Environmental carcinogenesis – 100th anniversary of creating cancer

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Asbestos is an environmental carcinogen, and asbestos-related diseases represent a global-scale environmental issue. Mesothelioma is an aggressive, malignant tumor that initially progresses along the surfaces of the pleura and peritoneum that is chiefly attributed to asbestos exposure. X-rays are commonly used for tumor screening in populations at risk for developing this cancer. We previously reported that the N-terminal of mesothelin may be a useful blood marker for early diagnosis method for mesothelioma and since then developed an N-terminal of mesothelin ELISA kit in collaboration with IBL Co., Ltd. and confirmed its utility as a diagnostic system for mesothelioma. Recently, we performed a large-scale research screening for mesothelioma and showed that it is a good model for early diagnosis in at-risk populations. The year 2015 is the 100th anniversary of Yamagiwa’s great work on coaltar-induced carcinogenesis by formative stimulation in 1915 and the 10th year since 2005, “Kubota shock”, people recognized that asbestos induces mesothelioma. We dedicate this review to this memorial year for environmental carcinogenesis.

Mesothelioma is generally known to be a rare cancer, although the evidence-based science on this cancer is limited, and it is a difficult disease to diagnose and to treat. Patients typically present with breathlessness and chest pain with pleural effusions. X-rays are commonly used for tumor assessment in populations that are at increased risk for developing this disease. When a patient is diagnosed with mesothelioma, physicians will choose surgery, radiation, or chemotherapy for disease treatment and management. Physicians who specialize in treating this cancer must select a treatment plan after carefully considering the cancer stage, the primary site affected, and cancer cell type.

Pleurectomy/decortication, in which the surgeon tries to remove as much of the tumor around the lung as possible and performs extrapleural pneumonectomy, in which the lung itself is removed, is the major surgical method used to treat mesothelioma. However, there are also some effective and curative treatments available that incorporate cisplatin, pemetrexed disodium, or a gemcitabine–cisplatin combination. Currently published data on mesothelioma report that the median survival time for stage I disease is 21 months and for stage IV disease is 12 months. Several clinical studies are being carried out to try and establish techniques for the early diagnosis for mesothelioma.

Pneumonectomy tends to be a better choice for younger patients with the epithelial form of the disease, no obvious lymph node involvement, and who are healthy enough to tolerate this serious procedure. Patients who receive chemotherapy...
have very frequent treatment-related side effects. However, there is no published evidence from a randomized trial showing a better outcome with surgery than with non-surgical management of mesothelioma.

We have previously reported that the N-terminal of mesothelin (N-ERC/mesothelin) may be a useful serum tumor marker for mesothelioma and have developed an N-ERC/mesothelin ELISA kit in collaboration with IBL Co., Ltd (Gunma, Japan). Furthermore, our research group has established a unique diagnostic system based on the large-scale screening of construction workers in Japan. In this review, we summarize the current data on this early diagnosis system and discuss future directions for mesothelioma research.

**Diagnosis using Blood**

We have previously found that multistep renal carcinogenesis occurs in Eker rats and reported that ERC, a rat renal carcinoma gene, is highly expressed in renal cancer. Rat ERC is a homolog of the human mesothelin gene and is localized to chromosome 16p13.3. Mesothelin is expressed in normal mesothelial cells, mesotheliomas, non-mucinous ovarian carcinomas, and pancreatic ductal adenocarcinomas. Although the human mesothelin gene encodes several proteins, its primary homolog is a 40-kDa precursor protein that is cleaved physiologically by a furin-like protease into a 40-kDa C-terminal fragment that remains membrane bound and a 31-kDa N-terminal fragment that is secreted into the blood. The resultant C-terminal 40-kDa fragment is classified as a mesothelin, and its presence in the serum has been reported to be a useful tumor marker in patients with mesothelioma. We have since developed 22A31, a C-ERC/mesothelin-specific mouse mAb directed against tumors derived from the human mesothelioma cell line ACC-MESO-4. To characterize this antibody, we carried out both in vitro and in vivo cell proliferation assays. Interestingly, the antibody did not inhibit the proliferation of the ACC-MESO-4 cell line in vitro, but it dramatically inhibited cell line-derived tumor growth in vivo. Thus, the C-ERC/mesothelin-specific mouse mAb 22A31 may be a potentially useful new tool for treating C-ERC/mesothelin-expressing cancers, including mesothelioma.

In contrast, the secreted N-terminal 31-kDa fragment, which has been cloned as a megakaryocyte-potentiating factor, has not been reported to be a useful serum marker for mesothelioma. Therefore, we developed an original sandwich ELISA system using specific antibodies raised against the 31-kDa N-terminal fragment of ERC, N-ERC/mesothelin. To test this ELISA system, we planned a 5-year, large-scale research screening program in collaboration with the Tokyo Doken National Health Insurance Association (Tokyo, Japan), which had worked in Japan from 2007 to 2012 at construction sites with a risk of asbestos exposure. As of 2007, approximately 220 000 blood samples were collected, and N-ERC/mesothelin levels were determined using the ELISA kit. Together with the participant’s medical history and related data, ELISA analysis identified approximately 60 high-risk individuals from among 30 000 participants. Based on the screening, we identified three participants with mesothelioma and 60 participants who were at high risk but had yet to develop mesothelioma.

