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Role of Inflammation and Angiogenic Growth Factors in Malignant Mesothelioma

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<http://dx.doi.org/10.5772/47951>

1. Introduction

Malignant mesothelioma (MM) is a highly aggressive tumor which arises from the mesothelial cell lining of the serosal surfaces, most cases (>90%) being of pleural origin (Attanoos & Gibbs, 1997; Robinson & Lake, 2005). The pathogenesis of MM has been mainly associated with previous asbestos exposure (Berman & Crump, 2008), with a latency period of up to 40 years, although other agents such as Simian virus 40 (SV40) or genetic susceptibility factors have been linked to the development of this tumor (Carbone et al., 2002; Pisick & Salgia, 2005). Indeed, human mesothelial cells are highly susceptible to SV40-mediated transformation *in vitro* and SV40 DNA sequences and large T antigen (Tag) have been detected in human MM cells (Bocchetta et al., 2000; Carbone et al., 2012; Gazdar et al., 2003).

MM is largely unresponsive to conventional chemotherapy or radiotherapy and, despite its low metastatic efficiency, it is highly invasive to surrounding tissues so that its extensive growth leads to the failure of the organs underlying the serosal membranes (Astoul, 1999). In fact, the primary cause of fatality in MM is related to the propensity of the tumor cells to invade locally, even though MM metastasis are more common after surgery and, at the autopsy, metastatic diffusion is observed in 50% of patients (Astoul, 1999). At present, the median survival from diagnosis of MM is less than two years (Palumbo et al., 2008).

The mesothelium is not just a passive protective surface, but a highly dynamic membrane (Mutsaers, 2004). It consists of a single layer of elongated, flattened, squamous-like cells of mesodermal origin, characterized by dual epithelial/mesenchymal features. Cuboidal mesothelial cells can also be found at various locations in physiological conditions. Further, mesothelial cells can adopt a cuboidal morphology, which reflects a metabolically activated state, after injury or stimulation of the serosal surface (Mutsaers, 2004). Indeed, mesothelial cells are sentinel cells that can sense and respond to a variety of signals within their

microenvironment. They participate in serosal inflammation by secreting both pro- and anti-inflammatory as well as immunomodulatory mediators. Besides, these cells can act as antigen presenting cells for T lymphocytes (Hausmann et al., 2000), regulate tissue repair, control fibrin deposition and breakdown, and modulate adhesion, growth and dissemination of tumor cells metastasizing to the serosal membranes (Mutsaers, 2002). In particular, in response to different types of stimuli, including cytokines and asbestos fibers, mesothelial cells have been reported to release prostaglandins, chemokines, reactive oxygen and nitrogen species and growth factors which represent key effectors in the modulation of inflammatory reactions that occur in response to pleural injury (Fleury-Feith et al., 2003; Mutsaers, 2002).

2. Asbestos-induced carcinogenesis as an inflammation-driven process

The association between exposure to asbestos fibers and development of lung cancer and mesothelioma is well established in both humans and animals models (Greillier & Astoul, 2008; Huang et al., 2011; Mossman & Churg, 1998; Yarborough, 2007). A variety of mediators, either generated directly from asbestos fibers or elaborated intracellularly or extracellularly by cells exposed to asbestos, are implicated in the initiation and promotion of mesothelial cell transformation.

The mechanisms underlying asbestos-induced carcinogenesis involve mutagenic and non-mutagenic pathways, the latter including inflammation, enhanced mitogenesis, cell signaling alterations, and cytotoxic apoptosis/necrosis. Neither of these two mechanisms alone fully accounts for the complex biological abnormalities produced by asbestos fibers, even though in MM asbestos appears to act as a complete carcinogen (Dong et al., 1994; Huang et al., 2011). Still, the chronic inflammatory response induced by asbestos inhalation seems to play a critical role in mesothelial cell transformation.

Asbestos exposure induces an inflammatory reaction with a large component of mononuclear phagocytes (Antony et al., 1993; Branchaud et al., 1993; Carbone et al., 2012; Choe et al., 1997). Upon differentiation into macrophages, these cells phagocytize asbestos fibers and, in response, release numerous cytokines and reactive oxygen species with mutagenic properties (Robledo & Mossman, 1999). Thus, many of the pathological consequences occurring in the lung following exposure to asbestos fibers are believed to arise from an inflammatory cascade involving both autocrine and paracrine events (Hillegass et al., 2010). Persistent pulmonary inflammation is observed in animal models of asbestosis that can be correlated with fibroproliferative responses (Mossman & Churg, 1998).

Experimental models, as well as *in vitro* studies, have shown that mesothelial cells are particularly susceptible to the cytotoxic effects of asbestos (Baldys et al., 2007; Bérubé et al., 1996; Broaddus et al., 1996). Asbestos does not induce transformation of primary human mesothelial cells *in vitro*, instead, it is very cytotoxic to this cell type, causing extensive cell death. This finding raised an apparent paradoxical issue of how asbestos causes MM if human mesothelial cells exposed to this mineral die (Liu et al., 2000). This apparent paradox is reconciled by the current hypothesis that the chronic inflammation induced by asbestos

leads to the persistent activation of the nuclear factor kappa B (NF- κ B) transcription factor, which in turn mediates the activation of prosurvival genes and prevents apoptosis of the damaged mesothelial cells (Mantovani et al., 2008; Micheau & Tschopp, 2003; Philip et al., 2004). This allows mesothelial cells with asbestos-induced DNA damage to survive and divide rather than die and, if sufficient genetic damage accumulates, to eventually develop into a MM (Miura et al., 2006; Nymark, 2007). In fact, apoptosis is an important mechanism by which cells with DNA damage are eliminated without eliciting an inflammatory response (Ullrich et al., 2008; Yoshida et al., 2010). However, failure of apoptosis in cells with unrepaired DNA and chromosomal damage after chronic exposure to asbestos may lead to permanent genetic alterations and trigger the development of a clone of cancerous cells (Roos & Kaina, 2006; Wu, 2006). Consistently, MM cells are found to be apoptosis-resistant as compared to primary cultured mesothelial cells (Fennel & Rudd, 2004; Villanova et al., 2008).

