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Review

The role of key genes and pathways involved in the tumorigenesis of Malignant Mesothelioma

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ABSTRACT

Malignant Mesothelioma (MM) is a very aggressive cancer with low survival rates and often diagnosed at an advanced stage. Several players have been implicated in the development of this cancer, such as asbestos, erionite and the simian virus 40 (SV40). Here, we have reviewed the involvement of erionite, SV40, as well as, the role of several genes ($p16^{INK4a}$, $p14^{ARF}$, *NF2*, *LATS2*, *SAV*, *CTNNB1* and among others), the pathways (RAS, PI3K, Wnt, BCL and Hippo), and their respective roles in the development of MM.

Contents

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1. An introduction to Malignant Mesothelioma

Malignant Mesothelioma (MM) is a slow-growing solid tumor arising from mesothelial cells that can develop in the pleural space, pericardium, peritoneum, tunica vaginalis testis and ovarian epithelium. In its early stage, it is not common for these tumors to suffer metastasis [1]. MM is divided into three categories according to its histological morphology: epithelial, biphasic, and sarcomatoid with median survival period of 18, 11, and 8 months, respectively [2]. Moreover, MM displays a long latency period that can take up to 40 years [3]. During this period, there is an accumulation of mutations on several key genes [4]. In the US alone, it is expected 70,000 new cases of MM over the next 20 years [5].

The Malignant Pleural Mesothelioma (MPM) is an aggressive form of cancer that affects the pleura. MPM is known to be very aggressive, and it is often diagnosed at a very advanced stage, which contributes to its very poor prognosis with a median survival of 11 months [6].

It has been more than 50 years since the first study correlating asbestos to the development of MM [7]. Evidence has shown a strong relationship between asbestos exposure and MM [8]. Exposure to simian virus 40 (SV40) [9], erionite [10], and genetic predisposition have been also implicated in the development of MM [11].

1.1. An overview of molecular biology of MM

MM frequently displays chromosomal loss involving the chromosomes 1, 3, 4, 6, 9, 13, 14 and 22 [12]. The most common genetic alterations in MM are the homozygous deletion of $p16^{INK4a}$ and $p14^{ARF}$ genes. It was found a homozygous deletion of $p16^{INK4a}$ and $p14^{ARF}$ in 72% of MM [13]. In addition, homozygous deletion of the $p16^{INK4a}$ was present in approximately 75% of MM, and it was associated with a more aggressive cancer, and with a reduction on survival [14].

The tumor suppressor Neurofibromatosis type II (*NF2*) has been reported to be altered in MM. *NF2* inactivation is a frequent event in MM with rates ranging from 20% to 60% [15]. The *NF2* gene encodes for the Merlin protein that is associated with the inhibition of several mitogenic signaling pathways [16].

The guardian of the DNA, the protein p53, is encoded by the *TP53*. The p53 plays a crucial role in the cellular response to DNA damage, and its expression is lost in many advanced cancers [17]. However, in MM only 20–25% of the tumors display mutations on *TP53*, a fairly low rate when comparing to other cancers [18]. In recent studies using MM samples, it was reported an overexpression of p53 in 58.2% [19], and in 81% of the cases [20].

The phosphatase and tensin homolog (PTEN), also known as MMAC (mutated in multiple advanced cancers) is a dual lipid and protein phosphatase encoded by the *PTEN*, which is a tumor suppressor gene (TSG) located on chromosome 10q23. PTEN is known to negatively regulate the AKT pathway; thus the loss of *PTEN* expression increases AKT pathway activation, which ultimately leads to an uncontrolled cell growth [21–23].

New studies have demonstrated that other genes play important roles in MM. Germline mutation of *BAP-1* has been identified in a cancer syndrome predisposing individuals to cancer, including MM; furthermore, it has also been shown *BAP-1* somatic mutations in MM samples [24]. Likewise, the *LATS2* has been recently implicated in the development of MM [25]. DNA methylation and MicroRNA (miRNA) expression have exhibited significant roles in MM, as it is described later on.

The PI3K/AKT/mTOR pathway is altered in MM and plays an important role in cell proliferation, survival and motility in many cancers. In 62% of MM cell lines, AKT activation was reported [26]. In another study, it was shown that 65% of human MM species displayed elevated levels of AKT activity [22].

Furthermore, other pathways are dysregulated in MM. The Receptor Tyrosine Kinases (RTKs) drive cell proliferation, survival, differentiation and cell cycle control. Several mechanisms can activate this pathway in cancer providing a good therapeutic option. The overexpression of the epidermal growth factor receptor (EGFR) plays an important role in the progression of several cancers [27]. In a study, the EGFR was present in 44% of MM samples; however, it is not found to be an independent prognostic factor [28].

The Vascular Endothelial Growth Factor Receptors (VEGF) are a potent inducer of the angiogenesis, and its role in the cancer is well established [29]. High levels of VEGF in MM have been demonstrated, being associated with a worse patient survival [30]. Moreover, the importance of this receptor in regulating the angiogenesis, and tumor progression was established; thus making this pathway as a therapeutic target in MM [31].

The retinoblastoma protein (pRb) pathway plays an important role in apoptosis and cell cycle regulation. Mutation on pRb is common in many cancers, but not in MM [32]. Nevertheless, the pRb and p53 pathways play an important role in MM. The $p16^{INK4a}$ and $p14^{ARF}$ exert effects on the pRb and on p53 pathways. The $p16^{INK4a}$ inhibits the cyclin dependent kinases (CDks), preventing the inactivation of pRb; on the other hand, the $p14^{ARF}$ promotes degradation of MDM2, leading then to the stabilization of p53 [33]. Indeed, mutations on *TP53* and on *RB* are not a common event in MM; however mutations and/or alterations on $p16^{INK4a}/p14^{ARF}$ are very common. Thus, alterations and/or mutations on $p16^{INK4a}/p14^{ARF}$ have the potential to disrupt key cell cycle control pathways.

The BCL-2 family of genes exerts a critical role in the apoptosis process. There are several proteins, which are divided into proapoptotic and antiapoptotic proteins. The proapoptotic proteins are thought to promote the permeability of the mitochondrial membranes, thus promoting the apoptosis; on the other hand, the antiapoptotic proteins are thought to inhibit cells from undergoing programmed death. Studies have found that BCL-2 expression is inversely associated with apoptosis; however this protein is not frequently expressed in MM [34,35]. High levels of BCL-XL are a common event in MM; however, downregulation of BCL-XL increases apoptosis and the cystostatic effects of cisplatin and gemcitabine [36].