Chapter

Suppressed Immune System Caused by Exposure to Asbestos and Malignant Mesothelioma

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Abstract

Mesothelioma is the most serious of the asbestos-related diseases. It is caused by exposure to relatively low doses of asbestos and takes a long period to develop, which suggests the enactment of gradual adverse effects other than cellular toxicity. The immune system, which can play a role in tumor prevention, is a presumable target of asbestos by accumulation in lymph nodes and then slowly affecting functions of immune cells. Here, we describe key findings obtained from our studies concerning the immune-suppressive effects of asbestos and functional alteration in immune cells of patients with mesothelioma as well as plaque-positive subjects. Asbestos exposure of cell cultures resulted in decreased natural and acquired cytotoxicity exerted by NK cells and CTLs and the ability of Th1 cells to activate and support antitumor immunity. In contrast, asbestos exposure augmented Treg cell function and generation of fibrogenic/suppressive macrophages. Mesothelioma patients also showed similar characteristics in certain alterations caused by asbestos exposure. Additionally, our recent study established immunological screening devices for mesothelioma and asbestos exposure on the basis of comprehensive analysis of peripheral blood. Those findings underscore the importance of the immunological effects of asbestos and should assist further understanding of the mechanism and early detection of mesothelioma.

Keywords: macrophage, NK cell, Th1, Treg, CTL

1. Introduction: immune system as a key player in malignant mesothelioma following exposure to asbestos

Although asbestos has been banned in many European countries and the USA, as well as Japan, it continues to be used globally, and a report in 2018 by the WHO estimated that about 125 million people in the world continue to be exposed to asbestos at the workplace [1]. Occupational exposure to asbestos causes the death of at least 107,000 people from lung cancer, malignant mesothelioma, and pneumoconiosis (asbestosis) every year. Additionally, countries where asbestos remains have an increasing number of newly exposed individuals, especially during activities related to the destruction of old houses and buildings made of materials including some kinds of asbestos. That type of exposure to asbestos can occur in a variety of contexts such as the illegal destruction of asbestos-containing
structures, the aftermath of natural disasters such as earthquakes and tsunamis, or even terrorism. It is known that the terrorist attacks in New York City on September 11, 2001, released 2000 tons of asbestos fibers into the air, subjecting an estimated 410,000 people to those fibers, including first responders, nearby residents, and workers in charge with cleaning up [2]. In the case of malignant mesothelioma, a poor prognostic disease specifically caused by the inhalation of asbestos, the disease develops silently and suddenly after about 40 years following the initial commencement of asbestos exposure, which means that deaths from malignant mesothelioma are increasing or achieving a peak in asbestos-banned countries. It has been estimated by Murayama T. that those deaths in Japan will peak around the year 2030 [3].

Thus, malignant mesothelioma is a global issue that needs to be solved. However, the following characteristics of mesothelioma make early diagnosis difficult to achieve. Malignant mesothelioma does not follow a dose-dependent rule in terms of toxicology but rather develops in people exposed to asbestos at low or middle doses of concentration [4]. Additionally, as mentioned above, it takes about 40 years to develop it. Therefore, sometimes people are suddenly informed that they have malignant mesothelioma, even though they do not remember any exposure to asbestos in their history, thereby leading to a delay in diagnosis. In the context of these characteristics of the relationship between asbestos exposure and malignant mesothelioma, we arrived at one possibility: alterations in immune functions might connect asbestos exposure to malignant mesothelioma. It is true that asbestos fibers cause cellular toxicity, mutagenicity, and the production of reactive oxygen species (ROS). Oxidized pyrimidine and alkaliized nucleic acid base components correlate with the time of asbestos exposure, and the mutation frequency of lung DNA increased following intratracheal instillation of rats with asbestos [5–9]. Those findings indicate that asbestos fibers have the potential to cause transformation of healthy mesothelial cells. However, the body is equipped with an immune system, which can detect and remove those abnormal cells transiently arising due to certain kinds of toxic effects. Therefore, it is reasonable to assume that the immune system plays a role in protecting the body from malignant mesothelioma following exposure to asbestos and that the immune system must be subject to some kind of impairment prior to the development of mesothelioma. In fact, inhaled particles and fibers reach draining lymph nodes, and it has been reported that people exposed to asbestos occupationally or nonoccupationally showed accumulation of asbestos fibers in their lymph nodes [10, 11]. It is possible for asbestos to accumulate in the body slowly at low doses of exposure, thus subjecting immune cells to chronic asbestos exposure. Those cells circulate through the peripheral blood which might then result in a suppressed immune system. Moreover, if some alterations in the immune system are observed upon exposure to asbestos as well as in patients with malignant mesothelioma, we might utilize those changes to establish immunology-based screening devices to assist in the early detection of malignant mesothelioma as well as in cases of general asbestos exposure. Thus, we believe that the immune system is a key player in the mechanism involving asbestos-induced malignant mesothelioma and therefore a prime target for the development of screening methodologies. Consequently, we have been investigating the immunological effects of asbestos exposure and immunological alterations in patients with malignant mesothelioma and in people exposed to asbestos using multiple analyses of peripheral blood. Here we present the results of our investigations in this field and finally propose immunological screening devices for the detection of mesothelioma and asbestos exposure.
2. TGF-beta production by macrophages is crucial for suppressed antitumor immunity/tumor progression as well as lung fibrosis following asbestos exposure

