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Review Article

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2. Asbestos-induced mesothelioma: Tumor escape and alteration of immune surveillance

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Abstract. Malignant mesothelioma (MM) is mainly caused by exposure to asbestos. Recent cellular and molecular analyses of mesothelioma cells have resulted in the discovery and development of newer altering genes such as BAP1, YAP and LATS2, as well as inactivated CDKN2 and NF2/Merlin. However, mesothelioma is still a poor prognostic disease and newer diagnostic and therapeutic methods are required in clinical investigations. Additionally, in order to ensure the capacity of host-tumor surveillance it is important to consider the bases of immunotherapy and also the prevention of carcinogenesis among the asbestos-exposed population. In this review, we summarize recent findings of host-

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tumor surveillance concerning mesothelioma and our results regarding the effects of asbestos exposure on immunocompetent cells in relation to tumor surveillance. The alteration of MM cells in relation to tumor escape has not been adequately investigated, whereas several significant findings have been obtained from clinical analyses and some animal models particularly in regard to Treg. On the other hand, asbestos exposure seems to reduce the capacity of host-tumor surveillance involving NK cells, CD4+ T cells, Treg and CTL functions according to our experimental results and data based on specimens obtained from asbestos-exposed patients such as those with pleural plaque (PP) and MM. Future studies are needed to clarify the relationship between the asbestos-exposed immune system and alteration of mesothelioma cell characteristics for the development of improved prevention and clinical therapy for this disease.

Introduction

Malignant mesothelioma (MM) is rare cancer [1-4]. However, there are many issues associated with this cancer regarding medical and social aspects that need to be solved. For example, Japan erupted in the summer of 2005 with a cancer scare. Residents were suddenly informed that asbestos, which was used in large amounts from the early 1950s up to the early 1990s in Japan with a maximum usage of approximately 352,000 tons in 1974, caused MM [5]. At the beginning of this period the news media revealed that residents who lived near the asbestos-handling manufacturer Kubota Corporation in Amagasaki City, Hyogo Prefecture, developed MM [6-8]. Additionally, many workers employed by this manufacturer either suffered or died from asbestos-induced diseases such as asbestosis and MM. People now knew MM might occur even if they never worked in the asbestos-handling industry. Furthermore, a plethora of information regarding MM caused a heightened sense of anxiety in the Japanese population for various reasons. First, people were informed that a relatively small amount of exposure caused MM despite a high-dose exposure needed to cause lung fibrosis in asbestos-handling workers. Additionally, people basically did not remember how they came into contact with asbestos or the level to which they were exposed. Second, information regarding the difficulty of diagnosis, the limited number of chemotherapeutic agents (it was several months before pemetrexed was approved for use against MM in Japan), and the very poor prognosis were now known by the population, which made people feel anxious. Third, people were not aware of the possibility of future exposure such as that resulting from building demolition sites and rubble processing. Furthermore, other factors increased their anxiety such as the cost of medical care, the disposal of waste including asbestos, and so on. This situation may be experienced by a population in any country that continues to use asbestos,

and several nations still export asbestos to developing countries where the ban of asbestos is not enforced [9].