2.1. Tumor Necrosis Factor- α and other pro-inflammatory cytokines

Tumor Necrosis Factor- α (TNF- α) is probably the most studied candidate for initiating inflammatory and fibrotic events linked to lung diseases such as asbestosis. Asbestos fibers cause the accumulation of macrophages in the pleura and lung. When these macrophages encounter asbestos, they release TNF- α . At the same time, asbestos induces the secretion of TNF- α and the expression of TNF- α receptor I (TNF-RI) in mesothelial cells (Yang et al., 2006). Remarkably, treatment of mesothelial cells with TNF- α significantly reduced asbestos cytotoxicity. Indeed, TNF- α activates NF- κ B, which in turn promotes mesothelial cell survival and resistance to the cytotoxic effects of asbestos. Thus, TNF- α signaling through NF- κ B-dependent mechanisms increases the percentage of mesothelial cells that survive asbestos exposure, thereby increasing the pool of asbestos-damaged cells susceptible to malignant transformation (Haegens et al., 2007; Janssen-Heininger et al., 1999; Yang et al., 2006).

It has been reported that rats receiving a single intratracheal instillation of fibrogenic chrysotile asbestos developed lung chronic inflammatory reactions characterized by the accumulation of alveolar macrophages producing elevated levels of both Interleukin (IL)-1 and IL-6 (Lemaire & Ouellet, 1996). An increased production and/or release of these cytokines triggers inflammatory cell recruitment, thus amplifying and sustaining local inflammation. It has also been demonstrated that crocidolite asbestos and TNF- α can stimulate a dose-dependent increase in IL-6 expression and secretion from cultured, transformed and normal, human alveolar type II epithelial cells that is dependent upon intracellular redox potential (Simeonova et al., 1997). Interestingly, although MM cells appear to express low levels of IL-6 receptor (IL-6R), IL-6 can act as a growth factor for these cells through a trans-signaling mechanism involving the interaction of macromolecular complexes of IL-6 and soluble IL-6R (sIL-6R) with the transmembrane glycoprotein gp130 expressed on the surface of MM cells (Adachi et al., 2006; Rose-John et al., 2007). High levels of both IL-6 and sIL-6R are typical of several chronic inflammatory conditions (Rose-John et al., 2007).

Thus, inflammatory cytokines such as TNF- α and IL-6 appear to play a dual role in MM pathogenesis: they induce and sustain pleural inflammation and at the same time can act as survival or mitogenic factors for normal and transformed mesothelial cells, respectively.

2.2. Reactive Oxygen and Nitrogen Species (ROS/RNS)

The mechanisms of injury and disease development caused by asbestos fibers are presumed to be related to their greater fibrogenic and carcinogenic properties in comparison to other minerals. Asbestos-induced mutagenicity is mediated through both direct and indirect pathways. Asbestos fibers may induce mutagenicity and genotoxicity directly through physical interaction with the mitotic machinery after being phagocytized by the target cells, or indirectly as a result of DNA and chromosome damage caused by asbestos-induced reactive oxygen (ROS) and nitrogen species (RNS) (Kamp & Weitzman, 1999; Shukla et al., 2003a, 2003b). ROS and RNS can be generated primarily by asbestos fibers or secondarily through fiber-induced inflammation (Aust et al., 2011; Gulumian, 2005; Hoidal, 2001). Free radicals generated from asbestos fibers plus the direct damage induced by the fibers are linked to cell signaling, inflammation, and a plethora of other responses (mutagenesis, proliferation, etc.) associated with the pathogenesis of asbestos-associated diseases (Heinz et al., 2010; Manning et al., 2002; Shukla et al., 2003a, 2003b).

Several evidences indicate that a main factor in determining the surface and biological reactivity of different types of asbestos fibers is their ability to participate in redox reactions that generate free radicals (Kamp & Weitzman, 1999; Shukla et al., 2003a). Although the nature of the free radical-generating surface sites on asbestos fibers is not yet clear, asbestos fibers have an intrinsic redox activity and contain ferrous iron, which catalyzes reactions generating active oxygen intermediates on the fiber surface. Within the tissues several asbestos fiber types can produce reactive oxygen free radicals from hydrogen peroxide, a common product of intermediary tissue metabolism. Epidemiological studies have identified crocidolite as one of the most potent forms of asbestos associated with the induction of MM (Heintz et al., 2010). Crocidolite has a greater surface-area and a higher ferrous iron content compared to other fiber types such as chrysotile, and it is more biologically active in the generation of free radicals (Toyokuni, 2009). However, the ability of asbestos fibers to elicit these effects is not related to total iron content, suggesting the presence of specific iron active sites at the fibers' surface (Shukla et al., 2003a).

