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# Stem Cells and Mesothelioma

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## 1. Introduction

Stem cells are self-renewing cells with the potential to differentiate into other cell types. Physiologically stem cells participate in hematopoiesis, wound healing, neuroregeneration, and many other important biological processes. It has been hypothesized that stem cells play a role in carcinogenesis. Although controversial, stem cell origin of cancers such as breast and prostate carcinomas and glioblastoma have been reported (Al-Hajj, 2003; Collins, 2005; Singh, 2004). In addition, stem cells are reported to be in the tumor microenvironment and potentially contribute to the tumorigenic process (Bergfeld & DeClerck, 2010). Such findings offer potentially new targets for tumor therapy.

Mesothelioma is an aggressive neoplasm of the mesothelial cell layer of pleura, peritoneum, pericardium and tunica vaginalis. Characterized by an aggressive disease course and resistance to current multimodality therapies, mesothelioma needs to be better characterized, including with an understanding of how stem cell biology and mesothelioma pathogenesis intersect. There is evidence for both a stem cell origin of mesothelioma, and a stem cell population in the mesothelioma tumor microenvironment. This review chapter aims to outline the evidence that stem cell biology does indeed intersect with mesothelioma pathogenesis, and that such findings offer important therapeutic targets for tumor therapy.

## 2. Stem cell origin of cancer

The concept of a stem cell origin of cancer was first described over fifty years ago as a small subset of cells capable of re-initiating a clonal tumor, and the first cancer stem cell population was identified in acute myeloid leukemia (Reya et al., 2001; Huntly & Gilliland, 2005). Cancer stem cells comprise only 0.01-1% of all cells in a tumor, but are capable of re-initiating the tumor while the other cell types cannot. Methods used to define the cancer stem cell vary, however at minimum require prospective selection by lineage; ability to re-initiate tumors that resemble the original tumor in serial tumor xenotransplantation; and display stem cell properties such as self-renewal and multipotential differentiation (Tang et al., 2007). Moreover, these assays most likely underestimate the percentage of cells capable of re-initiating tumor, given that xenotransplantation requires tumor re-initiation in a foreign environment lacking the presence of other cell types that play a supportive role in tumorigenesis (Adams & Strasser, 2008). Cancer stem cells are constituents of tumors that are not only capable of re-initiating tumors, but also likely contribute to resistance to therapy and metastasis. Recent evidence for a stem cell origin of solid tumors provides the

impetus to explore such mechanisms of tumorigenesis in mesothelioma (Al-Hajj et al., 2003; Collins et al., 2005; Singh et al., 2004).

It can be argued that a stem cell origin of mesothelioma would be consistent with the pathogenic course of this tumor. Asbestos exposure is reported in over 80% of cases of mesothelioma, and there is a latency period of several decades between exposure and diagnosis. Asbestos does not appear to be a direct mutagen, rather, alveolar macrophages undergo incomplete phagocytosis of the asbestos fibers and induce a chronic release of pro-inflammatory mediators that create a potentially mutagenic environment. Is the pathogenic time course and pro-inflammatory tumor microenvironment consistent with a stem cell origin of mesothelioma?

In 1975 Cairns hypothesized that adult stem cells minimize genetic mutations with asymmetric division that maintains an “immortal DNA strand” in the stem cell population, and passes along any mutations to the daughter cell that will terminally differentiate (Cairns, 1975). Therefore adult stem cells may have developed a protective mechanism against persistence of mutations in the stem cell population. However a dividing stem cell population under chronic mutagenic conditions such as the pro-inflammatory state in asbestos exposure, may be susceptible to mutagenesis and eventual tumorigenesis. The lengthy time course between asbestos exposure and development of mesothelioma may be a reflection of the longer length of time required to overcome the protective mechanism described by the Cairns hypothesis in stem cells (Browne, 1991). Although there is more supportive than conclusive evidence for the Cairns hypothesis, it offers a compelling explanation for a stem cell origin of mesothelioma.