MM cell biology has recently made good progress. In addition to increasing our understanding of the inactivation of the cyclin-dependent kinase inhibitor 2A (CDKN2A, $p16^{Ink4A}$) and Merlin (also called neurofibromin 2 (NF2) or schwannomin) [10-15], germline mutations in the gene encoding breast cancer susceptibility gene I (BRCA1) associated protein-1 (BAP1) were found in the familiar mesothelioma as well as solitary MM [16-18]. This is also closely related to other cancers such as uveal melanoma, melanocytic tumors and ovarian cancer. However, it is not known why asbestos exposure causes these specific gene alterations. To this end, it may be beneficial to consider the alteration of immunocompetent cells surrounding mesothelium. Asbestos may cause modification of immune surveillance and induce chronic inflammative status in immunocompetent cells. This may cause chronic and recurrent stimulation of mesothelial cells, and after a long latent period (epidemiologically it is assumed 40 years elapses for the development of mesothelioma following the initial exposure to asbestos fibers) the mesothelial cells gain the genetic changes for carcinogenesis and may rapidly progress and escape from the usual immune surveillance. Recent findings regarding the role of NALP3 (NACHT, LRR and PYD domains-containing protein) or cryopyrin, which is a protein that in humans is encoded by NLRP3 (NOD-like receptor family, pyrin domain containing 3), indicate that inflammasomes allow the initiation of alteration of antigen-presenting cells to cause chronic inflammation when silica particles or asbestos fibers are inhaled in the lung [18,19]. However, it is not clearly understood why silica mainly causes lung fibrosis by making fine nodules in the upper lung fields, while asbestos induces linear or honey-comb-like fibrosis mainly in the lower lung fields [21-23]. Moreover, although lung cancer caused by silica exposure was only recognized from epidemiological studies [24], basically silica does not cause MM. Although low-dose exposure to asbestos fibers causes MM, high-dose exposure to asbestos is thought to cause lung lesions such as those associated with asbestosis/fibrosis and lung cancer [25,26]. These phenomena may not be understood by simply considering the differences of the physiological configuration between particles and fibers.

In Japan, many medical research projects were conducted in an effort to reduce the anxieties of the people in regard to cancer. It is in this context that the authors were involved in the project “Comprehensive approach of asbestos-related diseases”, supported by the “Special Coordination Funds for Promoting Science and Technology” (Head: Dr. T. Otsuki, Department of Hygiene, Kawasaki Medical School, Kurashiki, Japan) from 2006 to 2010.

Clinically, this project conducted a case and clinical specimen registration system, a feasibility clinical trial using anticancer chemotherapeutic agents, extrapleural pneumonectomy with subsequent radiation therapy for early-stage MM, and efforts to develop early diagnostic markers such as soluble mesothelin-like peptide (SMRP) and establish endoscopic devices using narrow-band or autofluorescence imaging. In addition, the project included basic research such as analysis of cellular and molecular characteristics using mesothelioma cell lines, investigations of asbestos-induced carcinogenesis using an animal model, and study of the immunological effects of silica/asbestos. The first basic research group found that the LATS2 (large tumor suppressor homolog 2) gene is a novel tumor suppressor in MM and that the Yes-associated protein (YAP) exhibits oncogenic activity in MM [27-29]. Both genes and the NF2 gene were involved in the Hippo signaling pathway. The second research group discovered the importance of iron in MM carcinogenesis, and a comparison of asbestos with carbon nano-tubes indicated the importance of the physical configuration of asbestos [30,31].

In this review, tumor escape by MM cells is reviewed and our findings concerning reduction of immune surveillance for malignant tumor caused by asbestos are presented.

Mesothelioma and immune surveillance

For tumor surveillance, several lymphocytes function to facilitate tumor cell lysis and reduce developing tumor cells. CD8+ cytotoxic T lymphocytes (CTLs) are capable of inducing the death of infected somatic or tumor cells [32-34]. Most CTLs express T-cell receptors (TCRs) that can recognize a specific antigenic peptide bound to Class I MHC (major histocompatibility complex) molecules, present on all nucleated cells. The first signal is the peptide-bound MHC class I molecule on antigen presenting cells (APC). There is a second interaction between the CD8 co-receptor and the class I MHC molecule to stabilize this signal. Thereafter, the second signal uses the CD28 molecule on CTL, and on the T cell uses either CD80 or CD86 (also called B7-1 and B7-2) on APC. CD80 and CD86 are known as co-stimulators for T cell activation. This second signal can be assisted (or replaced) by stimulating the CTL cell with cytokines released from helper T cells. CTLs after recognition of tumor antigen release the cytotoxins perforin, granzymes and granulysin. In addition to these molecules, the Fas ligand is also expressed on CTLs. Furthermore, CTLs also release interferon-γ to kill tumor cells.