Cells exposed to asbestos have also been reported to produce a higher amount of nitric oxide (NO). In this regard, it has been reported that in human mesothelial cells crocidolite increases the expression of the inducible NO synthase (NOS) isoform (iNOS), the activity of the constitutive endothelial NOS (eNOS), and the synthesis of NO via NF- κ B and Akt activation (Riganti et al., 2007). Thus, the asbestos-induced upregulation of iNOS or NO in the lungs, as well as the induction of inflammation by fibers, may contribute along with ROS, to the pathogenesis of lung and pleural injury (Hussain et al., 2003; Tanaka et al., 1998). Indeed, ROS and RNS can cause breakage of DNA, lipid peroxidation, release of inflammatory cytokines such as TNF- α , and the modification of cellular proteins including phosphatases involved in cell signaling cascades (Gossart et al., 1996; Hussain et al., 2003), so that their increased synthesis by various cell types may have multiple roles in cellular events critical to the establishment of lung and pleural inflammation and uncontrolled cell proliferation.

Finally, in mesothelial and lung epithelial cells asbestos fibers, as opposed to nonpathogenic minerals, cause a persistent induction of the redox-sensitive transcription factors NF- κ B and Activator Protein-1 (AP-1), which is accompanied by chronic alterations in gene expression (Heintz et al., 1993; Janssen et al., 1995). As mentioned above, the aberrant activation of the NF- κ B pathway is regarded as a critical event for mesothelial cell transformation (Toyooka et al., 2008).

2.3. Transcription factors

2.3.1. NF- κ B

NF- κ B proteins are dimeric transcription factors composed of five different subunits, namely p65 (RelA), RelB, c-Rel, NF- κ B1 p50 and NF- κ B2 p52, which regulate gene expression events that impact on cell survival and differentiation. Moreover, since activation of NF- κ B is critical in up-regulating the expression of many genes linked to proliferation, apoptosis resistance, and chemokine/cytokine production, this is undoubtedly a critical transcription factor in inflammatory responses occurring in target cells of asbestos-related diseases (Janssen et al., 1995, 1997).

In unstimulated cells, the NF- κ B transcription dimers are retained in the cytoplasm in an inactive state through the interaction with a family of inhibitors called I κ Bs (Inhibitors of κ B) or with the p50 and p52 precursor proteins, p105 and p100, respectively (Hayden & Ghosh, 2008; Scheidereit, 2006). Indeed, p50 and p52 are translated as precursor proteins containing an I κ B-like C-terminal portion (Sun, 2011).

Two different NF- κ B-activation pathways exist: the classical and the alternative NF- κ B pathway. The classical NF- κ B pathway is initiated by signals elicited by diverse receptors, including TNF receptors type 1/2, Toll/IL-1 receptor, T-cell and B-cell receptors and EGF receptor, and also by cellular stresses and DNA damage (Hayden & Ghosh 2004; Le Page et al., 2005). These signals induce the activation of the I κ B kinase (IKK) complex, which is composed by the catalytic subunits IKK α and IKK β and by the regulatory subunit IKK γ /NEMO (Hayden & Ghosh, 2008; Scheidereit, 2006; Sun, 2011). The activated IKK complex phosphorylates I κ B proteins, thereby triggering their proteasomal degradation. As a consequence, NF- κ B dimers are released and can translocate into the nucleus. This pathway mainly leads to the activation of p50:RelA dimers (Sun, 2011). Conversely, the alternative NF- κ B pathway predominantly targets activation of RelB:p52 complexes. This pathway relies on the inducible processing of p100 triggered by signaling from TNF receptor family members via the NF- κ B-inducing kinase (NIK): NIK activates IKK α , which, in turn, phosphorylates p100 and triggers its processing to p52. This event results in the conversion of p100-inhibited NF- κ B complexes into p52-containing NF- κ B dimers, capable of translocating into the nucleus (Hayden & Ghosh, 2008; Scheidereit, 2006; Sun, 2011).

NF- κ B-regulated genes have distinct requirements for NF- κ B dimers. For instance, the NF- κ B binding site of the IL-2 gene has been reported to bind preferentially c-Rel homodimers

and p50:c-Rel, while that of the gene encoding IL-8 has been found to selectively bind Rel A (Hoffman et al., 2003, 2006). On the other hand, several genes are redundantly induced by more than one dimer (Hoffman et al., 2003, 2006; Sacconi et al., 2003).

A number of studies have shown that nuclear retention and DNA binding of NF- κ B protein complexes are increased following exposure of various cell types to a variety of extracellular stimuli that include oxidative stress (Bowie & O'Neill, 2000), hypoxia (Jung et al., 2003; Royds et al., 1998) and inflammatory cytokines (Mantovani et al., 2008). These observations are consistent with the hypothesis that persistent activation of NF- κ B can contribute to the induction of multiple genes that are critical to the pathogenesis of asbestos-associated diseases, since oxidants, local hypoxia and inflammatory cytokines are all components involved in the effects induced by asbestos exposure.

It is noteworthy that among various carcinogenic and non-carcinogenic fibers studied for their effect on nuclear translocation of NF- κ B, only carcinogenic fibers were found to cause a dose-dependent translocation of this transcription factor to the nucleus, and this effect was reported to be oxidative stress-dependent (Brown et al., 1999). In lung macrophages, the asbestos-induced expression and secretion of TNF- α are mediated by iron-catalyzed ROS products (Simeonova & Luster, 1995) through a process that involves NF- κ B activation (Cheng et al., 1999). In rat alveolar type 2 cells, the crocidolite-induced activation of NF- κ B as well as the expression of the macrophage inflammatory protein-2 (MIP-2) gene have also been shown to be dependent on mitochondrial-derived oxidative stress (Driscoll et al., 1998).

2.3.2. AP-1

AP-1 is a homo- or heterodimeric transcription factor composed by proteins encoded by the *fos* and *jun* early response proto-oncogenes. This family of proteins includes c-Fos, FosB, FosL1 (Fra-1), FosL2 (Fra-2), c-Jun, JunB and JunD (Milde-Langosch, 2005). Whereas Jun members are capable of forming homodimers able to bind DNA and regulate transcription, all Fos members must form heterodimers with Jun family members to bind DNA.