From these results, we predicted that N-ERC/mesothelin is a blood tumor marker that may be useful for large-scale population screening and the early diagnosis of mesothelioma following mass examination. Moreover, to more precisely measure N-ERC/mesothelin, we have developed a new 7–20 ELISA system. This system is clinically useful for the precise diagnosis of pleural mesothelioma. Over the next 4 years, we plan to carry out annual follow-up on all the participants in the high-risk population and to prospectively assess how many participants ultimately develop mesothelioma, while continuing to screen for any early signs of mesothelioma. The results from another study showed that members of a high-risk population who failed to undergo annual N-ERC/mesothelin screening were diagnosed with mesothelioma in the following year.

Therefore, we strongly recommended that participants who are identified as being at high risk for developing mesothelioma receive an additional health check-up and N-ERC/mesothelin test at least annually, even if they have no clinical symptoms.

In addition, a new potential marker for mesothelioma was recently reported. In that study, a rat model of peritoneal mesothelioma was established through exposure to commercially used asbestos. Transcriptome analysis of the rats with epithelioid and sarcomatoid types of mesothelioma defined connective tissue growth factor as a marker for malignant mesothelioma. In parallel, our research group has continued to seek a specific clinical marker for sarcomatoid, a rare form of mesothelioma with a particularly poor prognosis, and has already identified several specific markers for this tumor type.

Although additional research is needed, the results of our recent study and other published reports indicate the future direction for establishing new markers for the diagnosis and treatment of mesothelioma.

**Cooperative Research to Identify Risk and Early Diagnostic Markers of Mesothelioma in Asia**

Asian countries, such as Thailand, have experienced successful economic development in recent decades. With these advances, large populations have gradually begun to face many of the difficulties that large economies around the world have also faced in the past, such as air pollution and environmental issues. We now have to address these difficulties to protect our people’s lives and living environments.

One of the difficulties that we face is environmental carcinogenesis. In Asia, the proportion of all illnesses represented by cancer has been increasing recently. A significant portion of this increase is assumed to be the result of environmental changes, such as urbanization and air pollution.

Mesothelioma is one of the most understood examples of environmental carcinogenesis. It is an aggressive and a malignant tumor that is chiefly attributed to asbestos exposure.

In several Asian countries, including Japan, rapid economic growth has brought many changes, but asbestos is still widely used. We previously reported that N-ERC/mesothelin might be a useful blood tumor marker for mesothelioma. Furthermore, we developed and tested a unique diagnosis system in the large-scale screening of construction workers in Japan. We have also predicted that the incidence of mesothelioma will continue to increase in Asia in the near future. We intend to share this diagnosis system and all knowledge gained pertaining to mesothelioma and to continue to establish early diagnosis and treatment systems. Finally, our group will work to organize international seminars on environmental carcinogenesis once a year and an education program on the skills required for mesothelioma diagnosis.

Environmental carcinogenesis causes not only an asbestos-related mesothelioma but also lung cancer resulting from air...
pollutants. Throughout life, we are exposed to many environmental pollutants, and the environmental conditions of our surroundings vary between individuals. Thus, epidemiology research is also needed to help solve the issue of environmental carcinogenesis in Asia. Through Asian epidemiology research and advanced baseline studies in Japan, the problem of environmental carcinogenesis can be solved.

**Summary and Future Directions**

In 1775, the British surgeon Percival Pott reported that the incidence of scrotal cancer was increasing among chimney sweeps and predicted that the cancer was caused by chimney soot. This association indicated that the concept of environmental carcinogens causing cancer was understood. The industrialization that followed the industrial revolution in the latter half of the 18th century marked the large-scale introduction of environmental pollutants.

Regarding asbestos, our preventative measures and practical responses are decades behind, despite the fact that there has been ample pathological and epidemiological evidence establishing the risks with exposure. Future carcinogen research must include risk evaluation along with risk management and establish a good communication system for the people who have a relationship with the patient. In reality, almost everyone who has lived in an industrialized area has asbestos fibers in their lungs, and many can recall a specific incidence of incidental exposure (e.g., school teachers and students who handled asbestos samples, mats, or blankets and people in many other life situations). Asbestos fibers are long and thin and can penetrate the lung, repeatedly scratching the mesothelium surface and causing prolonged cycles of damage, repair, and local inflammation. The subsequent carcinomas typically develop 20–40 years after the exposure. The length of exposure and the amount of asbestos are positively associated with the risk of mesothelioma.

Our recent large-scale research study that screened for mesothelioma in Japan was effective for early diagnosis. To confirm this screening method, we have begun an international large-scale research screening program in Japan and other Asian countries. Since we established the International Environmental Carcinogenesis Research Center last year at Juntendo University (Tokyo, Japan), Japanese researchers have provided technical guidance on the use of this screening method as well as education on mesothelioma to Asian doctors and researchers. In the near future, we will confirm that this method is effective in another country and gather reliable evidence for blood diagnosis of mesothelioma. From this center, we have established early diagnosis and treatment systems not only for mesothelioma but also for other diseases resulting from environmental carcinogenesis. Moreover, the people living in Asian countries, including Japan, will understand and care about the risks of environmental carcinogenesis.

Dr. Hino opened the “Asbestos Mesothelioma Clinic” in 2005 at Juntendo University and since then has continuously taken care of patients with mesothelioma and people who fear asbestos exposure.

Mesothelioma remains a rare cancer, and its pathological mechanism is still unclear. Thus, we should establish holistic methods of caring for mesothelioma, including diagnosis, treatment, and end-of-life counseling.

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**Disclosure Statement**

The authors have no conflict of interest.

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