### 3. Mesothelial progenitor and side population cells

Proliferative tissues such as skin and bone marrow are maintained by a stable population of progenitor cells with self-renewing properties. Tumors are also proliferative tissues, possibly maintained by a self-renewing cancer stem cell population. Therefore leukemia can be viewed as a tumor maintained by a subset of bone marrow progenitor cells that have tumor-initiating properties. Analogously, mesothelioma may be a tumor maintained by a mesothelial progenitor cell population. Normal mesothelium consists of a single layer of simple squamous mesothelial cells of mesodermal origin that function to maintain serosal fluid production in order to provide a frictionless and protective surface for organ movement. Mesothelial cells also participate in material transport across the serosal membrane; and mediate regulatory inflammatory, immune and tissue repair responses (Mutsaers, 2007).

There is evidence for a mesothelial progenitor cell population (Herrick, 2004). First, mesothelial cells express characteristics of mesodermal, epithelial and mesenchymal phenotypes- supportive evidence for multipotential differentiation of a progenitor cell population. In addition, mesothelial cells exhibit plasticity by transforming into tissues such as myofibroblasts and vascular grafts under specific growth conditions (Lv, 2011 & Sparks, 2002). After mesothelial tissue injury, new mesothelium regenerates from both cells at the wound edge and from the surrounding serosal fluid, which may be mesothelial progenitor cells capable of tissue regeneration. Mesothelial progenitor cells with such stem cell-like properties are potentially a source of a cancer stem cell population in mesothelioma.

Another potential cancer stem cell population in mesothelioma is side population (SP) cells. Defined as cells that efflux the DNA-binding dye Hoechst 33342, SP cells can be enriched for using flow cytometry. Side population cells express ATP-binding cassette (ABC) membrane transporters that efflux the Hoechst 33342 dye, and these transporters are also involved in efflux of drugs such as chemotherapeutics. Side population cells are found in both normal and malignant tissues. In cancer, SP cells have been considered a potential cancer stem cell population as well as a cell population responsible for resistance to therapy. SP cells have been identified as a potential cancer stem cell population in various tumors, including ovarian carcinoma and osteosarcoma (Fong, 2010 & Murase, 2009). A group that isolated SP cells from human malignant mesothelioma cell lines illustrated that SP cells had enhanced proliferation and higher expression of stem-cell genes (Kiyonori, 2010). However, the SP cells did not have increased tumorigenic potential in immunodeficient mice. A more recent study reported that SP cells isolated from malignant pleural mesothelioma not only expressed stem cell markers, but also showed self-renewal, chemoresistance, and tumorigenicity (Frei, 2011). Further the subset of SP cells characterized as WT1 negative/D2-40 positive/CD105 (low) were found to be even more tumorigenic. The increased stem cellness of the SP cells isolated from this study by Frei *et al.* compared to the study by Kiyonori *et al.* could be due to their isolation from malignant tissue rather than from mesothelioma cell lines. Since cancer stem cells remain to be fully characterized and defined, a diversity of cell types- including progenitor cells and side population cells- may qualify as cancer stem cells in tumors (Bjerkvig, 2005).

How a normal mesothelial progenitor cell or side population cell transforms into a cancer stem cell remains to be elucidated. Traditional thinking of transformation of a normal differentiated cell into a tumor cell requires multiple hits to the genome resulting in genetic instability and a selective survival advantage. Cancer stem cells may be products of a similar transformative process. Human mesothelial cells exposed to asbestos and SV40 virus were reported to transform via an Akt-mediated cell survival mechanism (Cacciotti, 2005). These authors concluded that mesothelioma originates from a subpopulation of transformed stem cells. More work illustrating this important concept is necessary and offers potential targets for therapy to abrogate this transformation process. Hypothetically, the advantage for a tumor to arise from a transformed stem cell rather than from a transformed differentiated cell includes the ability for the tumor to have multiple phenotypes for growth in different microenvironments; an additional mechanism for a metastatic phenotype; and resistance to current therapies. Interestingly, mesothelioma exhibits aspects of all three of these tumor characteristics.

Diffuse malignant mesothelioma can be classified histologically into three major classes: epithelioid, sarcomatoid, and mixed-type. Epithelioid is the most common phenotype and the mixed-type can be found in 30% of tumors. Sarcomatoid tumors are rare but carry the worst prognosis. There are also rare variants including desmoplastic, undifferentiated and deciduoid types. This wide variety of phenotypes could be explained by a cancer stem cell origin for mesothelioma, such as a transformed mesothelial progenitor cell population that has been shown to differentiate into multiple cell types. Currently, determining the histological subtype is important for diagnosis, prognosis and treatment (Tischoff, 2011). If, however, all the histological subtypes are derived from a single stem cell population, earlier diagnosis could be determined before histological differentiation

occurs; prognosis could be improved overall; and treatment could be focused on targeting these stem cells.