AP-1 is a redox-sensitive transcription factor typically associated with cell proliferation and tumor promotion (Eferl & Wagner, 2003). The first evidence showing that asbestos exerts regulatory effects linked to aberrant transcriptional responses, cell proliferation and cell transformation derives from studies in which asbestos fibers caused induction of *c-fos* and *c-jun* proto-oncogene mRNAs in pleural mesothelial cells and tracheo-bronchial epithelial cells in a dose-response fashion (Heintz et al., 1993).

The persistent induction of AP-1 by asbestos suggests a model of asbestos-induced carcinogenesis involving chronic stimulation of cell proliferation through activation of early response genes (Schonthaler et al., 2011). Of note, early response genes are a set of genes whose transcription is rapidly induced in response to growth factors. Furthermore, AP-1 activity is induced by growth factors, pro-inflammatory cytokines and genotoxic stress (Jochum et al., 2001; Shaulian & Karin, 2002). These stimuli activate mitogen-activated protein kinase (MAPK) cascades through the phosphorylation of distinct substrates such as

ERK, JNK and p38 MAPK (Chang & Karin, 2001). Indeed, the MAPK signal transduction pathway uses AP-1 as a converging point not only to regulate the expression of various genes but also to autoregulate AP-1 gene transcription (Reuter et al., 2010).

Several genes, which play very important roles in injury, repair, and differentiation, contain binding site(s) for AP-1 in their promoter and/or enhancer regions (Chang & Karin, 2001). These genes include extracellular matrix metalloproteinases (MMPs), antioxidant enzymes, growth factors and their receptors, differentiation markers, cytokines, chemokines and other transcription factors (Shaulian & Karin, 2001).

2.3.3. Nuclear Factor of Activated T Cells (NFAT)

The Nuclear Factor of Activated T cells (NFAT) family of transcription factors consists of five proteins that are evolutionarily related to the Rel/NF- κ B family. NFAT can be present in both the cytoplasm and the nucleus. In the cytoplasm NFAT is in a highly phosphorylated, inactive state. Cell stimuli leading to the elevation of intracellular Ca^{2+} levels induce the activation of the phosphatase PP2B/Calcineurin which dephosphorylates NFAT. This results in its nuclear relocation and transcriptional activation. Interestingly, NFAT family members can act synergistically with AP-1 on composite DNA elements which contain adjacent NFAT and AP-1 binding sites (Macián et al., 2001). A functional cooperation has also been reported to occur between NFAT and NF- κ B (Jash et al., 2012).

Initially, NFAT was identified in lymphocytes and was reported to be expressed in activated but not resting T cells (Macián et al., 2005; Shaw et al., 1988). NFAT regulates not only T cell activation and differentiation but also the function of other immune cells, including dendritic cells (DCs), B cells and megakaryocytes. In addition, NFAT has crucial roles in numerous developmental programs in vertebrates.

Dysregulation of NFAT signalling is now known to be associated with malignant transformation and the development of cancer (Mancini & Toker, 2009; Müller & Rao, 2010). The observation that NFAT can be activated by asbestos-induced oxidative stress suggests that this transcription factor may play multiple roles in asbestos-induced inflammation and carcinogenesis (Li et al., 2002). Indeed, NFAT mediates the expression of several inflammatory cytokines, including TNF- α , and is involved in cell transformation, proliferation, invasive migration, tumor cell survival and tumor angiogenesis (Mancini & Toker, 2009).

3. Multifaceted role of angiogenic growth factors in MM

Angiogenesis is a common feature of solid tumors. Indeed, the development of a clinically observable tumor requires the neoformation of a vascular network sufficient to sustain tumor growth (Ribatti et al., 2007). Tumor angiogenesis is stimulated by the secretion of angiogenic molecules which induce endothelial cells from nearby vessels to switch from a quiescent to an activated state. Further, upon the stimulation of angiogenic growth factors, activated endothelial cells disrupt the extracellular matrix, proliferate and migrate (Ribatti et

al., 2007). Angiogenic growth factors include, among the others, Vascular Endothelial Growth Factor (VEGF), Placenta Growth Factor (PlGF), Platelet-Derived Growth Factor (PDGF) and acidic and basic Fibroblast Growth Factors (FGF-1 and -2, respectively). VEGF is regarded as the most important player in angiogenesis (Ono, 2008).

The link between angiogenesis and tumor progression is provided by the negative prognostic value of intratumoral microvascular density (IMD) (Folkman, 2006; Kerbel, 2008). In MM the IMD has an independent prognostic value (Kumar-Singh et al., 1997). MM demonstrates a higher IMD than colon and breast tumors and, consistently, presents with minimal central necrosis despite its huge size (Gasparini & Harris, 1995; Kumar-Singh et al., 1997).

On the other hand, the involvement of angiogenic growth factors in MM goes beyond the stimulation of angiogenesis. Indeed, as discussed below, MM cells express receptors for several angiogenic factors which, accordingly, can directly modulate MM cell behavior.

3.1. Angiogenic growth factors of the VEGF family

The human VEGF family consists of five members: VEGF (VEGF-A), VEGF-B, VEGF-C, VEGF-D and PlGF. These growth factors are secreted as dimers and their biological effects are mediated by binding to three tyrosine kinase receptors, *i.e.* VEGF-R1/Flt-1, VEGF-R2/KDR (whose murine homologue is known as Flk-1) and VEGF-R3/Flt-4, and two non-enzymatic co-receptors known as neuropilin-1 and -2 (Ferrara et al., 2003; Koch et al., 2011; Roskoski, 2007).

