Editorial

Malignant pleural effusion: further translational research is crucial

Yasuhiko Nishioka

Department of Respiratory Medicine and Rheumatology, Institute of Health Biosciences, The University of Tokushima Graduate School, 3-18-15 Kuramoto-cho, Tokushima, 770-8503 Japan

Corresponding to: Yasuhiko Nishioka. Department of Respiratory Medicine and Rheumatology, Institute of Health Biosciences, The University of Tokushima Graduate School, 3-18-15 Kuramoto-cho, Tokushima, 770-8503 Japan. Email: yasuhiko@clin.med.tokushima-u.ac.jp.

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Malignant pleural effusion (MPE) is common and debilitating complications of various types of cancers (1,2). More than 75% of MPEs are caused by carcinomas of the lung, breast, or ovary, with metastatic adenocarcinoma being the most common histological type. Malignant pleural mesothelioma (MPM) is also an important cause as a primary cancer growing in pleural cavity despite the low frequency. There are some patients who have no symptoms, but MPE commonly decreases quality of life (QOL) due to dyspnea and cough, and is associated with a poor prognosis (3).

Although there are several options for treatment of MPE, no available treatment prolongs survival (4,5). Therefore, appropriate managements of MPE are required to improve QOL and not to decrease survival. Depend on the condition of patients, a recommended therapy for MPE is thought to be pleurodesis using several sclerosants. In general, talc pleurodesis is commonly used in USA, and OK-432 is in Japan (6-8).

However, for the better management of MPE, translational research analyzing the underlying mechanisms in the progression of MPE would be needed to produce therapeutic biomarkers. There are two ways to analyze the molecular pathogenesis of MPE; the first approach is to use the pleural effusion harvested from patients by thoracentesis. The other is to develop animal models of MPE. The latter is more useful to investigate the specific mechanisms underlying pleural fluid accumulation as well as to evaluate therapeutic approaches against MPE.

From 1962, Wagner *et al*. reported MPM model in rats by intra-pleural injection with asbestos (9). Subsequently, the several MPE models have been developed and applied for therapeutic experiments (10,11). Yano *et al*. used human cancer cells to develop MPE models of lung cancer in mice (12). They injected intravenously with human lung adenocarcinoma into SCID mice. On the other hand, Stathopoulos *et al*. developed MPE models by direct injection of Lewis lung carcinoma (LLC) into pleural cavity in C57BL/6 mice (13). If we would like to focus on the biology of human cancer cells, the models with human cancer might be useful. In the case of analysis of host-tumor interaction, immunocompetent mice would be better since immunological cells could be involved in the progression of MPE. From several reports, the critical factors involved in pathogenesis of MPE have been demonstrated. The underlying mechanism in the emergence of MPE is due to the blockade of fluid removal from pleuropulmonary lymphatics by invasion of tumors. However, the hyper-permeability by vascular endothelial growth factor (VEGF) is critical to explain the efficient volume of MPE (14). Recent studies also showed that, in addition to VEGF, tumor necrosis factor (TNF)-α produced by tumor cells directly stimulated the vascular permeability in MPE model (15). TNF-α also stimulates productions of both TNF-α and VEGF by tumor cells in an autocrine fashion, indicating that TNF-α might be a controller of vascular permeability in MPE. Furthermore, nuclear factor kappa-B (NF-κB) is reported to play a role in upstream regulation of TNF-α (15). It was demonstrated that monocyte chemoattractant protein (MCP)-1 derived from tumors induced vascular permeability in a direct manner (16). On the other hand, soluble or cellular factors which indirectly promote MPE formation have been demonstrated. Interleukin (IL)-5 derived from host cells induced MPE via accumulating eosinophils and $CD11b^{+}Gr\text{-}1^{+}$ myeloid-derived suppressor cells (17). The secreted phosphoprotein-1 (SPP1) also directly provokes

vascular leakage to foster malignant pleural effusion (18).

From the therapeutic point of view, several approaches have been examined in MPE model. The anti-angiogenic therapy targeting to VEGF is expected for treatment of patients with MPE. In the model of MPM which we recently generated by direct injection with human MPM cells into pleural cavity in mice, neutralizing antibody of VEGF as well as small molecule inhibitor against VEGF receptor demonstrated the significant inhibition of progression of MPE (19,20). In fact, bevacizumab is a recombinant humanized IgG monoclonal antibody against VEGF and its use for MPM is being explored in phase II trials with pemetrexed and carboplatin or cisplatin. However, data from recent randomized phase II trials failed to demonstrate an increase in survival when bevacizumab was given in addition to gemcitabine-carboplatin therapy (21). Proteasome inhibition with bortezomib blocked NF-κB activation and inhibited MPE (22). Since bortezomib also induced apoptosis of MPM cells *in vivo* and *in vitro* (23), clinical trials with bortezomib against MPM have been initiated in Europe. Although most clinical trials do not include the endpoints to control MPE, therapy targeting to the molecules related with MPE might be initiated in the future trials since MPE is closely associated with patient's QOL and survival.

