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Review article

The resistance related to targeted therapy in malignant pleural mesothelioma: Why has not the target been hit yet?

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ABSTRACT

Malignant pleural mesothelioma (MPM) is an aggressive tumor of the pleura with a poor prognosis. The most active first-line regimens are platinum compounds and pemetrexed. There is no standard second-line treatment in MPM. Advances in the understanding of tumor molecular biology have led to the development of several targeted treatments, which have been evaluated in clinical trials. Unfortunately none of the explored targeted treatments can currently be recommended as routine treatment in MPM.

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Targeted therapy
Resistance

We reviewed the biological pathways involved in MPM, the clinical trials about targeted therapy, and possible related mechanisms of resistance. We suggest that specific genetic markers are needed as targets of selective therapy. By this way the selection of patients based on the molecular profile may facilitate a therapeutic strategy that allows the use of the most appropriate drug for each patient.

1. Introduction

Malignant pleural mesothelioma (MPM) is the most common primary tumor of the pleura, and is related to asbestos exposure in more than 80% of cases (McDonald and McDonald, 1996).

Asbestos, intended as a group of natural crystalline silicates, have been used in various industrial applications (Frank and Joshi, 2014). Occupational exposure to asbestos entails highest risk of asbestos-related diseases. There is no safe level of exposure. Repair, renovation, and demolition of asbestos-containing buildings induces soil contamination and environmental pollution (Marinaccio et al., 2015). Current regulation regards only actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite, but other mineral fibers in the environment, such as erionite has even greater carcinogenic activity and is involved in asbestos-related diseases (Baumann et al., 2013).

Since mineral fibers of asbestos are inhaled, they accumulate in the lungs. A variety of negative effects are developed, such as the production of reactive oxygen species (ROS), chromosome damage, disturbance of mitosis, gene mutations, alteration of growth factor signaling, defects in the apoptotic machinery, deregulation of methylation status, chronic inflammation, phagocytosis, and aberrant microRNA expression (Benedetti et al., 2015). In lung tissue these fibers can cause inflammatory reactions with fibrosis termed as asbestosis. Asbestos bodies accumulate, in the form of fibers coated by iron-containing protein, causing the formation of pleural plaques. Abnormal fluid is collected, and fibers are trapped between the pleural layers. So the wall of the chest cavity induce oxidative stress and chronic inflammation, thus promoting carcinogenesis (Yusa et al., 2015). A cumulative exposure of 25 fibers/year has been estimated to double the risk of lung cancer. About 25% of all cases of malignant mesothelioma are attributed to occupational exposure, 25% to familial exposure, and 50% to environmental exposure (Mensi et al., 2015).

Despite improvements in diagnostic methods and therapeutic strategies, the prognosis of MPM remains poor (12–18 months average survival following diagnosis) except in some exceptional cases (Merritt et al., 2001). For the majority of patients who are not candidate for radical surgical treatment, systemic therapy remains the only valid option.

The first-line therapy for such patients is based on a combination of cisplatin and pemetrexed (Goudar, 2008). Multimodal therapy, which includes extrapleural pneumonectomy or pleurectomy/decortication (with or without radiation therapy), is being studied in selected patients. There are currently no defined standards for second-line therapy (Baas et al., 2015).

1.1. Search strategy

A literature search strategy was done using the online databases (Medline – Pubmed, EMBASE, Cochrane Library) for the most updated article on the topic. The keywords were "Mesothelioma", "Advanced" OR "Metastatic", "Target therapy", "PI3K", "C-MET", "mTOR", "FAK", "HSP", "PTEN", "NF-KB", "Immunotherapy", and "Resistance" as a free text or through the Medical Subject Headings (MeSH).

2. Somatic mutations in mesothelioma

The most common somatic mutations in mesothelioma are:

CDK2NA (this gene is altered in about 80% of cases of MPM). There is a loss of Cyclin-Dependent Kinase control with subsequent loss of cellular cycle regulation.

The CDKN2A/ARF (Cyclin-Dependent Kinase Inhibitor 2/Alternative reading frame) gene is also known as $p16^{INK4a}$/$p14^{ARF}$ and is located on chromosome 9p21. It is an important tumor suppressor gene that codes for two proteins: $p16^{INK4a}$ and $p14^{ARF}$ (Ruas and Peters, 1998; Thillainadesan et al., 2012).

In physiological conditions, $p16^{CDKN2A}$ inhibits the protein kinase Cyclin-Dependent Kinase 4/6 (CDK4/6)/Cyclin D1 system, which, in turn, inhibits the antiproliferative activity of RB (retinoblastoma) protein that binds and blocks the E2F transcription factor, stopping the transition of the cell cycle from G1 to S phase. In case of failure or lack of p16, pRb remains phosphorylated and E2F stays constitutively active, leading to uncontrolled cell proliferation.

Similarly, $p14^{CDKN2A}$ interferes with the Murine Double Minute 2 (MDM2) protein, preventing the degradation of p53 and promoting its control in cell cycle progression; an increase in the level of p53 expression in response to genotoxic damage in fact prevents cell division and induces apoptosis (Fig. 1).

These changes play an important role in the cell cycle regulation and are linked to a more aggressive tumor and a poor prognosis (Xio et al., 1995; Ladanyi, 2005).

Some experiments have shown that if CDKN2A/ARF is in its "off" state, there is a cancerogenesis acceleration after asbestos exposure (Kamijo et al., 1997; Altomare et al., 2011).

Gene therapy studies are aimed at p16INK4a/p14ARF gene reactivation, in order to restore the functions that are lost when this is mutated. These investigations have shown that reactivating the gene in mesothelioma cells induces cell cycle arrest, an inhibition of pRb phosphorylation, and a decrease in cell growth. All of these modifications may therefore be related to an increase in survival, an increase in the levels of p53 protein, and a shift towards cellular apoptosis (Frizelle et al., 2000; Tsao et al., 2007; Yang et al., 2000). Gene therapy aimed at restoring the function altered by gene mutations seems to be showing promising preliminary results.

NF2 (neurofibromatosis 2) is a tumor suppressor gene located on chromosome 22q12 that codes for the merlin protein (Moesin ezrin radixin like protein). Loss of NF2 function occurs in about 40% of patients with MPM. The NF2 pathway suppresses tumorigenesis, even though it is not completely understood. The absence of the merlin protein causes activation of multiple signaling pathways, such as HER1/2, mTOR, FAK and ERK. Consequently it has been assumed that the merlin protein inhibits the signaling pathway by down-regulating several membrane receptors (Ladanyi et al., 2012) (Fig. 2). Preclinical data show that inactivation of the merlin protein plays a critical role in the pathogenesis of MPM increasing cell invasive capacity, through the up-regulation of FAK (Focal Adhesion Kinase) expression; the lack of the merlin protein is associated with increased sensitivity to FAK inhibitors (Poulikakos et al., 2006).

BAP-1 (BRCA1 – Associated protein1) is a nuclear enzyme encoded by the BAP-1 gene, which is implicated in the regulation