Macrophages are the first population of immune cells which interact with inhaled asbestos in the body. It is well-known that alveolar macrophages (AMs) play a role in inflammation following inhalation of asbestos, where AM-mediated activities include the generation of reactive oxygen species (ROS), reactive nitrogen species (RNS), and inflammatory cytokines such as TNF-α [12–16]. Those inflammatory responses continue chronically since inhaled asbestos accumulates in the lungs, which induces overproduction of the extracellular matrix (ECM) and leads to asbestos-induced lung fibrosis, known as asbestosis [6, 17]. TNF-α chronically produced by AMs is a key phenomenon upstream of fibrosis because it induces production of transforming growth factor-beta (TGF-β) by fibroblasts and other cells, which in turn induces production of ECM. In fact, it has been reported that TNF-α-deficient mice showed decreased TGF-β as well as ECM following exposure to asbestos [17, 18]. Additionally, we also demonstrated in a previous study that the macrophage cell lines of RA W264.7 and J774 showed production of O$_2^-$ and NO$_2^-$ upon exposure to asbestos [14].

Thus, it is not unexpected that AMs have received attention given their role in inflammatory responses upon exposure to asbestos. However, we decided to focus on the fact that AMs also have the potential to produce TGF-β and that AMs can migrate away from the local site with chronic inflammation to other areas, where they are able to exert their effect in the absence of asbestos, which is more crucial for the induction of fibrogenic responses than simple production of TGF-β only at inflammatory sites. First, we noted that high doses of asbestos caused apoptosis of AMs during culture, while low doses failed to do so but did induce production of TGF-β. Therefore, we compared the ex vivo production of TGF-β by AMs from rats instilled with asbestos via the trachea with the in vitro production of TGF-β by AMs during culture upon exposure to asbestos. AMs collected at 5 days after instillation of rats with asbestos showed significantly higher amounts of TGF-β production in the culture for 5 days than AMs collected from control rats. However, it was surprising that AMs collected from control rats showed the same amount of TGF-β in the 5-day culture as AMs collected from rats exposed to asbestos in vivo. Moreover, AMs came to produce much greater amounts of TGF-β during continuous culture in fresh medium, and these viable AMs upon exposure to asbestos showed increased intracellular expression of Bcl-2, the product of a representative anti-apoptotic gene [19]. Those findings indicate that asbestos-exposed AMs can acquire the ability to produce high amounts of TGF-β in the absence of other cell types and with long survival supported by an anti-apoptotic gene, which might contribute to the progression of lung fibrosis following exposure to asbestos. That study was originally performed from the viewpoint of investigating the fibrogenic role of AMs as mentioned above. However, we believe that this functional alteration in AMs upon exposure to asbestos can be meaningfully interpreted as antitumor immunity upon exposure to asbestos. TGF-β is a representative cytokine that functions to suppress cell proliferation and survival of immune cells, natural killer (NK) cell function, and generation of cytotoxic T lymphocytes (CTLs) specific for tumors, as well as function in the induction of regulatory T cells [20–28]. TGF-β is produced by lymphoid cells as well as myeloid lineage cells, and those myeloid-derived suppressor cells play a role in angiogenesis which leads to tumor promotion [29]. Taken together, our findings underscore the significance of TGF-β production by macrophages which is crucial for suppressed antitumor immunity and tumor progression as well as lung fibrosis following asbestos exposure.
3. Impaired cytotoxicity of NK cells with altered expression of activating receptors caused by asbestos related with mesothelioma