Another main player in tumor surveillance is the natural killer (NK) cell [35-38]. NK cells recognize tumor cells and release perforin and granzyme A

and B to cause tumor cell apoptosis. NK cells express MCH class I receptor molecules such as those of the KIR (killer inhibitory receptor/killer cell immunoglobulin-like receptor) family and NKG2 family characterized by a lectin-like domain [39,40]. The KIR family mainly binds to typical HLA-A, B, and C. The CD94/NKG2 family binds to HLA-E and also MHC class I chain-related protein A (MICA) and B (MICB), and UL16-binding protein (ULBP) [40,41]. Both families include an activating and inhibitory function for NK cell activity. In addition, natural cytotoxic receptors (NCRs), including NLp46, NKp44 and NKp30, also play a major role in NK-mediated tumor cell killing [42-44]. Although the ligand for this receptor family has not been identified, it has been demonstrated that NKp46 contributes to various types of tumor cells.

Recent progress regarding the CD4+25+Foxp3 (Forkhead box P3, Scurfin)+ regulatory T cell (Treg) highlights its role in tumor immunity [45-47]. Treg plays an indispensable role in maintaining immunological unresponsiveness to self-antigens and in suppressing excessive immune responses deleterious to the host. Thus, if the function and/or number of Treg increase, stimulation of responder T cells against foreign or self-antigens may not cease by the Treg inhibitory function and might yield an allergic status or dysregulation of self-tolerance. In contrast, if the function and/or number of Treg increase, there must be an inhibition of anti-tumor immunity, graft-versus-host reaction, etc. Particularly in regard to anti-tumor immunity, if the circulating Treg does not change its function or number, an increase of Treg at areas surrounding a tumor occurs and Treg near the tumor suppresses the function of CTL and NK cells, which allows tumor cells to escape from host-tumor surveillance.

In addition, tumor cells sometimes express or alter their tumor antigen or immunological molecules. Regarding MM, expression of interleukin (IL)-4α has been reported in mesothelioma cells associated with poor prognosis [48]. These IL-4α expressing MM cells increased production of some inflammatory cytokines such as IL-6, IL-8 and vascular endothelial growth factor (VEGF). Although detailed mechanisms have not been elucidated, this may represent one example of mesothelioma cell alteration that results in escape from immune surveillance.

Another interesting finding regarding mesothelioma and anti-tumor immunity is related to exosomes secreted by MM cells. Exosomes are small membrane vesicles secreted into the extracellular compartment [49-51]. Tumor exosomes may react with tumor-killing molecules derived from immunocompetent cells functioning as anti-tumor antigens such as NK cells and CTLs. Hegmans *et al.* [49] reported that MM cell lines secreted exosomes and Clayton *et al.* [50,51] demonstrated that MM cell-derived

exosomes down-modulate NKG2D expression in human NK cells. In the latter study, researchers analyzed a cell line and cells isolated from pleural effusions of MM patients and found that these MM-derived exosomes triggered down-regulation of surface NKG2D expression on NK cells and CD8+ CTL. These events also change MM cells to alter their features in order to escape from host-anti-tumor immunity.

Several investigations have focused on Treg and MM, especially in humans [52-56]. CD4+ T cells co-expressing CD25 and FoxP3 have been found in MM biopsy specimens. Additionally, higher levels of CD4+25+ tumor-infiltrating T cells indicated poor prognosis. Furthermore, Treg was identified from MM pleural effusions showing a high concentration of transforming growth factor (TGF)-β, which is one of the main soluble factors with IL-10 for Treg function in addition to cell-cell contact. However, the population of circulating peripheral Treg did not differ between MM patients and healthy donors. These findings indicate that MM cells may produce soluble factors to bring Treg in close proximity and allow Treg to be safeguarded against host-anti-tumor immunity.

