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Review Article

Malignant mesothelioma as an oxidative stress-induced cancer: An update

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ABSTRACT

Malignant mesothelioma (MM) is a relatively rare cancer that occurs almost exclusively following respiratory exposure to asbestos in humans. Its pathogenesis is closely associated with iron overload and oxidative stress in mesothelial cells. On fiber exposure, mesothelial cells accumulate fibers simultaneously with iron, which either performs physical scissor function or catalyzes free radical generation, leading to oxidative DNA damage such as strand breaks and base modifications, followed by activation of intracellular signaling pathways. Chrysotile, per se without iron, causes massive hemolysis and further adsorbs hemoglobin. Exposure to indigestible foreign materials also induces chronic inflammation, involving consistent generation of free radicals and subsequent activation of NALP3 inflammasomes in macrophages. All of these contribute to mesothelial carcinogenesis. Genomic alterations most frequently involve homozygous deletion of *INK4A/4B*, and other pathways such as Hippo and TGF-β pathways are also affected in MM. Recently, analyses of familial MM sorted out *BAP1* as a novel responsible tumor suppressor gene, whose function is not fully elucidated. Five-year survival of mesothelioma is still ~8%, and this cancer is increasing worldwide. Connective tissue growth factor, a secretory protein creating a vicious cycle mediated by β-catenin, has been recognized as a hopeful target for therapy, especially in sarcomatoid subtype. Recent research outcomes related to microRNAs and cancer stem cells also offer additional novel targets for the treatment of MM. Iron reduction as chemoprevention of mesothelioma is helpful at least in an animal preclinical study. Integrated approaches to fiber-induced oxidative stress would be necessary to overcome this currently fatal disease.

Contents

Abbreviations: α-TOS, α-tocopheryl succinate; BAP1, BRCA1 associated proteins 1; BRCA1, breast cancer susceptibility gene 1; CDK4, cyclin-dependent kinase 4; CEA, carcinoembryonic antigen; CSC(s), cancer stem(-like) cell(s); CTGF, connective tissue growth factor (CCN2); EGCG, epigallocatechin-3 gallate; EMT, epithelial mesenchymal transition; FHC, ferritin heavy chain; FOXM1, forkhead box M1; HMGB1, high motility group box 1; IARC, International Agency of Research on Cancer (World Health Organization); IMP3, insulin-like growth factor 2 mRNA-binding protein 3; IRS-1, insulin receptor substrate-1; MAPK, mitogen-activated protein kinase; miRNA, microRNA; MDM2, mouse double minute 2; MM, malignant mesothelioma; MPF, megakaryocyte potentiating factor; MPM, malignant pleural mesothelioma; MWCNT(s), multiwalled carbon nanotube(s); NALP3, NACHT, LRR, and PYD domains-containing protein 3; NF2, neurofibromatosis type 2; NTA, nitrilotriacetate; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; pRB, retinoblastoma protein; PRX3, peroxiredoxin 3; RAGE, the receptor of advanced glycation end products; RASSF1A, *ras* association domain family 1 isoform A; RNS, reactive nitrogen species; ROS, reactive oxygen species; RTKs, receptor tyrosine kinases; SBL, sialic acid-binding lectin; SMRPs, soluble mesothelin-related peptides; SP, side population; TLR, toll-like receptor; TR, thioredoxin reductase; TRAIL, tumor necrosis factor-related apoptosis inducing ligand; TXNIP, thioredoxin interacting protein; TRX2, thioredoxin 2; YAP, Yes-associated protein.

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Introduction

Malignant mesothelioma (MM) originates from the thin monolayer of mesothelial cells, lining the body cavities and surfaces of internal organs. It can arise in the pleural cavity, peritoneal cavity, pericardial cavity, or tunica vaginalis, but the pleural cavity is most frequently involved (~80%) [1]. A study based on the WHO mortality database reported a death toll of 92,253 from MM within 1994–2008 in 83 countries [2] and global cases of MM are projected to be on the rise for decades to come [3]. Although not as common as other types of human cancer, this tumor is nevertheless very aggressive in nature and is usually in the advance stage when diagnosed, resulting in a short median survival (~9 to 12 months) [4,5]. Development of MM is closely related to exposure to fibrous particles, the most widely known of which are the asbestos fibers (Group 1, definite carcinogen to humans by International Agency of Research on Cancer [IARC], World Health Organization). Asbestos fibers were discovered to be the causative agent of MM in the 1960s [6]. More recent data from animal experiments also suggested that carbon nanotubes, a kind of synthetic fiber (Group 2B, probable carcinogen to humans by IARC) [7], that share needle-like characteristics similar to those of asbestos fibers, are able to induce MM [8–10].