NK cells represent one population of cells involved in innate immunity and play a role in tumor-surveillance as a first line of defense. One previous study has reported that people with low natural cytotoxic activity of peripheral blood lymphocytes showed higher cumulative incidence rates of cancer diseases than people with high activity in both men and women [30]. This highlights the importance of NK cell function in the prevention of tumor diseases including malignant mesothelioma following asbestos exposure. NK cells have a different machinery to recognize target cells compared with T lymphocytes. NK cells equip activating and inhibitory receptors against ligands expressed on the cell surface of targets, thereby determining whether or not to attack targets [31–37]. Finally, activating receptors engage in signal transduction to degranulate cytotoxic granules, including perforin and granzymes, which cause apoptosis of target cells [38]. Therefore, we focused on the effect of asbestos exposure on the expression of receptors on NK cells. First, we commenced continuous exposure of human NK cell line YT-A1 culture to asbestos. Following 1 month of culture, YT-A1 cells did not show any alterations in natural cytotoxic activity as measured by incubation with K562 cells. However, cells showed marked decreases in cytotoxicity after 4–5 months of culture with asbestos. It was also found that intracellular levels of granzyme A and perforin decreased in cells cultured with asbestos at the same time, but granzyme B did not decrease [39]. Furthermore, YT-A1 cells continuously exposed to asbestos (YT-CB5) showed decreases in cell surface expression of activating receptors NKG2D and 2B4 but did not show any alterations in the expression of NKG2A or CD94, which form a heterodimer that functions as an inhibitory receptor. NKG2D and NKG2A are members of the NKG2 family, members of which contain a lectin-like domain, whereas 2B4 (CD244) is a representative member of the signaling lymphocytic activation molecule (SLAM) family expressed on NK cells [32, 34]. Since NKG2D is known to contribute to natural cytotoxicity against K562 cells [40], it is reasonable to suggest that decreased cytotoxicity of YT-CB5 can be attributed to low expression of NKG2D. Signals from many activating receptors are mediated by extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) to effect degranulation [40]. In fact, it was found that YT-CB5 showed decreases in degranulation as well as phosphorylation of ERK1/2 following stimulation with antibodies to NKG2D [41]. 2B4 can receive stimulation with CD48 as ligand or anti-2B4 antibody to generate a signal that leads to cytotoxicity [35–37]. As 2B4 is not involved in the cytotoxicity of K562 cells, we utilized P815 cells bound to anti-2B4 antibody as targets to measure cytotoxicity with 2B4 receptor. It was found that YT-CB5 showed decreases in cytotoxicity against those P815 cells and in the degranulation induced by plate-coated antibodies to 2B4 [39]. Those findings indicate that asbestos exposure causes impaired cytotoxicity of NK cells attributable to alterations in cell surface expression of activating receptors. Moreover, we also examined the effect of asbestos exposure on NK cells using human peripheral blood mononuclear cells (PBMCs). Unlike the result obtained from cultures of YT-A1, NK cells in PBMC culture upon exposure to asbestos showed clear decreases in cell surface expression of NKp46 but not in NKG2D or 2B4 compared with grass wool representative man-made mineral fiber. NKp46 is a member of the natural cytotoxicity receptor (NCR) family, and it is known that the density of NKp46 is correlated with cytotoxicity against K562 cells [32–34]. Finally, we examined the natural cytotoxicity and expression of activating receptors of NK cells in PBMCs prepared from healthy volunteers and patients with malignant mesothelioma. Interestingly,
NK cells of mesothelioma patients showed low natural cytotoxicity as well as low expression of NKp46, but not of NKG2D or 2B4 in a similar manner to NK cells in PBMC culture exposed to asbestos. Taken together, our investigations of NK cell functions indicate that exposure to asbestos has the potential to decrease expression of activating receptors on NK cells, where NKp46 is a representative target for the effects of asbestos exposure, in addition to the NK cells of patients with malignant mesothelioma.