Mesothelioma is an aggressive tumor that often metastasizes. In tumor biology epithelial-mesenchymal transition (EMT) is associated with increased tumor invasiveness and metastasis. This transition is reminiscent of the epithelioid versus sarcomatoid type of mesothelioma, and therefore has important implications in the metastatic feature of this tumor. EMT is a transdifferentiation program used in normal embryonic development. Activation of this program in carcinogenesis would confer a metastatic phenotype to the tumor cells. Not only can EMT increase cell invasiveness and migration, but it also contributes to additional properties that promote tumor cell survival; such as resistance to apoptosis and senescence, and increased immunosuppression (Thiery, 2009). In addition, EMT has been shown to induce stem cell-like properties. Many cancer stem cell traits are consistent with a metastatic phenotype- self-renewal, ability to initiate tumors in a new environment, motility, invasiveness, and resistance to apoptosis (Chaffer, 2011). Evidence of EMT occurring in mesothelioma includes expression of proteins involved in the EMT axis in malignant pleural mesothelioma tissue samples from untreated patients, and expression of the periostin protein in particular by sarcomatoid tumors, which in turn correlated with shorter survival in these patients (Schramm, 2010).

Successful colonization of metastatic cells to the distant tissues requires activation of genetic and epigenetic programming for survival in the new tissue environment. This area of research is relatively new, but it is believed that the self-renewal property of stem cells offers one explanation for homing success. Once in the new microenvironment, metastatic cells need to successfully utilize the local growth factors and cytokines to gain mitogenic potential and the ability to self-renew. Subsequently the metastatic cells would need to recruit the stroma to aid in cell survival, such as inducing a blood supply (Chambers, 2002). Distant metastatic lesions of mesothelioma, amongst other tumors both epithelial and non-epithelial, have been reported to highly express the self-renewal gene Bmi-1, suggesting that a state of self-renewal is linked to metastatic potential (Glinsky, 2005). Whether the metastatic cells in mesothelioma represent a cancer stem cell population derived from the primary tumor, or mesothelioma cells that acquired stem cell-like properties such as self-renewal en route to and after homing to the distant metastatic site, remains to be studied. However these findings support a role for stem cells in the pathogenesis of mesothelioma.

Epigenetic mechanisms that do not change the DNA sequence but that do alter gene expression at the mRNA and protein levels are exciting new potential targets for therapy. A number of epigenetic mechanisms have been described in tumors, including microRNA (miRNA) regulation of mRNA expression, histone acetylation/deacetylation, and gene promoter methylation/demethylation. By suppressing expression of tumor suppressor genes or increasing expression of oncogenes, these epigenetic proteins regulate tumorigenesis at an additional level of complexity. A study identifying a panel of miRNAs downregulated in malignant pleural mesothelioma tissue samples found redundant miRNA regulators of Wnt signaling, an important pathway in stem cell self renewal (Gee, 2010). Wnt signaling in mesothelioma suggests a cell population with stemness properties, and whose expression appears to be regulated at an epigenetic level.



The existence of a cancer stem cell population in mesothelioma is supported by evidence of cells with stem cell-like properties in normal mesothelium, primary mesothelial tumors, and metastatic lesions. A definitive cancer stem cell population capable of re-initiating mesothelioma tumors remains to be identified. If such a cancer stem cell population is discovered, the prospects of earlier diagnosis and novel therapy for malignant mesothelioma would be of utmost importance for further research.

#### **4. Stem cells in the tumor microenvironment**

A cancer cell cannot survive without a hospitable microenvironment. If the microenvironment consists of immune cells that attack the cancer, or if the microenvironment does not support cancer cell growth by providing growth factors, cytokines or blood supply, the cancer cell will not survive in the host. Interestingly, stem cells in the tumor microenvironment have been found to support tumor growth by contributing to a hospitable microenvironment. Here we evaluate the evidence for a host-derived stem cell population in the mesothelioma microenvironment, not a tumor-initiating cancer stem cell population as previously discussed.