3.1.1. VEGF

VEGF is regarded as the major mediator of tumor angiogenesis. It is expressed in the majority of cancers and has a central role in tumor growth and metastasis. In fact, this growth factor is essential for the mobilization of bone-marrow-derived endothelial precursors in neovascularization (Asahara et al., 1999), and stimulates vascular endothelial cells mobility, proliferation and survival (Waltenberger et al., 1994).

High levels of VEGF are present both in malignant and non-malignant pleural effusions leading to increased vascular permeability. On the other hand, VEGF levels in serum or pleural effusions of MM patients are higher than those found in patients with non-malignant pleuritis or lung cancer involving malignant pleural effusions. Further, in MM patients elevated serum or pleural effusion levels of VEGF correlate with a worse prognosis and may also contribute to increase resistance to chemotherapy (Hirayama et al., 2011; Yasumitsu et al., 2010; Zebrowski et al., 1999). In fact, VEGF status has proved to be of value in predicting the effectiveness of radiotherapy and chemotherapy on different cancers (Choi et al., 2008; Kumar et al., 2009; Toi et al., 2001).

In addition to its role in tumor vascularization, VEGF can directly affect the behavior of cancer cells in an autocrine or paracrine manner. Indeed, many tumor cell types express VEGF receptors. VEGF has been found to promote the growth of transformed cell lines *in vitro* (Masood et al., 2001) and to act as a survival factor for tumor cells by enhancing the

expression of the antiapoptotic factors bcl-2 (Harmey & Bouchier-Hayes, 2002) and survivin (Kanwar et al., 2011). In this context, MM cells have been shown to express high amounts of VEGF, VEGF receptors and co-receptors both *in vitro* and *in vivo*, and VEGF has been demonstrated to act as an autocrine growth factor for this tumor cell type (Albonici et al., 2009; Ohta et al., 1999; Pompeo et al., 2009; Strizzi et al., 2001a).

VEGF-R1 participates in cell migration; it has an important role in monocyte chemotaxis and promotes recruitment of circulating endothelial precursor cells from bone marrow (Hattori et al., 2002). Its expression is increased in various tumors, correlates with disease progression and can predict poor prognosis, metastasis and recurrent disease in humans (Dawson et al., 2009; Fischer et al., 2008; Kerber et al., 2008). This receptor is also expressed by MM cells *in vitro* and *in vivo*, where it appears to mediate proliferative and cell survival responses (Albonici et al., 2009; Strizzi et al., 2001a).

VEGF-R2 is the main mediator of VEGF-stimulated endothelial cell migration, proliferation, survival and enhanced vascular permeability (Olsson et al., 2006; Shibuya, 2006). VEGF-R2 expression is induced in conjunction with active angiogenesis, such as during the reparative process, and in pathological conditions associated with neovascularization, such as cancer (Plate et al., 1993). VEGF-R2 is overexpressed in MM cells and specimens, and VEGF-R2 silencing by small interfering RNA has been shown to induce cell death in MM or immortalized mesothelial cells *in vitro* (Albonici et al., 2009; Catalano et al., 2009; Pompeo et al., 2009; Strizzi et al., 2001a). Interestingly, it has been reported that in MM cells this receptor can be activated also via the semaphorin-6D receptor Plexin-A1, triggering a prosurvival program that promotes anchorage-independent growth through a NF- κ B-dependent pathway (Catalano et al., 2009). Remarkably, the expression of plexin-A1 is induced by asbestos fibers and overexpression of plexin-A1 in non-malignant mesothelial cells inhibits cell death after asbestos exposure, thus suggesting a role for this receptor not only in MM promotion and progression but also in asbestos-induced mesothelial carcinogenesis (Catalano et al., 2009).

In vitro studies have shown that transfection of normal mesothelial cells with SV40 Tag potently increases VEGF protein and mRNA levels (Cacciotti et al., 2002) as well as mesothelial cell proliferation (Catalano et al., 2002). These data indicate that VEGF regulation by SV40 transforming proteins can also represent a key event in MM onset and progression.

3.1.2. PlGF

PlGF, originally identified in the placenta during the early embryonic development (Khaliq et al., 1996; Maglione et al., 1991), is expressed in several other organs including the heart, lung, thyroid, skeletal muscle and adipose tissue (Persico et al., 1999) but not normal mesothelium (Albonici et al., 2009).

Although the role exerted by PlGF in tumor growth is controversial yet, PlGF can stimulate vessel growth and maturation directly by affecting endothelial and mural cells, as well as indirectly by recruiting pro-angiogenic cell types (Barillari et al., 1998; Carmeliet, 2003). It

also promotes the recruitment and maturation of angiogenesis-competent myeloid progenitors to growing sprouts and collateral vessels (Hattori et al., 2002; Luttun et al., 2002; Rafii et al., 2003). Further, PlGF is able to protect endothelial cells from apoptosis, in a similar manner as VEGF, by inducing the expression of antiapoptotic genes such as survivin (Adini et al., 2002).

Under pathological conditions, PlGF abundance is elevated in various cell types and tissues, including vascular endothelial cells, and many different tumor cells (Albonici et al., 2009; Cao et al., 1996; Fischer et al., 2007; Oura et al., 2003). PlGF expression is switched on in hyperplastic/reactive mesothelium and in MM cells (Albonici et al., 2009). Moreover, in MM as well as in different types of cancer, including melanoma, gastric, colorectal and breast carcinomas, PlGF plasma levels and intratumoral expression have been found to correlate with tumor stage, vascularity, recurrence, metastasis and survival (Chen et al., 2004; Marcellini et al., 2006; Parr et al. 2005; Pompeo et al., 2009; Wei et al., 2005).

