhibition of IGF-1R phosphorylation, and decreased activity of downstream PI-3 kinase/Akt and MAP kinase signal transduction pathways following treatment with an orally bioavailable IGFR inhibitor, NVP-AEW541 (Whitson, Jacobson et al. 2006).

3.5 Proteasome inhibitors

Investigation has revealed that the ubiquitin-proteasome pathway plays a key role in regulating homeostasis of cellular proteins that involve cell cycle, survival, and apoptosis. Therapeutically, targeting the proteasome with a specific inhibitor, bortezomib (Velcade), has been successful in selectively inducing apoptosis in a variety of human cancer cells

including mesothelioma. Bortezomib is a selective inhibitor of the 20S proteasome. Its actions are pleiotropic and include inhibition of NF- κ B activation by preventing degradation of its inhibitor I κ B (Zucali, Ceresoli et al. 2011). Inhibition of constitutively activated NF- κ B by bortezomib resulted in cytotoxicity and apoptosis in vitro and regression of mesothelioma xenografts in mice (Sartore-Bianchi, Gasparri et al. 2007). Furthermore, bortezomib potentiated the activity of pemetrexed and cisplatin in mesothelioma cell lines (Gordon, Mani et al. 2008). Bortezomib is currently under investigation in a number of mesothelioma trials, both as a single agent and in combination with chemotherapy. While bortezomib is approved for the treatment of multiple myeloma, cellular resistance to bortezomib-induced apoptosis may limit its successful application as a therapeutic agent in this context (Richardson, Sonneveld et al. 2007). In vitro development of a bortezomib-resistant mesothelioma cell line has demonstrated that evasion of the unfolded protein response (UPR) and concomitant reduction in pro-apoptotic gene induction accounts for resistance in bortezomib-adapted mesothelioma cells (Zhang, Littlejohn et al. 2010).

4. Conclusions and future directions

Despite modest advances in clinical treatment over the past decade, malignant pleural mesothelioma remains a vexing clinical problem. The mean overall survival for patients with MPM is approximately 12 months. Highly selected patients appear to benefit from aggressive surgical debulking followed by intensity-modulated radiation therapy (IMRT) to achieve local control of disease followed by systemic chemotherapy. Modest improvements in the treatment of unresectable mesothelioma have been made utilizing combination chemotherapy with cisplatin and pemetrexed. This combination is the current standard of care in the adjuvant setting as well.

Studies of human cell lines and tissues as well as animal models of MPM have demonstrated genetic and epigenetic events which contribute to the multistep process of mineral fiber carcinogenesis. These events include inactivation of tumor suppressor genes, modulation of signal transduction pathways including receptor tyrosine kinases (RTKs), avoidance of apoptosis, and inhibition of the ubiquitin-proteasome degradation pathway. Preclinical investigations of targeted therapies such as tyrosine kinase, histone deacetylase, and proteasome inhibitors have been promising. However, randomized clinical trials utilizing many of these same agents have been disappointing to date. Pharmacologic inhibitors of anti-apoptotic Bcl-2 family members continue to undergo refinement, and there is hope that they will emerge as a promising new class of anticancer agent. Preclinical data suggests they could demonstrate therapeutic effect in a number of tumor types, including mesothelioma.

Autophagy, a concerted process of intra-cellular breakdown within specialized double membrane vesicles, occurs in response to events such as metabolic stress. It is an evolutionarily conserved pro-survival mechanism, regulated downstream of MTOR in the PI-3kinase/Akt cell-survival pathway. While generally cytoprotective, excessive autophagy results in a type of programmed cell death that is morphologically distinct from apoptosis (Sinha and Levine 2008). It has been noted that, depending on context, autophagy can augment either cellular demise or protection. Apoptosis and autophagy are not mutually exclusive programmed cell death pathways, as evidenced by a specific physical interaction between regulators of the two pathways: Beclin-1 (autophagy) and Bcl-XL (apoptosis). Bcl-

XL has recently been determined to inhibit autophagy via a direct functional and physical interaction with Beclin-1, a protein essential for the initiation of autophagy (Maiuri, Le Toumelin et al. 2007). Beclin-1, characterized as a haploinsufficient tumor suppressor, is a known cytosolic mediator of autophagy, and a recent addition to the BH3-only members of the Bcl-family of proteins. These proteins govern intrinsic apoptosis, via selective interaction with the BH3 binding pocket of Bcl-XL (Oberstein, Jeffrey et al. 2007). Autophagy is likely important in response to toxic insults such as chemotherapy or irradiation, but its exact role in the context of a growing solid tumor remains unclear (Degenhardt, Mathew et al. 2006). Beclin-1 is known to promote cell survival in solid tumors via facilitation of autophagy, yet has also been shown to suppress tumorigenicity (Degenhardt, Mathew et al. 2006; Oberstein, Jeffrey et al. 2007). In malignant glioma cells, it has been shown that the anti-tumor effect of temozolomide can be suppressed by inhibiting early autophagy, but that inhibition of late autophagy enhances cytotoxicity (Kanzawa T 2008). Inhibition of autophagy in radiation resistant cell lines of breast, lung, pharyngeal, and cervical cancers resensitized them to radiation treatment (Apel, Herr et al. 2008). Thus, it is becoming clear that a greater understanding of autophagy in the context of chemotherapy-induced apoptosis within a growing solid tumor could add to our understanding of chemotherapeutic response and development of resistance.

Ongoing studies in our laboratory have demonstrated that both apoptosis and autophagy occur in malignant mesothelioma following histone deacetylase inhibition through mutually exclusive processes. Autophagy appears to occur much earlier than apoptosis, suggesting that autophagy may play a cytoprotective role in mesothelioma cells following cytotoxic therapy, thus subverting their entry into the apoptotic pathway.

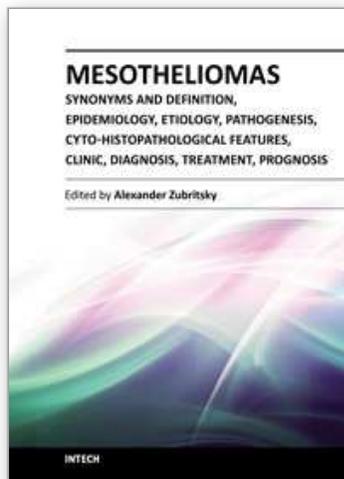
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Mesotheliomas - Synonyms and Definition, Epidemiology, Etiology, Pathogenesis, Cyto-Histopathological Features, Clinic, Diagnosis, Treatment, Prognosis

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Mesotheliomas are mysterious mesothelial tumors in that they are relatively rare, difficult to diagnose, with a large number of synonyms, and the etiology and pathogenesis of the disease are still not fully disclosed. This problem attracts the attention of various specialists in the field of medicine and biology every year. In recent years there has been a significant increase of mesothelioma morbidity in most of the countries, due to the further industrialization of society. In this regard, this book has been published with the participation of an international group of experts with rich experience from around the world. The book consists of 14 chapters containing the most advanced achievements of all aspects of the various types of mesotheliomas, both in humans and domestic animals, at a high methodological level. This book is intended for biologists and all health care workers, mostly oncologists of different profiles, as well as students of medical educational institutions engaged or even just interested in the problems of mesotheliomas.

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