The alteration of NK cells and MM has not been well demonstrated [57]. The important factor in MM cells is HLA expression, and it has been reported that all MM cell lines examined constitutively expressed class I, but not class II, surface antigen, and that all three class I loci (HLA-A, HLA-B, and HLA-C) are expressed [58]. This information may be encouraging for NK cell-mediated tumor surveillance for MM; however, MM cells may introduce dysfunction of NK cell tumor killing activity such as that associated with the above-mentioned exosomes. In addition, we demonstrated that asbestos exposure reduced NK cell function. NK cells and other immunocompetent cells associated with anti-tumor immunity showed a reduction of anti-tumor immunity when exposed to asbestos experimentally as detailed in our investigations [59,60] and in the next chapter.

Immunological effects of asbestos causing reduction of anti-tumor immunity

We have been conducting detailed studies to determine which people exposed to asbestos slowly progress toward a reduced tumor surveillance capacity [61,62]. This is important because the development of MM involves a relatively long period of 30 to 40 years following the initial exposure, and the exposed population has a relatively high risk of cancers other than MM and lung cancer such as laryngeal, gastrointestinal and bladder [63-65].

Firstly, the effects of asbestos on the function of NK cells were analyzed using a human NK cell line (YT-A1, kindly provided by Dr. Y. Yodoi, Kyoto University) and freshly isolated NK cells from healthy donors (HDs) exposed *ex vivo* to chrysotile asbestos. NK cell cytotoxicity was reduced when YT-A1 cells were continuously exposed to a relatively low-dose concentration. Regarding cytotoxic granules, the intracellular expressions of granzyme B and perforin were reduced as analyzed by flow cytometry. Moreover, among the various NK cell activating receptors, the expression of NKG2d and 2B4 was reduced. In addition, freshly isolated NK cells from HDs exposed *ex vivo* revealed the same reduction of cytotoxicity, whereas the key molecule particularly influenced by chrysotile exposure was the NKp46 activating receptor belonging to NCR. Furthermore, analysis of freshly isolated NK cells from patients with MM revealed a reduction of NKp46, but not NKG2D or 2B4. Taken together, and considering that the results obtained from the cell line may not be natural, the target of asbestos to reduce NK cell cytotoxic activity is the NKp46 molecule. It may therefore be possible to use the expression level of NKp46 in peripheral NK cells as a marker for asbestos-exposure or tumor-bearing in people who have come in contact with asbestos through work or live/lived near asbestos-handling industries as shown in Fig. 1 [66].

As mentioned above, NK cell activity was reduced by asbestos exposure. Due to the reduction of NKG2D and 2B4 expression levels in the NK cell line we used, the alteration of signaling pathway was analyzed. Although NK cell-activating receptors possess different adaptor molecules to induce degranulation, the most important of these molecules is extracellular signal-regulated kinase (ERK). Thus, the phosphorylation status of ERK1/2 was examined using the YT-A1 subline exposed continuously to chrysotile. In spite of enhancement of ERK1/2 phosphorylation when YT-A1 original cells were cultured with target tumor cells, K562, the subline did not show any increase in phosphorylation of ERK1/2. In addition, the reduction in phosphorylation of ERK1/2 in the YT-A1 cell line was also obtained when cells were treated with wortmannin and PP2, inhibitors of phosphoinositide 3-kinase (PI3K) and Src-family kinase, respectively, when NK cells were cultured with target K562 cells and anti-2B4 or NKp46 antibodies were added to the culture [67].