Stem cells found in the tumor microenvironment include mesenchymal stem cells (MSCs) with multipotential differentiation and self-renewal properties. Initially MSCs were believed to be derived from the bone marrow, and now there is increasing evidence for MSCs existing in other tissues. The bone marrow houses two types of stem cells- hematopoietic and mesenchymal. Hematopoietic stem cells give rise to all the blood cell lineages. Mesenchymal stem cells can differentiate into a number of cell types, including osteoblasts, chondrocytes, and adipocytes. MSCs have been found to travel from bone marrow into the bloodstream and home to sites of tissue injury for repair (Prockop, 2009). MSCs have also been found to home to tumor microenvironments and play a potential role in tumorigenesis. The anti-tumorigenic and pro-tumorigenic roles MSCs play in tumors will be discussed and evidence for MSCs in malignant mesothelioma will be summarized.

The mechanisms by which MSCs travel to tumors are similar to the MSC homing mechanisms to sites of injury and inflammation. Recruitment of MSCs to tumors involves a number of chemokines and growth factors. Tumor-produced vascular endothelial cell growth factor (VEGF), transforming growth factor (TGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF) and platelet derived growth factor (PDGF) have been reported to recruit MSCs to tumors (Bergfeld, 2010). Mesothelioma is known to secrete VEGF, EGF, HGF and PDGF; and these growth factors are used as biomarkers for diagnosis as well as potential targets for therapy (Ray, 2009). Chemokines and their receptors such as CCL2 (MCP-1) and CXCL12 (SDF-1) and the cognate receptor CXCR4, as well as extracellular matrix proteases and related interleukins (IL-6) have been shown to recruit MSCs (Spaeth, 2008). Both CCL2 and CXCL12 and the cognate receptor CXCR4, as well as IL-6, are found to be upregulated in mesothelioma (Miselis, 2009). Mesothelioma appears to have a microenvironment rich in growth factors, chemokines, and interleukins conducive for MSC homing.

Many of the factors secreted by malignant mesothelial cells have multiple roles in tumorigenesis, such as in angiogenesis and immunomodulation. The prospect of an additional role of these factors in recruitment of stem cells to the tumor microenvironment is

attractive from the standpoint of tumor growth and metastasis. MSCs have been found to be pro-tumorigenic via a number of reported mechanisms. Once in the tumor microenvironment, MSCs differentiate into pericytes, cancer-associated fibroblasts and myofibroblasts (Bexell, 2009; Quante, 2011). Pericytes were first described in the 1870's as cells adjacent to capillaries supporting microvessel growth in normal tissue. Analogously, tumor pericytes support angiogenesis, one of the hallmarks of cancer (Hanahan, 2011). Hence therapies targeting MSCs in the tumor microenvironment are potentially anti-angiogenic therapies.

Cancer-associated fibroblasts (CAFs) and myofibroblasts in the tumor microenvironment appear to play a prominent role in tumor growth and progression. Unlike resting fibroblasts, CAFs and myofibroblasts are activated cells capable of secreting growth factors and extracellular matrix proteins that support tumor growth (Kalluri, 2006). Identifiable by expression of alpha-smooth muscle actin ( $\alpha$ -SMA) and fibroblast activation markers such as fibroblast activating protein (FAP), CAFs and myofibroblasts in tumors can be derived from the bone marrow precursors via the same factors known to recruit MSCs (Quante, 2011). The interplay between MSCs and CAFs remains to be fully elucidated, but it does appear there is overlap in the pro-tumorigenic factors secreted by both.

There is recent evidence of a tumor-associated fibroblast population in human malignant pleural mesothelioma (MPM) cell lines orthotopically implanted into SCID mice, as well as in histological analyses of human biopsies of MPM (Li, 2011). These fibroblasts secreted the growth factors FGF, PDGF, and HGF. While this study did not show a MSC origin for these tumor-associated fibroblasts, these growth factors are known to recruit MSCs as well as be secreted by MSCs.

