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Commentary on "Mechanisms of asbestos-induced carcinogenesis" published in 2009

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Respiratory exposure to asbestos fibers has been associated with diffuse malignant mesothelioma (DMM) in humans. Despite advancements in the molecular analyses of human DMM and the development of animal models, the carcinogenic mechanisms of the disease remain unclear. There are basically three hypotheses regarding the pathogenesis of asbestos-induced DMM, which may be summarized as follows: (1) the "oxidative stress theory" is based on the fact that phagocytic cells that engulf asbestos fibers produce large amounts of free radicals due to their inability to digest the fibers, and epidemiological studies indicating that iron-containing asbestos fibers appear more carcinogenic; (2) the "chromosome tangling theory" postulates that asbestos fibers damage chromosomes when cells divide; and (3) the "theory of adsorption of many specific proteins as well as carcinogenic molecules" states that asbestos fibers in vivo concentrate proteins or chemicals including the components of cigarette smoke. Elucidation of the major mechanisms underlying DMM would be helpful for the development of novel strategies to prevent DMM induction in people who have already been exposed to asbestos.
Keywords: Asbestos, Mesothelioma, Iron, Oxidative stress

Asbestos is a natural fibrous mineral, which has been used abundantly for various industrial purposes especially in the last century. It is unfortunate that this material has been used till 2006 in Japan and is still in use in many developing countries due to the economical merits though International Agency for Research on Cancer (IARC) in World Health Organization announced that all the asbestos is a definite carcinogen to humans in 1987. Chrysotile, crocidolite and amosite are the major three asbestos mined, manufactured and used.[1] I am excited to know that this review article on the mechanism of asbestos-induced carcinogenesis published in the Nagoya Journal of Medical Science in 2009[2] attracted the interests of many researchers with high citation.

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Of note, mesothelial cells are the major target cells in asbestos-induced carcinogenesis. In this review article, I for the first time summarized the carcinogenic mechanism into three distinct processes: 1) scavenging of asbestos fibers by macrophages, leading to persistent free radical generation (frustrated phagocytosis), 2) unexpected intense phagocytic activity of mesothelial cells, and 3) adsorption of specific proteins on asbestos surface (Ex. hemoglobin and histone). Notably a combination of the 2nd and the 3rd mechanisms I proposed can explain the specific mutagenic activity of asbestos in mesothelial cells via providing oxidative damage through the attraction of iron-loaded asbestos to chromosomal histones. In this review article,[2] I also suggested the mechanisms why chrysotile, white asbestos with no iron in itself, can induce similar oxidative DNA damage, where high hemolytic activity via chrysotile was the key phenomenon.

