Editorial

Establishment of a malignant pleural effusion mouse model: pathogenesis pathways

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A malignant pleural effusion (MPE), a significant clinical problem, may indirectly be caused by the cancer or its treatment, predominantly lung and breast adenocarcinoma or may appear as pleural effusion unrelated to the cancer (1). More specifically, the development of malignant mesothelioma or, most commonly, pleural metastasis of different cancers, are the main causes for resulting MPE. Systemic spread of disease and reduction of life expectancy and quality are the main implications of MPE (1).

Management of MPE centers on palliation of symptoms because no available treatments prolong survival (1). However, the limited treatment options which are nonspecific and often ineffective, include, treatment of the primary tumor, draining of pleural cavity and pleurodesis, the best method so far to control re-accumulation of the pleural fluid (2).

It is a fact that the pathogenesis of MPE is not fully understood. However, recently several considerable efforts have been made towards this target. These efforts include the development of animal models of MPE which have contributed significant advances in the understanding of the pathogenesis of MPE. In most studies, mice have been used and occasionally rats and rabbits. The different models vary in terms of the immune status of hosts, selection of tumor cells, and location/pathway of the inoculation of tumor cells (3).

The most common practice in animal models of MPE is the introduction of tumor cells or tissue into the pleural cavity of a recipient animal (host). Although it is different from the spontaneous metastasis of tumor cells from a primary site to the pleural cavity, it provides a useful way for research on the subsequent behaviors (including tumor angiogenesis, tumor growth, invasion, metastasis, and the formation of MPE) of tumor cells after they reach the pleural cavity (4).

A novel approach is by spontaneous genetically induced carcinogenesis in the absence of any exposure to asbestos (5) in contrast to traditionally requirement of some form of asbestos exposure, either via inhalation or intrapleural delivery (6,7). To facilitate tumor take of allogeneic (most of the times human) cancer cells or tissues in an alien host, animal models of MPE have mostly been developed as in immune-deficient hosts, including severe combined immunodeficient (SCID) and athymic (nude; natural cytotoxicity receptor, NCR-deficient) mice as well as immune-deficient rats (3). In recent studies immunocompetent hosts implanted with syngeneic tumors, have been used, such as when the VX2 tumor is propagated in the pleural space of New Zealand White (NZW) rabbits (8-10) or the MethA fibrosarcoma is injected into the pleural cavities of syngeneic Balb/c mice (11), and investigators reported that syngeneic models are superior to those employing immunecompromised animals (12,13).

Furthermore, tumor cell suspensions or tissue can be done either by tying cancerous tissues in the pleural space of animals, which is tedious and time-consuming, or by injection via fine needles which is easier and more

reproducible (3). In addition, as far as histologic type and organ of origin is concerned, the greatest applicability is found when animal models employ cancer types greatly associated with MPE, such as lung and breast adenocarcinoma and lymphoma (2). The majority of studies have reported intraperitoneal rather than intrapleural introduction of tumors, which is easier, however, intrapleural (orthotopic) models are advantageous in the study of MPE (3).

Finally, delivery of tumor cells to the pleural space can be achieved in three ways: (I) by intravenous injection with subsequent blood-borne translocation to lung vasculature and lung/pleural outgrowth (14) by intratracheal; (II) intrabronchial, intrapulmonary; (III) subpleural injection with subsequent outgrowth into the pleural space (15) and by direct introduction into the pleural cavity (8-10,16,17).

A very important step in the study of animal models of MPE is the determinations of tumor progression which is shown either by cachexia (16,18), or mostly by determination of pleural fluid accumulation (8-10,17-20). Pleural tumor dissemination can be assessed by counting the number/size of pleural tumor implantations (15-18). In addition, the number or fraction of animals surviving is also an important end-point (5,16-18).

Imaging modalities are easy and rapid assessment of pleural effusion and tumor and include photography (14,17,18,20), radiography, computed tomography magnetic resonance and positron emission imaging (21,22), as well as bioluminescent/biofluorescent imaging of relevant tumor cell reporters (21,22).

Since according to recent studies tumor-induced inflammation, new vessel formation (angiogenesis), and vascular hyperpermeability are important in MPE pathogenesis (18,20,22,23), determinations relevant to these biologic processes may serve as additional end-points in animal models of MPE.

Inflammation can be measured by the closed confines of the pleural space, the tumor tissue, and the blood of MPE animals (3,18). Angiogenesis is quantified by immunolabeling of endothelial cells with factor VIII-related antigen or CD34 with subsequent assessment of the amount/density of new vessels in pleural tumor tissue (17-20,22). In addition, angiogenic mediators such as VEGF are an important end-point in the pathogenesis of MPE (23).

Vascular permeability is also a very important phenomenon for understanding the pathogenesis of MPE. It can be determined by several ways, such as the measurement of protein or albumin in pleural fluid or blood (3). Recent studies indeed, have shed light in the pathogenesis of MPE. More specifically, researchers concluded that the VEGF and its receptor 1 (VEGF1) play a significant role in MPE formation (20,23). Others reported that autocrine IL-6/Stat3/VEGF signaling pathway may also be activated in patients with MPE (19).

In another study, IL-5 was identified as a promoter to MPE formation by adenocarcinoma through effects on the MPE-associated inflammatory response (12). The same group experimented with aminobiphosphonates, such as zoledronic acid (ZA), which has potent indirect antitumor effects and concluded that ZA limited the expression of pro-inflammatory and angiogenic mediators, as well as the activity of small GTP proteins Ras and RhoA, in tumor cells in vivo and in vitro. They suggested that this intervention should be considered for testing in clinical trials (18).

Other investigators concluded that tumor-derived osteopontin plays an important role in MPE formation (17), and that vinorelbine may improve the final outcome (24). More groups found that pleural fibrinolytic activity and MYO18B gene repression is an important pathway in the pathogenesis of MPE (8-10,25). Recently, researchers tried to establish a MPE nude mouse model by trans-pleural inoculation of Lewis lung carcinoma cell lines expressing enhanced green fluorescent protein (LLC-EGFP) by observing the tumor growth with in vivo fluorescence imaging system (4). They suggest that this fluorescent model is a powerful and reliable tool in the investigation of pleural metastasis of lung cancer.

In conclusion, the study of MPE models has elucidated MPE pathobiology and has provided proof-of-concept evidence for the paracrine effects of genetic alterations in cancer cells on the host. Preclinical models of MPE could result in finding several potential therapeutic targets against this condition and hopefully will halt or even prevent MPE in cancer patients.

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