In vitro studies have shown that administration of recombinant PlGF to MM cells triggers the activation of Akt but does not elicit a significant stimulation of cell growth. Conversely, the administration of PlGF-neutralizing antibodies causes a significant reduction of MM cell viability, demonstrating the PlGF acts as a survival factor for MM cells (Albonici et al., 2009).

PlGF binds VEGF-R1 and the co-receptors neuropilin-1 and -2, but, unlike VEGF, it does not bind VEGF-R2. Accordingly, it can act independently of VEGF in cells which primarily express VEGF-R1 (Fischer et al., 2007). Worthy of note, even though VEGF and PlGF both bind VEGF-R1, PlGF was reported to stimulate the phosphorylation of specific VEGF-R1 tyrosine residues and the expression of distinct downstream target genes as compared to VEGF (Autiero et al., 2003). On the other hand, PlGF can also sustain VEGF activity through different mechanisms involving both VEGF-R1 and VEGF-R2. One of these mechanisms relies on the formation of PlGF:VEGF heterodimers. Indeed, PlGF:VEGF heterodimers have been isolated from cells producing both factors and shown to bind VEGF-R1:VEGF-R2 receptor complexes, thus inducing receptor cross-talk and activation of VEGF-R2, the major mediator of VEGF activities (Autiero et al., 2003; Cao et al., 1996). In addition, the activation of VEGF-R1 by PlGF homodimers may induce the intermolecular transphosphorylation and activation of VEGF-R2 (Carmeliet et al., 2001).

It is noteworthy that *in vivo* anti-PlGF treatment was reported to inhibit tumor growth without affecting healthy vessels, thus reducing tumor infiltration by angiogenic macrophages and severe tumor hypoxia, and preventing the switch on of the angiogenic rescue program leading to the enhanced release different angiogenic factors responsible for resistance to VEGF receptors inhibitors (Fischer et al., 2007).

3.2. PDGF

PDGFs comprise a family of dimeric growth factors structurally and functionally related to VEGFs (Andrae et al., 2008). PDGF homodimers are formed by four different chains, *i.e.* PDGF-A, PDGF-B, PDGF-C and PDGF-D. In addition, PDGF-A and -B chains can form the

heterodimeric PDGF-AB. The biological effects of PDGF are mediated by two tyrosine kinase receptors, namely the PDGF receptor alpha (PDGFR α), which binds PDGF-A, -B, and -C chains, and the PDGF receptor beta (PDGFR β), which binds PDGF-B and -D. Accordingly, upon ligand binding different receptor dimers may form depending on ligand configuration and the pattern of receptor expression. Cellular responses to PDGF signaling include stimulation of cell growth, differentiation, migration and inhibition of apoptosis (Andrae et al., 2008).

An increased PDGF activity has been linked with tumors, vascular and fibrotic diseases (Andrae et al., 2008). Autocrine PDGF signaling leading to enhanced proliferation of tumor cells occurs in several types of cancer (Ostman, 2004). In addition, PDGF secretion by cancer cells and activated endothelial cells promotes the formation of both fibrous and vascular tumor stroma. In particular, PDGF-BB participates in tumor angiogenesis by stimulating endothelial cell motility and pericyte recruitment to neoformed vessels, thus leading to vessel stabilization, tumor cell survival and growth. Instead, both PDGF-AA and PDGF-BB appear involved in tumor recruitment of PDGFR-positive fibroblasts which, in turn, can be activated by PDGFs to produce VEGF and other tumor-promoting growth factors (Andrae et al., 2008; Cao et al., 2008; Homsí & Daud, 2007).

Either high PDGF-AB serum levels or a strong expression of PDGFR signaling effectors in MM tissues have been associated with a lower survival in MM patients (Filiberti et al., 2005; Kothmaier et al., 2008). In fact, several evidence support a role for PDGF in MM promotion and progression through both autocrine and paracrine mechanisms.

While PDGFR α expression levels are lower in MM than in normal mesothelial cells, PDGFR β , PDGF-A and PDGF-B are overexpressed in MM cells as compared to their non-transformed counterparts (Langerak et al., 1996a, 1996b; Metheny-Barlow et al., 2001). Functional studies have shown that transduction of MM cells with a hammerhead ribozyme against PDGFR β mRNA reduced both PDGFR β expression and MM cell proliferation, demonstrating the involvement of a PDGF-BB autocrine loop in MM cell growth (Dorai et al., 1994). Conversely, the role of PDGF-A in MM cell proliferation is controversial. Indeed, the transfection of MM cells with antisense oligonucleotides to PDGF-A has been reported to either inhibit or stimulate MM cell growth *in vitro* (Garlepp & Leong, 1995; Metheny-Barlow et al., 2001). On the other hand, PDGF-A appears to play an important role in sustaining MM cell growth *in vivo* through paracrine mechanisms. Indeed, PDGF-A overexpression in MM cells inoculated in nude mice was found to increase tumor incidence, tumor growth rate and to decrease the latency period to tumor formation (Metheny-Barlow et al., 2001). In this regard, it has been suggested that PDGF-A participates in a malignant cytokine network through which MM cells instigates tumor-associated fibroblasts to produce growth factors, such as hepatocyte growth factor (HGF), with tumor-promoting activities (Li et al., 2011).

3.3. FGF

The FGF family encompasses 22 structurally related ligands in mammals. The effects of most FGF family members, including FGF-1 and -2, are mediated by binding to a family of

tyrosine kinase receptors designated FGF receptors (FGFR1 to FGFR5), whereas a smaller number of FGF isoforms does not bind FGFRs but interacts with voltage-gated sodium channels (Knights & Cook, 2010).