The use of asbestos has been banned in many developed countries since the discovery of its carcinogenic property, but some developing countries such as China and India still permit its usage [2]. Moreover, the rapid advancement in nanotechnology also poses potential health hazards as more widespread use of nanoproducts can be anticipated in the near future. Cases of MM without evidence of asbestos exposure have also been reported [11,12]. Considerable progress has been made regarding the mechanisms of mesothelial tumorigenesis over the past decade. Numerous evidence suggests that oxidative stress is crucially involved in mesothelial carcinogenesis. Many aspects nonetheless remain unclear and the prognosis of MM patients is barely improved. This review aims to summarize what we know up until now about this malignancy from different perspectives.

Physiology of mesothelial cells

Mesothelial cells form a thin protective layer (called "mesothelium") covering the whole serous cavities and the entire surface of internal organs. The mesothelium is known to function primarily in preventing adhesion and promoting movements of internal organs by providing nonadhesive, slippery surface. It also forms a physical barrier to guard against the intrusion of pathogens. However, it was later found that mesothelial cells are also involved in a multitude of other physiological functions such as antigen presentation, transport of fluid and cells, inflammation and tissue repair, coagulation, and fibrinolysis. The physiological functions of the mesothelium have been well-reviewed elsewhere [13].

Normal mesothelial cells are predominantly flattened, but cuboidal mesothelial cells can be found at certain anatomical sites. In addition, mesothelial cells can also become cuboidal with a cobblestone-like shape during regeneration in response to tissue injury [13,14]. The surface of mesothelial cells especially the luminal surface is covered by many microvilli.

Normal mesothelium, under resting conditions, renews rather slowly. However, in response to tissue injury, mesothelial cells begin to proliferate and repopulate the wounded area. There are several theories as to how repopulation of mesothelial cells at the wounded area occurs: (1) mesothelial cells migrate from the edge of wounds toward the center, termed as "centripetal migration"; (2) mesothelial cells shed off from adjacent or opposing surfaces which then repopulate the wounded area; (3) preexisting free-floating mesothelial reserve cells attach to the wound followed by proliferation and repopulation; (4) mesothelium regenerates from multipotential mesenchymal precursors that exist in the submesothelial space; (5) mesothelium regenerates from bone marrow-derived circulating precursors; (6) serosal macrophages transdifferentiate into mesothelium [13]. A few studies demonstrated that the last two theories are more unlikely [15–18]. Some have suggested that the two main mechanisms in the process of mesothelial regeneration are incorporation of free-floating mesothelial cells in addition to centripetal migration of mesothelial cells [19].

Physical and biological characteristics of asbestos fibers

The term asbestos is used to refer to a group of naturally occurring silicate minerals that were extensively mined until a few decades ago. At that time, asbestos had broad industrial applications due to its several valuable features such as high tensile strength, high durability, and resistance to high temperatures and chemicals. Asbestos is classified into two major categories, known as amphibole and serpentine, respectively. Under amphibole, there are five members: crocidolite (blue asbestos), amosite (brown asbestos), tremolite [20], anthophyllite, and actinolite. Serpentine consists of only one member: chrysotile (white asbestos). All types of asbestos fibers have a needle-like shape with a high aspect ratio but the amphiboles are more rigid and have a rod-like appearance. On the other hand, chrysotile fibers are curly and more pliable. Crocidolite, amosite, and chrysotile are the three major commercially used asbestos. Hence almost all research regarding asbestos has been carried out using these three commercial types. Data from epidemiological studies generally suggested that the amphiboles are more carcinogenic than chrysotile fibers, as they consistently found a higher number of amphiboles in individuals with either lung carcinoma or mesothelioma [21–23]. Amphiboles are known to be more biopersistent whereas chrysotile fibers can be broken into smaller fibrils more easily followed by clearance by macrophages from the lung. In addition, chrysotile fibers present poorer penetration through the lungs due to the curly structure. Some claimed that chrysotile fibers present little risk of MM while others argued that chrysotile is as carcinogenic as the amphiboles, if not more [24–26]. A number of studies reported the presence of chrysotile fibers in the lung tissue of mesothelioma patients [27–29]. Experimental studies using animals further supported the carcinogenicity of chrysotile fibers [30,31]. Our

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