These results strongly suggest that NK cells exposed to asbestos reduced their cytotoxic activity through inhibition of signaling pathways converging on the ERK1/2 molecule and a decrease in degranulation of perforin and granzyme B as shown in Fig. 1. Further investigation is needed regarding modification of NK cell activity as influenced by asbestos-exposed dendritic cells or monocyte/macrophage lineage cells because their production of

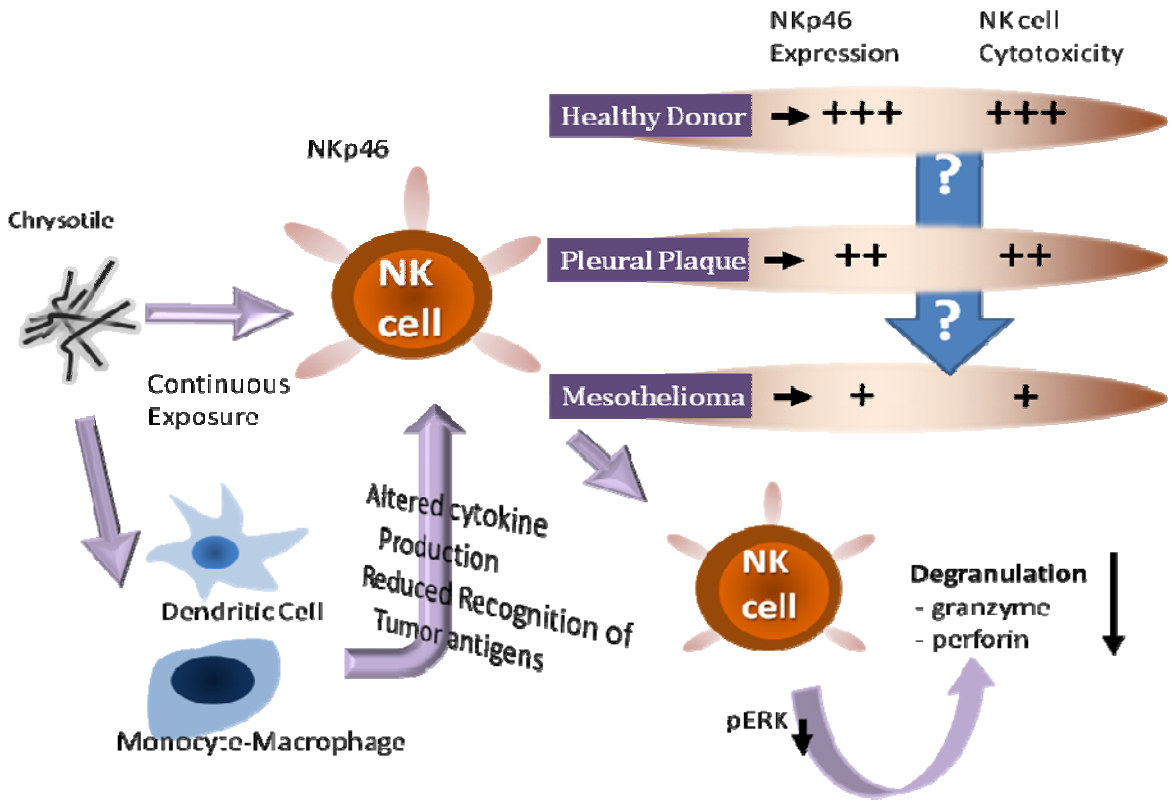

Figure 1. Schematic representation of the effects of asbestos directly on NK cells or indirectly via dendritic cells or monocyte-macrophage lineage cells, reduction of NK cell activating receptor, NKp46, including the relationship with disease status in regard to HD, PP or MM, and reduction of ERK1/2 phosphorylation and degranulation in NK cells resulting in reduction of their cytotoxicity due to asbestos exposure.

cytokines may affect K cell activity and production may be altered by asbestos exposure on these types of cells [68-71].