It is still hard to prolong survival of patients with MPE. Translational studies from bench to clinic are definitely important. In addition, the reverse translational studies from clinic to bench might be more critical to develop novel therapy. Recent advances in the specific therapy for bone metastasis such as bisphosphonate and anti-RANKL antibody (24) suggest us the notion that metastasis including MPE should be treated with organ-specific therapeutic modalities in addition to conventional systemic therapy with anti-cancer agents. Animal models could contribute to discover novel druggable targets specific for MPE, leading to the future advances in treatment of patients with MPE.

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References

1. Heffner JE. Diagnosis and management of malignant pleural effusions. Respirology 2008;13:5-20.
2. Neragi-Miandoab S. Malignant pleural effusion, current and evolving approaches for its diagnosis and management. Lung Cancer 2006;54:1-9.
3. Goya T, Asamura H, Yoshimura H, et al. Prognosis of 6644 resected non-small cell lung cancers in Japan: a Japanese lung cancer registry study. Lung Cancer 2005;50:227-34.
4. Heffner JE. Management of the patient with a malignant pleural effusion. Semin Respir Crit Care Med 2010;31:723-33.
5. Kaifi JT, Toth JW, Gusani NJ, et al. Multidisciplinary management of malignant pleural effusion. J Surg Oncol 2012;105:731-8.
6. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Cochrane Database Syst Rev 2004;1:CD002916.
7. Zahid I, Routledge T, Billè A, et al. What is the best treatment for malignant pleural effusions? Interact Cardiovasc Thorac Surg 2011;12:818-23.
8. Yoshida K, Sugiura T, Takifuji N, et al. Randomized phase II trial of three intrapleural therapy regimens for the management of malignant pleural effusion in previously untreated non-small cell lung cancer: JCOG 9515. Lung Cancer 2007;58:362-8.
9. Wagner JC, Berry G. Mesotheliomas in rats following inoculation with asbestos. Br J Cancer 1969;23:567-81.
10. Pimm MV, Hopper DG, Baldwin RW. BCG treatment of malignant pleural effusions in the rat. Br J Cancer 1976;34:368-73.
11. Yoshimoto T, Azuma I, Nishikawa H, et al. Experimental immunotherapy of neoplastic pleural effusion with oil-attached BCG cell-wall skeleton in mice. Gann 1976;67:737-40.
12. Yano S, Nokihara H, Hanibuchi M, et al. Model of malignant pleural effusion of human lung adenocarcinoma in SCID mice. Oncol Res 1997;9:573-9.
13. Stathopoulos GT, Zhu Z, Everhart MB, et al. Nuclear factor-kappaB affects tumor progression in a mouse model of malignant pleural effusion. Am J Respir Cell Mol Biol 2006;34:142-50.
14. Yano S, Shinohara H, Herbst RS, et al. Production of experimental malignant pleural effusions is dependent on invasion of the pleura and expression of vascular endothelial growth factor/vascular permeability factor by human lung cancer cells. Am J Pathol 2000;157:1893-903.
15. Stathopoulos GT, Kollintza A, Moschos C, et al. Tumor necrosis factor-alpha promotes malignant pleural effusion. Cancer Res 2007;67:9825-34.
16. Stathopoulos GT, Psallidas I, Moustaki A, et al. A central role for tumor-derived monocyte chemoattractant protein-1 in malignant pleural effusion. J Natl Cancer Inst

2008;100:1464-76.
17. Stathopoulos GT, Sherrill TP, Karabela SP, et al. Host-derived interleukin-5 promotes adenocarcinoma-induced malignant pleural effusion. Am J Respir Crit Care Med 2010;182:1273-81.
18. Psallidas I, Stathopoulos GT, Maniatis NA, et al. Secreted phosphoprotein-1 directly provokes vascular leakage to foster malignant pleural effusion. Oncogene 2012. [Epub ahead of print].
19. Li Q, Yano S, Ogino H, et al. The therapeutic efficacy of anti vascular endothelial growth factor antibody, bevacizumab, and pemetrexed against orthotopically implanted human pleural mesothelioma cells in severe combined immunodeficient mice. Clin Cancer Res 2007;13:5918-25.
20. Ikuta K, Yano S, Trung VT, et al. E7080, a multi-tyrosine kinase inhibitor, suppresses the progression of malignant pleural mesothelioma with different proangiogenic cytokine production profiles. Clin Cancer Res 2009;15:7229-37.
21. Fennell DA, Gaudino G, O'Byrne KJ, et al. Advances in the systemic therapy of malignant pleural mesothelioma. Nat Clin Pract Oncol 2008;5:136-47.
22. Psallidas I, Karabela SP, Moschos C, et al. Specific effects of bortezomib against experimental malignant pleural effusion: a preclinical study. Mol Cancer 2010;9:56.
23. Sartore-Bianchi A, Gasparri F, Galvani A, et al. Bortezomib inhibits nuclear factor-kappaB dependent survival and has potent in vivo activity in mesothelioma. Clin Cancer Res 2007;13:5942-51.
24. Bundred N. Antiresorptive therapies in oncology and their effects on cancer progression. Cancer Treat Rev 2012;38:776-86.

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