

Detection of Mesothelioma-Specific ENOX2 Isoforms 4-10 years in Advance of Clinical Symptoms

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Malignant mesothelioma is the most common cancer induced by exposure to asbestos. Recently, a retrospective analysis of banked serum samples collected from individuals who developed asbestos-induced mesothelioma was undertaken to determine if ENOX2 isoforms may serve as biomarkers for this disease and to investigate how long in advance of clinical symptoms ENOX2 proteins could be detected in patient sera. Interestingly, two mesothelioma-specific ENOX2 isoforms were detected in serum samples of asbestos-exposed individuals, 4-10 years in advance of a clinical diagnosis of mesothelioma (1). This is the very first published evidence that the ONCOblot test is able to detect ENOX2 produced by a malignancy in advance of clinical symptoms. This work was a collaboration between MorNuCo Inc. and Drs. Jenette Creaney, A. W. Musk and Bruce Robinson of the National Center for Asbestos Related Diseases and the School of Medicine and Pharmacology at the University of Western Australia.

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Banked serum samples from 17 individuals who were diagnosed with malignant mesothelioma were investigated for the presence of ENOX2 isoforms. Each of these serum samples contained two ENOX2

proteins with average molecular weights of 64 kDa and 41 kDa and average isoelectric points of 3.9 and 4.3, respectively. The simultaneous detection of these two ENOX2 isoforms was mesothelioma-specific and has not been observed within serum samples derived from patients diagnosed with cancers other than mesothelioma. For seven of these individuals, annual serum samples were available for 8-13 years prior to a diagnosis of mesothelioma. For these samples, both mesothelioma-specific ENOX2 isoforms could be detected 4-10 (average 6.2) years prior to clinical diagnosis of mesothelioma. Serum samples of 15 asbestos-exposed individuals currently diagnosed with benign disease (pleural plaques with or without accompanying asbestosis) were also analyzed. Of the serum samples from these subjects, 9 (60%) lacked detectable ENOX2, 5 (33%) contained only one mesothelioma-specific ENOX2 isoform and only 1 (7%) contained both mesothelioma-specific ENOX2 isoforms. It is possible that the presence of ENOX2 within the serum of these subjects diagnosed with benign disease is an early indicator of the development of mesothelioma. However, additional follow-up will be required to test this hypothesis.

Asbestos-Induced Malignant Mesothelioma

Asbestos microfibers are easily aerosolized. Once inhaled, these carcinogenic fibers cling to the respiratory tract and eventually become embedded in soft tissues. The primary respiratory diseases associated with asbestos exposure are lung cancer, mesothelioma, formation of pleural plaques, and asbestosis, a benign, chronic respiratory disease. Importantly, patients diagnosed with asbestosis are at a higher risk of both lung cancer and mesothelioma.

Malignant mesothelioma is an aggressive and almost uniformly fatal cancer. It is a tumor of the mesothelium, predominantly of the pleura, and it is often widespread at the time of presentation. Patients who are treated with supportive care have a median survival time of 9 months. The latency period for asbestos-induced mesothelioma (the time between asbestos exposure and diagnosis) is 10 to 50 years with an average of approximately 35 years. Thus, asbestos-induced mesothelioma develops relatively slowly and often presents clinically only in late stages.

Patient Population Investigated

Crocidolite (blue asbestos) was mined and milled in the town of Wittenoom in Western Australia from 1943 to 1966, primarily by a single company, the Australian Blue Asbestos Company. Beginning in the late 1970's, a cohort of more than 6,000 men and 400 women who were employed in this asbestos mining and milling operation have been followed longitudinally to investigate the prevalence of asbestos-related morbidity and mortality (2, 3). Although asbestos exposure for this population was often brief, with 74% of the workforce employed for less than 1 year and only 5% for 5 years or longer, asbestos exposure was estimated to be high, particularly for mill workers. A

subset of these individuals have elected to participate in an ongoing cancer surveillance and prevention program (4, 5). Serum samples from some of these individuals, collected on a yearly basis for over a decade, were utilized in our study.

Summary

Two mesothelioma-specific ENOX2 isoforms were detected in the serum of asbestos-exposed subject 4-10 years in advance of clinical diagnosis. Importantly, asbestos-induced mesothelioma is characterized by a long latency period and often does not induce significant symptoms until later stages, delaying diagnosis. If validated in larger clinical trials, the ENOX2 cancer marker may aid early detection with the goal of reducing mesothelioma-related mortality.

References

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