4. Decrease in Th1 phenotype caused by asbestos exposure and shown in mesothelioma patients more strongly than plaque-positive subjects

In an effort to examine the effect of asbestos exposure on CD4$^+$ T lymphocytes, our study utilized the human polyclonal T-cell line MT-2 [42, 43], and cells were cultured with continuous exposure to asbestos. From those cultures we obtained six asbestos-exposed sublines (MT-2CA1-3, MT-2CB1-3) and the original control MT-2 cell line (MT-2Org). Those cell lines were subjected to DNA microarray assays followed by clustering analyses. From the results, it was found that expression of 84 genes increased and 55 genes decreased by ca. twofold in the asbestos-exposed sublines and that all of the asbestos-exposed cell lines showed similar gene expression patterns [44]. Pathway and network analysis using the MetaCore System clarified that the Top 30 pathway results included the IFN-γ signaling pathway. Additionally, our previous study also identified decreases in IFN-γ production by MT-2CB1 cells [45]. In fact, the asbestos-exposed sublines showed decreases in expression of IFN regulatory factor 9 (IRF9) and IFN-stimulated gene factor-3 (ISGF3) as well as a chemokine receptor of CXCR3, which is positively regulated by IRF9. Th1 cells induced by stimulation are known to show increases in IFN-γ production and CXCR3 expression, which contribute to antitumor immune function [46, 47]. Flow cytometric analyses and real-time PCR (RT-PCR) confirmed that the percentage of cells positive for CXCR3 and mRNA levels of CXCR3 decreased in asbestos-exposed sublines, whereas that of CCR5, another chemokine receptor of the Th1-type, remained unchanged [44]. Moreover, CD4$^+$ T lymphocytes prepared from PBMCs were cultured in a similar manner upon exposure to asbestos. First, freshly purified CD4$^+$ T cells were expanded by stimulation with CD3 and CD28 to obtain sufficient cell numbers, and then those cells were utilized for culture in media supplemented with IL-2 upon exposure to asbestos. After 7 days of culture, there was no difference in %CXCR3$^+$ cells between cultures with and without asbestos exposure, although the percentage of those cells decreased 28 days later, in contrast to no changes being observed in %CCR5$^+$ cells. Additionally, asbestos-exposed CD4$^+$ T cells also showed decreases in intracellular expression of IFN-γ. Those findings are consistent with the results obtained from the experiment with MT-2 and indicate that asbestos exposure has the potential to effect a decrease in Th1 cell function of human primary T helper cells [48]. Finally, PBMCs from patients with malignant mesothelioma and subjects positive for pleural plaque, a representative sign of asbestos inhalation [5], were analyzed in a manner similar to the in vitro experiments mentioned above. Compared with healthy volunteers, both mesothelioma and plaque-positive groups showed low %CD4$^+$CXCR3$^+$ cell numbers in PBMCs and were much lower in the mesothelioma than in the plaque-positive group, whereas %CD4$^+$CCR5$^+$ numbers did not differ among the groups. Additionally, the mesothelioma group (but not the plaque-positive group) showed lower IFN-γ mRNA levels in CD4$^+$ T cells compared with healthy people [48]. Taken together, the results obtained from our studies demonstrate that asbestos exposure...
causes decreases in the Th1 phenotype of CD4+ T cells, which is shown in patients with malignant mesothelioma more strongly than in plaque-positive subjects.

5. Augmented Treg function mediated through cell–cell interaction and suppressive cytokines caused by exposure to asbestos