Next, we observed the effect of chrysotile exposure on CD4+ T cells using the Human Adult T Cell Leukemia Virus-I(HTLV-I) immortalized human polyclonal T cell line, MT-2 [70,71]. As schematically summarized in Fig. 2, the transient exposure to chrysotile and crocidolite on this cell line caused apoptosis through production of reactive oxygen species (ROS), activation of pro-apoptotic mitogen-activated protein kinase (MAPK) signaling molecules such as p38 and c-Jun N-terminal kinase (JNK), activation of mitochondrial apoptotic pathway with upregulation of BAX, release of cytochrome c from mitochondria to the cytosol, and cleavage of caspase 9 [70]. Continuous (more than eight months) and low-dose (dose of chrysotile or crocidolite causing less than half of the cells to proceed to apoptosis) exposure induced resistance to asbestos-induced apoptosis through

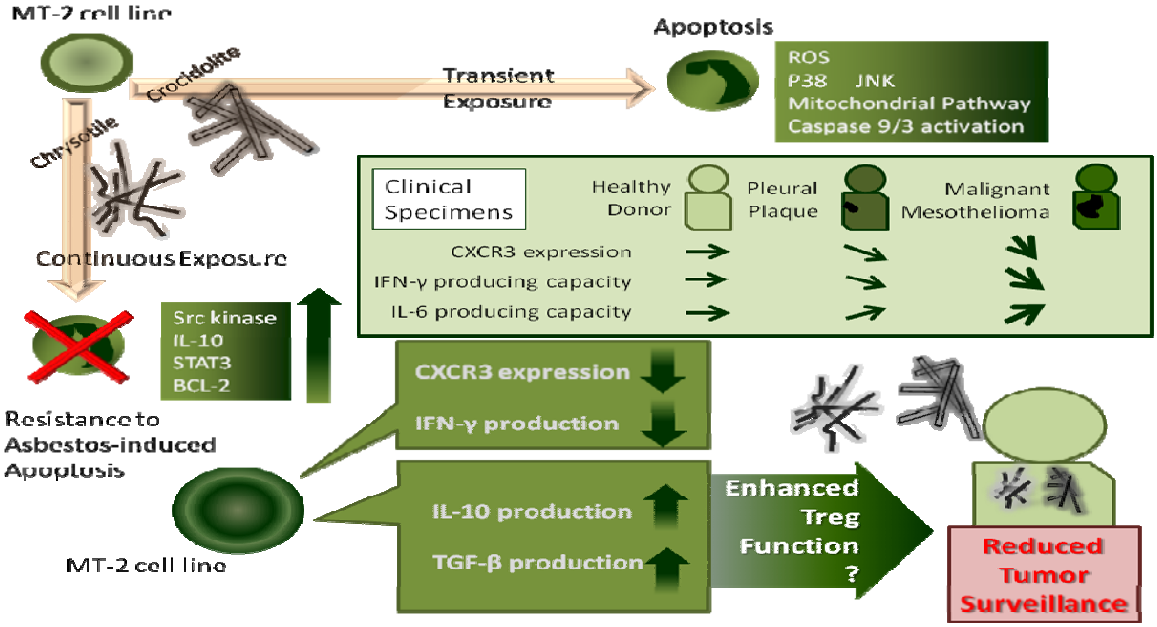

Figure 2. Schematic representation of asbestos-induced reduction of expression of a chemokine receptor, CXCR3, and expression and production of IFN-γ with increasing IL-6 using the MT-2 cell line model exposed continuously to a low dose of chrysotile (upper left), an *ex vivo* exposure model using freshly isolated CD4+T cells from healthy donors (HD) (upper right), as well as analyses of freshly isolated CD4+ T cells from HDs and patients with pleural plaque (PP) and malignant mesothelioma (MM) (lower panels).