MSCs, staying undifferentiated or differentiating into pericytes or CAFs, appear to be pro-tumorigenic via three mechanisms. First, MSCs secrete growth factors and cytokines that support tumor growth. Second, MSCs secrete many proangiogenic factors, including VEGF, angiopoietin, IL-6, IL-8, TGF- $\beta$ , PDGF, bFGF, and FGF-7 (Feng, 2009). And three, MSCs contribute to tumor immunotolerance. As previously described, a tumor requires a hospitable environment to grow, and preventing attack of the tumor cells by the host immune system is crucial to promoting tumor survival. MSCs modulate innate immunity by inhibiting natural killer cell activation and dendritic cell maturation (Sotiropoulou, 2007). Acquired immune modulation by MSCs include inhibition of T cell proliferation, inhibition of B cell activation, and increasing the production of regulatory T cells (Sotiropoulou, 2007).

While a MSC population remains to be described in mesothelioma, there is supportive evidence for such a stem cell population given that the mesothelioma microenvironment has been shown to be pro-tumorigenic in similar fashion to the three mechanisms described above. First, there is upregulated expression of growth factors and extracellular matrix proteins in mesothelioma (Miselis, 2010). It could be hypothesized that a stem cell population in the mesothelioma tumor microenvironment is secreting these factors, since MSCs are known to secrete these same factors in other tumors. However, the specific cell types secreting these factors in mesothelioma remain to be fully elucidated.

Secondly, mesothelioma patients have the highest levels of VEGF compared to other patients with solid tumors (Linder, 1998). This pro-angiogenic factor has been targeted for therapy with some success (Zucali, 2011). It could be hypothesized that MSCs in the tumor

microenvironment contribute to the high VEGF levels found in mesothelioma patients. Thirdly, mesothelioma in part is such an aggressive tumor secondary to its successful immunosuppressive strategies. Similar to the mechanisms of immunomodulation demonstrated by MSCs, mesothelioma is characterized by inhibition of NK cells, dendritic cells, cytotoxic T cells; while showing upregulation of regulatory T cells, and secretion of the immunosuppressive cytokine TGF $\beta$  (Gregoire, 2010). These findings correlate with clinical presentation, where a high lymphocytic infiltration is associated with a better prognosis in patients. It would be interesting to see if an increased infiltration of MSC in the mesothelioma tumor microenvironment would correlate with an immunosuppressive profile leading to poorer prognosis in mesothelioma.

Finally, MSCs have been shown to be pro-metastatic. Distant metastasis of Stage IV malignant mesothelioma is rare compared to other solid tumors that spread to bone, brain, and other metastatic sites. However there are case reports of mesothelioma metastasizing to brain, oral gingiva, and skin (Ishikawa, 2010; Moser, 2011; Terada, 2011). In breast cancer, MSC secretion of CCL5 induced a prometastatic effect on breast cancer cells; and tumors coinjected with MSCs showed multiple fold increase in the number of breast cancer cells metastasized to the lungs (Karnoub, 2007). The chemokine CCL5 is overexpressed by mesothelioma (Miselis, 2010), and one could hypothesize that MSCs in mesothelioma may secrete CCL5 and promote a pro-metastatic state.

## 5. Conclusion

While many more studies need to be executed in order to elucidate the role of stem cells in mesothelioma, there is mounting evidence that there is a stem cell/progenitor population in mesothelioma. Whether this cell population is a cancer stem cell one capable of repopulating the tumor or host-derived stem cells in the tumor microenvironment capable of promoting tumor growth and metastasis; it is highly likely that stem cells in mesothelioma are a potential target for therapy. With the potential of stem cells playing a role in mesothelioma growth, angiogenesis, immunomodulation, metastasis, resistance to therapy, and even epigenetic control of tumorigenesis; there is great impetus to explore how stem cell biology and malignant mesothelioma tumorigenesis intersect.

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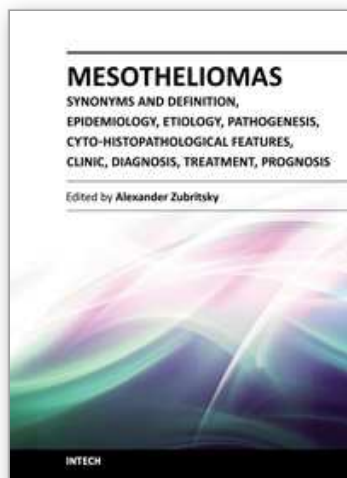


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Mesotheliomas are mysterious mesothelial tumors in that they are relatively rare, difficult to diagnose, with a large number of synonyms, and the etiology and pathogenesis of the disease are still not fully disclosed. This problem attracts the attention 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.

**How to reference**

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