FGFs regulate cell proliferation, differentiation, survival, wound healing and angiogenesis. In cancer, FGF signaling is frequently de-regulated, resulting in mitogenic, anti-apoptotic and angiogenic responses (Knights & Cook, 2010). FGF-1 and -2, but also other less-studied FGF isoforms, exert pro-angiogenic effects by modulating proliferation and migration of endothelial cells and by stimulating the production of proteases (Lieu et al., 2011; Saylor et al., 2012). Worthy of note, it has been demonstrated that FGF-2 can synergize with both VEGF and PDGF-BB in stimulating neovascularization, this synergism relying on multiple mechanisms. For instance, FGF-2 promotes hypoxia-induced VEGF release by cancer cells and the expression of both VEGF and VEGFRs in endothelial cells, whereas VEGF, in turn, upregulates the expression of FGF-2 (Lieu et al., 2011; Saylor et al., 2012). Moreover, FGF-2 upregulates PDGFRs expression and increases the responsiveness to PDGF-BB in endothelial cells, whereas PDGF-BB enhances FGFR1 expression and FGF-2 responsiveness in vascular smooth muscle cells (Cao et al., 2008; Liu et al., 2011). Remarkably, FGFs are thought to play a critical role in the resistance to anti-VEGF therapy (Lieu et al., 2011; Saylor et al., 2005). Besides, both FGF-1 and -2 may also be involved in tumor cell growth through cell-autonomous, autocrine mechanisms (Kumar-Singh et al., 1999).

FGF-1 and -2 are expressed in the majority of MMs *in vivo* and high levels of FGF-2 in tumor tissues, serum or pleural effusions are associated with a worse prognosis in MM patients (Davidson et al., 2004; Kumar-Singh et al., 1999; Strizzi et al., 2001b). Furthermore, the combined expression levels of FGF-1, FGF-2, VEGF and Transforming Growth Factor beta (TGF β) in MM tissues correlates with both IMD and a poorer prognosis (Kumar-Singh et al., 1999). In addition to their role in tumor angiogenesis, FGFs act as autocrine growth factors for MM cells. Indeed, MM cells express FGFs and FGF receptors and the transfection with short interfering RNAs to FGF-1 and FGF-2 reduces MM cell proliferation (Kumar-Singh et al., 1999; Liu & Klominek, 2003; Stapelberg et al., 2005). It has also been reported that treatment of MM cells with exogenous FGF-2 stimulates the secretion of matrix metalloproteinases involved in tumor invasion and angiogenesis (Liu & Klominek, 2003).

4. Cross-talk between inflammation and angiogenic growth factors

Experimental and epidemiological evidences indicate that chronic inflammation is associated with most, if not all, tumors and supports their progression (Coussens & Werb 2002; Mantovani et al., 2008; Mantovani et al., 2010; Porta et al., 2009). Chronic inflammation appears to have a versatile function in tumor onset and progression. Indeed, as discussed above, a long-lasting inflammation can contribute to cancer initiation through the production ROS and RNS with DNA-damaging properties. On the other hand, it can also participate in cancer promotion and progression by increasing the availability of mediators (growth factors, cytokines, chemokines, prostaglandins) which contribute to the growth of initiated cells and to neoangiogenesis (Mantovani, 2010). Besides, once a tumor is

established, cancer cells promote a constant influx of myelomonocytic cells that express inflammatory mediators supporting pro-tumoral functions. In this regard, myelomonocytic cells are key orchestrators of cancer-related inflammatory processes supporting proliferation and survival of malignant cells, subversion of adaptive immune responses, stromal remodeling and angiogenesis (David Dong et al., 2009; Loges et al., 2009; Porta et al., 2009).

Tissue infiltration by macrophages is a dramatic and common feature of inflammation, angiogenesis and cancer (Pollard, 2004; Sica, 2010). High densities of tumor-infiltrating macrophages are associated with poor survival in patients with MM (Burt et al., 2011). In fact, the recruitment and infiltration of macrophages in the tumor microenvironment can activate them to support the malignant progression of cancer cells. These macrophages are called tumor-associated macrophages (TAMs) (Lawrence, 2011; Sica, 2010). Cancer cells co-cultured with macrophages and incubated with inflammatory cytokines are synergistically stimulated to produce various angiogenesis-related factors (Izzi et al., 2009; Ono, 2008). This inflammatory angiogenesis is mediated, in part, by activation of NF- κ B and AP-1 (Angelo & Kurzrock, 2007; Huang et al., 2000; Ono, 2008). In fact, treatment of both vascular endothelial cells and cancer cells with IL-1 α/β , TNF- α and ROS *in vitro* results in a marked induction of VEGF and FGF-2, through the transcriptional activation of NF- κ B, Specificity protein 1 (Sp-1), AP-1 and hypoxia response elements.

In addition to macrophages, other tumor-infiltrating immune cells including T cells, B cells, natural killer cells and neutrophils can release cytokines, such as IL-1 α/β , TNF- α and IL-6, able to sustain the synthesis of angiogenic growth factors (Angelo & Kurzrock, 2007). As for, IL-6, this pro-inflammatory cytokine has been reported to play a critical role in the stimulation of VEGF synthesis by different cell types, including MM cells (Adachi et al., 2006; Angelo & Kurzrock, 2007). Of note, MMs usually produce high levels of IL-6 but express low levels of IL-6R, so that the presence of sIL-6Rs, which may be provided by inflammatory cells recruited to the tumor region, is essential for the IL-6-dependent stimulation of VEGF expression by MM cells (Adachi et al., 2006). Inflammation can also induce the expression of receptors for angiogenic growth factors. In this regard, the expression of PDGFRs is known to be induced by inflammatory cytokines such as TNF- α and IL-1 (Andrae et al., 2008). Besides, inflammatory cells themselves can directly release angiogenic factors such as VEGF, PlGF, FGF-2 and PDGF, among many others, which exert mitogenic and migratory effects on surrounding cells (Sica 2010, Ono 2008). Inflammatory cells recruited in the tumor microenvironment can also produce matrix metalloproteinases which promote the formation of new vessels by degrading the basement membrane and by releasing angiogenic growth factors, such as VEGF, PlGF-2 and FGF-2, stored in the extracellular matrix (Barillari et al., 1998; Cao et al., 2008; Lieu et al., 2011).