upregulation of IL-10 mediated by Src-family kinase, autocrine usage with increased IL-10, and activation of the signal transducer and activator of transcription 3 (STAT3) with upregulation of BCL-2 located down-stream of STAT3 [71]. Thereafter, experiments with continuously exposed sublines (we established several independent sublines) revealed reduced expression of chemokine (C-X-C motif) receptor 3 (CXCR3) as examined by cDNA microarray and real-time reverse transcription polymerase chain reaction (RT-PCR), and protein levels were analyzed by flow cytometry, western blotting and immunofluorescent staining 70,71]. The reduced expression of CXCR3 was found not only in the cell line model, but also in the *ex vivo* exposure model using freshly isolated CD4+ peripheral T cells derived from HDs or CD4+ T peripheral T cells derived from asbestos-exposed patients such as those with pleural plaque (PP) and MM [73]. Similar to CXCR3, other Th1-type molecules such as IFN-γ, C-X-C motif chemokine 10 (CXCL10)/IFN-γ-induced protein 10 (IP-10) as the ligand for CXCR3, and chemokine (C-C motif) ligand 4 (CCL4)/Macrophage inflammatory protein-1 (MIP-1)-β exhibited reduced production or mRNA expression in all the MT-2 sublines. In addition, peripheral CD4+ T cells from patients with PP or MM

showed increased IL-6 production compared with those from HDs when these cells were stimulated *in vitro* with anti-CD3/CD28 antibodies for five days. Finally, peripheralCD4+ T cells derived from PP or MM patients exhibited CXCR3 surface expression [72,73].

Since CXCR3 is a G-protein-coupled seven-transmembrane receptor expressed on various lymphocytes including T, B and natural killer (NK) cells, it binds to IFN-γ-inducible chemokines such as CXCL9/Monokine induced by IFN-γ(MIG), CXCL10/IP10 and CXCL11/ IFN-inducible T-cell α chemoattractant (I-TAC) that recruit leukocytes to inflammatory sites such as tumors [74-76]. In the case of CD4+ T cells, CXCR3 is preferentially expressed and IFN-γ-producing Th1/effector T cells exhibit high-level production of inflammatory cytokines. As described above, anti-inflammatory cytokine IL-10 was highly produced in MT-2 sublines and in plasma from PP or MM patients. However, CD4+ T cells from these patients showed the potential for a high production of IL-6 [71,77]. Taken together, continuous exposure to asbestos caused reduction of tumor immunity induced by CXCR3 and IFN-γ cytokine networks, whereas the lesions where asbestos fibers are localized may be modified immunologically and chronic inflammation may have occurred as suggested by potential IL-6 production to result in molecular changes leading to carcinogenesis [59]. IL-10, which is highly produced in MT-2 sublines exposed continuously to asbestos, may have a later effect when cells start to transform at the locus. Overall, the effects of asbestos on CD4+ T cells modify the inflammatory and transforming status in the lesion where asbestos and mesothelial cells are co-localized, and slowly progress towards carcinogenesis over 30 to 40 years, which is considered the latency period for the occurrence of mesothelioma (Fig. 2) [1-4].

Use of the MT-2 cell line model revealed the interesting fact that MT-2 can be considered an immortalized cell line of Treg, since MT-2 possesses inhibitory effects like Treg, it express CD4, CD25 and FoxP3, and HTLV-1 is thought to possess an affinity to Treg [78-80]. Therefore, we are now investigating Treg function in the MT-2 original cell line (which was never exposed to asbestos) and the continuously exposed sublines. At the very least, we found that the sublines expressed and produced much higher IL-1-0 and TGF-β at their mRNA and protein levels [71,77]. These findings indicate that continuous exposure to asbestos on Treg enhances production of typical functional soluble factors [54-56]. We have now been conducting analyses of Treg function in sublines continuously exposed to asbestos to investigate cell-cell contact as well as cellular and molecular changes in sublines regarding the Treg phenotype such as FoxP3 expression and other Treg-specific surface markers (cytotoxic T-lymphocyte antigen 4/CD152 (CTLA-4),

glucocorticoid-induced TNFR (tumor necrosis factor-receptor)-related protein (GITR), etc.) [54-56]. Although these findings will be reported in the near future, our results show that soluble factors are highly produced in asbestos-exposed sublines and indicate that Treg function may be enhanced in asbestos-exposed people and might influence the reduction of tumor surveillance in these populations.