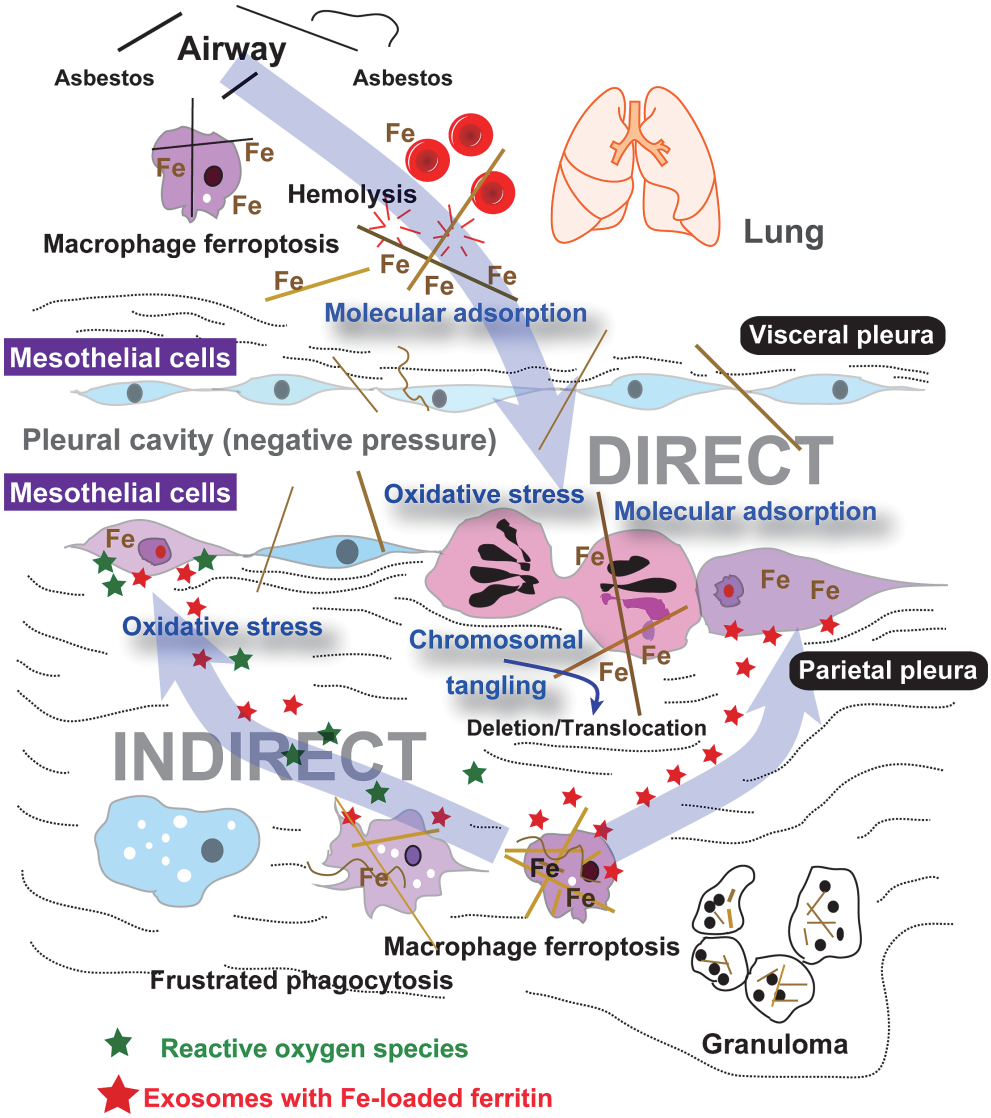

Fig. 1 Current understanding of asbestos-induced mesothelial carcinogenesis

More than 10 years after the publication, there have been great advancements in the understanding of molecular mechanisms. We have revealed that chrysotile-induced malignant mesothelioma in rats shows excess iron pathology with homozygous deletion of *p16*^{Ink4a} tumor suppressor gene,[3] which we believe is the evidence of iron-induced carcinogenesis.[4] Carbon nanotubes are an essential material for modern electronic technologies, such as semiconductors and lithium batteries. Multiwalled carbon nanotube of ~50 nm diameter shows the similar pathologic processes to those of asbestos,[5] which has to be carefully handled as assigned Group 2B by IARC. Iron removal either by iron chelating agents or phlebotomy could work as cancer prevention of asbestos-induced mesothelial carcinogenesis at least in the preclinical animal models.[4]

Recently, further advances have been achieved on this topic. It is well established that exosomes, containing various intracellular molecules, are used for multicellular communications in vivo. Our laboratory recently found a link between exosome production and iron metabolism. Specifically, CD63, a representative exosome marker, is regulated posttrancriptionally via iron-regulatory protein/iron-responsive element system, which is specific for iron metabolism.[6] Furthermore, macrophages exposed to the asbestos of diameter and/or length which they cannot cope with die in the form of ferroptosis. In those situations, iron-loaded ferritin is released as exosomes from the dying macrophages representing ferroptosis. Notably, these exosomes are received by mesothelial cells where oxidative DNA damage, such as DNA double-strand breaks and 8-hydroxy-2'-deoxyguanosine, is induced[7]. This is a novel indirect mechanism of asbestos-induced mesothelial carcinogenesis (Fig. 1). In this way, this review article worked as a detonator for further elucidation of asbestos-induced mesothelial carcinogenesis.

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