The high amount of chemokines/cytokines, growth factors, proteolytic enzymes, proteoglycans, lipid mediators and prostaglandins which is typically found in the tumor microenvironment sustains and exacerbates both inflammation and angiogenesis (Costa et al., 2007; Lin & Karin, 2007; Ono, 2008). In this context, the cross-talk between inflammation and angiogenesis is further corroborated by the evidence that, if on one hand inflammatory mediators have significant effects on angiogenesis, on the other hand angiogenic factors can

effectively promote inflammation. As a matter of fact, in addition to their angiogenic role, VEGF and PlGF appear to act as direct proinflammatory mediators in the pathogenesis of different inflammatory conditions (Angelo & Kurzrock, 2007; Yoo et al., 2008). In this regard, VEGF was found to increase the production of TNF- α and IL-6 by human peripheral blood mononuclear cells and macrophages (Yoo et al., 2008). Moreover, VEGF stimulates monocyte recruitment to tumor areas (Barleon et al., 1996). An additional link between inflammatory and angiogenic growth factors has been provided with the demonstration that in myelomonocytic cells TNF- α is upregulated by PlGF in a NFAT1-dependent manner and, in turn, contributes to PlGF-induced myelomonocytic cell recruitment (Ding et al., 2010). PlGF can also contribute to inflammation by acting as survival factor for monocytes and macrophages (Adini et al., 2002).

5. Cooperation between asbestos and angiogenic growth factors in MM onset and progression

As reported above, asbestos stimulates the expression of *c-fos* and *c-jun* mRNA in mesothelial cells in a dose-dependent fashion (Heintz et al., 1993; Ramos-Nino et al., 2002). One of the mechanisms by which VEGF and PlGF elicit biological responses is the induction of Fos-B and c-Fos expression in endothelial cells and monocytes (Holmes & Zachary, 2004). The coexistence of different stimuli, such as asbestos fibers and angiogenic growth factors, concurring to the activation of early response genes might lead to the persistent induction of AP-1 in mesothelial cells and to the chronic stimulation of mesothelial cell proliferation, thus favoring cell transformation.

Further, asbestos and angiogenic growth factors can cooperate in inducing an immunosuppressive tumor microenvironment. Indeed, asbestos has been found to possess immunosuppressive properties. For example, chrysotile fibers have been shown to depress the *in vitro* proliferation of phytohemagglutinin-stimulated peripheral blood lymphocytes and to suppress natural killer activity. Moreover, asbestos significantly reduces the generation and activity of lymphokine-activated killer (LAK) cells, which are immune effectors with a strong lytic activity against MM cells (Manning et al., 1991; Valle et al., 1998).

Immunosuppressive properties have been reported for angiogenic growth factors as well (Ohm et al., 2001; Ziogas et al., 2012). Impaired antigen-presenting function in DCs as a result of abnormal differentiation is an important mechanism of tumor escape from immune control. It has been demonstrated that VEGF can inhibit the maturation of DCs induced by lipopolysaccharide (Takahashi et al., 2004). VEGF can also affect the ability of hematopoietic progenitor cells (HPCs) to differentiate into functional DCs during the early stages of hematopoiesis *in vivo* (Gabrilovich et al., 1996; Oyama et al., 1998). In this regard, it has been shown that VEGF binds to specific receptors on the surface of HPCs and this binding appears to involve VEGF-R1. Interestingly, the number of binding sites available for VEGF decreased with DC maturation and correlated with decreased levels of VEGF-R1 mRNA expression in the late-stage cells (Gabrilovich et al., 1996). PlGF was also found to inhibit the

activation and maturation of human DCs effectively and rapidly through the NF- κ B pathway (Lin et al., 2007). The results of this study further indicate that by modulating the function of DCs, PlGF can down-regulate T helper immune responses (Lin et al., 2007). In addition, both VEGF and PlGF are also involved in the recruitment of macrophages with immunosuppressive, tumor-promoting roles to the tumor stroma.

On the whole, these findings suggest mechanisms by which tumor-derived soluble factors such as VEGF or PlGF may synergize with asbestos to down-regulate immune responses to MM antigens.

6. Conclusions

Collectively, the reported findings demonstrate that a complex network involving asbestos, inflammation and angiogenic factors upregulation is involved in the pathogenesis of MM. In particular, the abnormal expression of angiogenic factors appears to play multiple roles in MM: it stimulates tumor neovascularization, increases pleural effusion formation by increasing vascular permeability, supports autocrine tumor cell growth and finally, in synergism with asbestos fibers, can sustain inflammation and bias host immune responses. Accordingly, the upregulation of angiogenic growth factors appears to be a crucial event in mesothelial cell transformation and MM progression.

Given the involvement of multiple angiogenic growth factors in the formation of tumor vessels, in tumor inflammation and MM cell growth and survival, the therapeutic development of antiangiogenic agents for the treatment of this tumor should be aimed at blocking multiple growth factor signaling pathways and their complex interactive network (Cao et al., 2008; Ikuta et al., 2009; Homsí & Daud, 2007; Lieu et al., 2011).

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7. References

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