Treg cells represent a key population of cells with the phenotype CD4+CD25+Foxp3+ and function to suppress excess activation of immune responses as well as allow tumor cells to escape from immune surveillance [49, 50]. It has been reported that MT-2 cells also show this phenotype of cell surface markers and Treg-like suppressive function [51–54]. Additionally, MT-2 is a human polyclonal T-cell line immortalized by human T-cell leukemia virus type-1 (HTLV-1) and infection which causes adult T-cell leukemia (ATL) [42, 43]. Most CD4+CD25+ ATL cells express Foxp3, and some ATL cells have Treg-like suppressive function [51, 52, 54–56]. As a result, it has been suggested that ATL cells are derived from Treg cells. Therefore, MT-2 is useful in examining Treg cell function as well as Th cell function. Accordingly, we examined the Treg cell function of the MT-2 cell line continuously exposed to asbestos in the same manner as described above. First, we determined that the production of IL-10 increased twofold in the cell line exposed to asbestos relative to the original cell line, while the production of IFN-γ, TNF-α, and IL-6 decreased. IL-10 and TGF-β are immune-suppressive cytokines produced by Treg cells [26]. To examine phenomena upstream of the increase in IL-10 production, cells were treated with PP2, a specific inhibitor of Src family kinases (SFKs) which positively control IL-10 through transcription factors [57–59]. PP2 suppressed IL-10 mRNA levels, resulting in no difference between asbestos-exposed and nonexposed MT-2 sublines. Additionally, the subline exposed to asbestos showed increased Bcl-2 mRNA levels and a decrease in Bax, consistent with the fact that those cells survived in the toxic environment induced by exposure to asbestos. In fact, bcl-2 siRNA caused a decrease in cell growth upon exposure to asbestos. Moreover, phosphorylation of STAT3, part of the signaling pathway downstream of stimulation with IL-10 and target transcription of the bcl-2 gene, increased in the MT-2 subline exposed to asbestos [45]. Those findings indicate that asbestos induced an SFK-mediated increase in production of IL-10, in other words increased “Treg function,” with increased survival ability attributed to high bcl-2 expression through the STAT pathway downstream of IL-10 in an autocrine manner. Furthermore, MT-2 subline exposed to asbestos was analyzed for Treg function in terms of suppressing the proliferation of CD4+CD25− responder T (Tresp) cells, to express GITR and CTLA-4 cell surface markers and to produce suppressive cytokines such as TGF-β as well as IL-10. The asbestos-exposed subline showed enhanced suppression of Tresp cell proliferation stimulated with anti-CD3 antibody and induced dendritic cells (DCs), whereas there were no differences in cell proliferation stimulated with anti-CD3 and anti-CD28 antibodies between the sublines, suggesting the importance of cell–cell interactions for the enhanced suppression. Consistent with those findings, it was found that MT-2 subline exposed to asbestos tended to have decreased cell surface CTLA-4, which exerts suppressive function by cell–cell interactions with CD80 or CD86 on DCs [60, 61]. Additionally, TGF-β was produced at high concentrations by MT-2 subline exposed to asbestos, as IL-10 was also produced. It is interesting that the inhibited production of IL-10 or TGF-β by shRNA for those cytokine genes decreased the suppression efficiency of Tresp cell proliferation in the culture with transwell, indicating the absence of cell–cell interactions. Taken together, our
results indicate that exposure to asbestos causes augmentation of Treg function mediated through cell–cell interactions as well as the production of suppressive cytokines.

6. Interfered induction and maintenance of cytotoxic T lymphocyte activity caused by asbestos and shown in mesothelioma, but not plaque-positive, subjects