We have also been investigating the role of asbestos exposure on the differentiation and proliferation of CTL. Although these findings have not been published, preliminary data indicate that asbestos exposure may inhibit CTL characteristics for tumor attack.

Conclusion and future investigations

Tumor escape of MM from host-tumor surveillance should be considered because of the cellular and molecular changes exhibited by MM cells and the effects of asbestos on the capacity for anti-tumor immunity. The alteration of MM cells in regard to tumor escape has not been thoroughly investigated, although several important findings have arisen following clinical analyses and the use of some animal models particularly in relation to Treg [52-56]. On the other hand, our experimental results with data based on specimens obtained from asbestos-exposed patients with PP and MM indicate that asbestos exposure seems to reduce the capacity of host-tumor surveillance

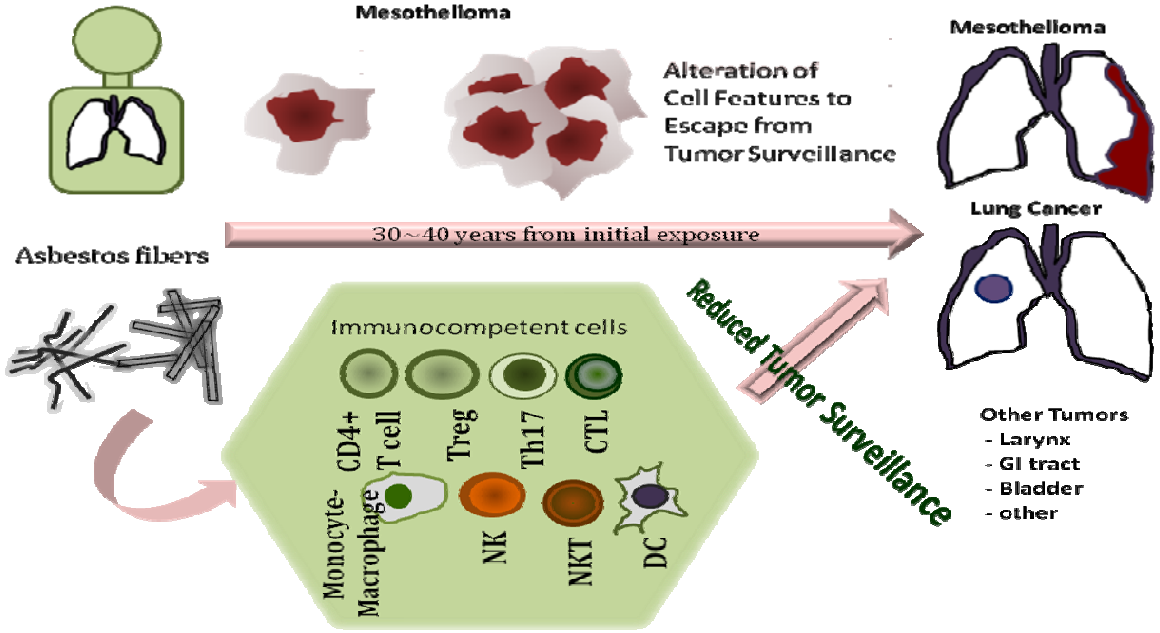

Figure 3. Schematic representation of tumor escape and alteration of immune surveillance in mesothelioma.

involving NK cells, CD4+ T cells, Treg and CTL functions. Future research should investigate antigen-presenting cells such as macrophages, dendritic cells, Th17 cells [81-84], which are thought to be related to carcinogenesis and dysregulation of autoimmunity, and NKT cells (Fig. 3). Overall, the relationship among these immunocompetent cells and the roles they play in tumor surveillance may affect the asbestos-exposed population [85-87] and lead to a slow reduction of tumor surveillance, including progression towards carcinogenesis after a long-term latency period following the initial exposure to asbestos.

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