CD8⁺ cytotoxic T lymphocytes (CTLs) play a crucial role in antitumor immunity where they function to attack tumor cells together with NK cells [62]. Both NK cells and CTLs utilize perforin and granzymes to attack targets [63]. However, in contrast to NK cells, CTLs need to be induced from naïve CD8⁺ T cells by stimulation with antigen for activation, which occurs upon interaction with DCs as well as CD4⁺ T lymphocytes in lymph nodes [64–67], where inhaled asbestos fibers accumulate as mentioned above. Therefore, we sought to examine the effect of asbestos exposure on the induction phase of functional CTLs following stimulation with antigen. The mixed lymphocyte reaction (MLR) is an experimental and useful method to induce cell-mediated immunity by culturing two kinds of whole immune cells that differ allogenically from each other, such as CD8⁺ T as well as CD4⁺ T cells and DCs. Therefore, we employed MLR by culturing PBMCs as responder with allogenically different and irradiated PBMCs as stimulator upon exposure to asbestos in an effort to examine a variety of characteristics such as cell proliferation, cytotoxicity for allogenic target cells, and cytokine production by CD8⁺ T cells. Asbestos exposure during culture for MLR caused suppressed cytotoxic activity of CTLs with decreased proliferation of CD8⁺ T cells and production of IFN-γ and TNF-α, representative cytokines produced by activated CTLs [68]. Additionally, those CTLs harvested from culture with asbestos showed decreases in CD25 and CD45RO and an increase in CD45RA, which are activated and antigen-encountered markers and naïve markers on the cell surface, respectively [69]. Moreover, it is possible that prolonged exposure to asbestos might affect the functional activity of CTLs following antigen stimulation. EBT-8 is a cell line established from large granular lymphocyte leukemia of T-cell origin and shows surface expression of CD2, CD3, CD8, HLA-DR, and T-cell receptor alpha/beta, which are characteristic of cytotoxic T lymphocytes. Therefore, we examined alterations in the function of EBT-8 cells continuously exposed to asbestos for greater than 1 month. EBT-8 cells exposed to asbestos showed decreases in the percentage of cells positive for intracellular perforin, but not granzyme B. Additionally, those cells showed significantly decreased production of IFN-γ following stimulation with anti-CD3 antibody compared with control cells [70]. Those findings indicate that asbestos exposure interfered with the induction of functional CTLs following stimulation with antigen and that prolonged exposure to asbestos disrupts the functionality of CTLs, thereby leading to decreases in cytotoxic potential as well as production of IFN-γ. Along with those studies, we examined the functionality of CD8⁺ T cells in peripheral blood of patients with malignant mesothelioma and pleural plaque-positive subjects. Mesothelioma patients showed decreases in the percentage of stimulation-induced intracellular perforin⁺, but not granzyme⁺, cells in CD8⁺ T cells compared with healthy people, whereas plaque-positive subjects did not show any decrease [71]. Taken together, our results indicate that asbestos exposure interferes with induction and maintenance of functional CTLs, similar to peripheral CD8⁺ T cells of mesothelioma patients.
7. Conclusion

Thus, our studies clarified a number of characteristics pertaining to asbestos-induced immunological impairment in acquired immunity as well as in innate immunity, some of which were also actually observed in patients with malignant mesothelioma. Figure 1 summarizes those immune-suppressive effects of asbestos which presumably contribute to the development of malignant mesothelioma. Asbestos exposure suppressed immune-activating functions (Th1) and natural (NK) and acquired cytotoxicity (CTLs), whereas asbestos augmented functions of suppressive T lymphocytes (Tregs). Additionally, high production of TGF-β by long-surviving macrophages (Mφ) caused by asbestos contributes to lung fibrosis as well as immune suppression. The immunological conditions generated by those characteristics allow abnormal cells caused by cellular toxicity of asbestos to escape from immune surveillance and survive to develop malignant mesothelioma. As mentioned above, it is actual that some of the characteristics caused by asbestos exposure were also shown in patients with malignant mesothelioma. Interestingly, plaque-positive subjects (without tumors) showed no impairment in some functions compared with mesothelioma patients, suggesting that their sustained immune functions protected them from malignant mesothelioma following asbestos exposure. On the basis of our present knowledge, we recently undertook a comprehensive analysis of the immunological characteristics of peripheral blood of mesothelioma patients as well as plaque-positive subjects. Parameters examined included cell surface markers, mRNA expression, and plasma cytokine concentrations. From the results of these analyses, we established three formulae for scoring mesothelioma, pleural plaque without tumors, and asbestos exposure (for both mesothelioma patients and plaque-positive subjects) (international patent...
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The immunological screening devices might contribute to the detection of subgroups of people who have suppressed immune functions among people exposed to asbestos prior to diagnosis by CT images and histological observations. Moreover, those of our knowledge encourage us to treat mesothelioma with some kinds of immunotherapy. It is reasonable to assume that inhibitors targeting on Treg cells or suppressive macrophages might contribute to treatment of malignant mesothelioma. In addition, it has also been found that asbestos-caused decrease in cytotoxicity of CTL was improved by exogenous IL-2, but not accompanied with restoration of cell surface markers [72], which suggests that an appropriate immunotherapy might be developed to augment antitumor immunity in patients with mesothelioma as well as subjects exposed to asbestos. Thus, our studies could further our understanding of the immunological mechanisms associated with asbestos-induced malignant mesothelioma and perhaps facilitate the development of methodologies that can be employed for the early detection as well as treatment of mesothelioma. These are issues we intend to further address in the future.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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