We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter

Oncogenetics of Lung Cancer Induced by Environmental Carcinogens

Victor D. Martinez, Adam P. Sage, Erin A. Marshall, Miwa Suzuki, Aaron A. Goodarzi, Graham Dellaire and Wan L. Lam

Abstract

The molecular landscape of non-tobacco-induced primary lung tumors displays specific oncogenetic features. The etiology of these tumors has been largely associated with exposure to well-established environmental lung carcinogens such as radon, arsenic, and asbestos. Environmental carcinogens can induce specific genetic and epigenetic alterations in lung tissue, leading to aberrant function of lung cancer oncogenes and tumor suppressor genes. These molecular events result in the disruption of key cellular mechanisms, such as protection against oxidative stress and DNA damage-repair, which promotes tumor development and progression. This chapter provides a comprehensive discussion of the specific carcinogenic mechanisms associated with exposure to radon, arsenic, and asbestos. It also summarizes the main protein-coding and non-coding genes affected by exposure to these environmental agents, and the underlying molecular mechanisms promoting their deregulation in lung cancer. Finally, the chapter examines the anticipated challenges in personalized intervention strategies in non-tobacco-induced lung cancer.

Keywords: lung cancer, environmental carcinogens, radon, arsenic, asbestos

1. Introduction

Lung cancer remains the deadliest form of cancer across the globe [1]. While smoking rates have decreased in many areas, it remains to be seen if the incidence and mortality of primary lung cancer will experience a similar shift, particularly in light of the observation that close to 25% of cases arise in individuals who have never smoked [2]. As one of the most environmentally-influenced malignancies, lung tumorigenesis can result from exposure to both physical and chemical carcinogens. Exposure to the mix of compounds present in particulate matter is another well-known factor affecting the development of lung cancer [3]. However, a number of single-agent compounds in the environment have been identified as key lung carcinogens, particularly arsenic, asbestos and radioactive radon (^{222}Rn) gas [4]. These compounds are distributed at varying, potentially-dangerous concentrations in the environment, affecting hundreds of millions of people worldwide.

Exposure to each of arsenic, asbestos, and radon has been shown to induce widespread genetic and epigenetic alterations, which may account for their strong carcinogenicity, independent of smoking status [4]. Interestingly, the molecular aberrations associated with these compounds and the onset of lung cancer in never-smokers follows a mechanism distinct from that of tobacco smoke [5]. While strict guidelines regarding exposure to these compounds have been implemented in some regions, mounting evidence suggests that carcinogenic effects may result from chronic exposure to environmental levels that are well below those currently deemed "safe" [6, 7]. Additionally, individual differences may contribute to varying degrees of susceptibility to the carcinogenic effects of these compounds. For instance, women have been shown to have a higher incidence of lung cancer arising in never-smokers. This inequality can potentially be attributed to a historical bias towards women being more present in the home, resulting in increased exposure to high radon concentrations and polyaromatic hydrocarbons from various home combustion sources [8]. As these genetic and epigenetic aberrations might be indicative of specific molecular damage induced by these carcinogens, they may be able to be used to develop personalized approaches for risk assessment, monitoring and subsequent disease treatment. Thus, it is critical to uncover the extent of these events associated with exposure to environmental carcinogens.

Arsenic is a class I International Agency for Research on Cancer (IARC) carcinogen that threatens global health through its persistent accumulation in drinking water sources, leading to the onset of skin and lung cancers, among other diseases [9]. Asbestos fibers are naturally occurring silicate mineral fibers that have long been used in industry as building insulation, and are closely linked with not only the well-known outcome of mesothelioma, but also to 5–7% of all lung cancer cases [10]. Radon gas accounts for between 3 and 14% of all lung tumors in a given country and is the second most-common cause of lung cancer, behind smoking [11]. While the radioactive gas normally diffuses easily in open air, it can build up in indoor environments and is readily dissolved into water, which can lead to malignancies through radioactive decay and alpha particle emission [11]. Moreover, drinking water may be a particularly prevalent source of exposure to environmental carcinogens, as it is a primary route of exposure for both arsenic and radon, emphasizing the need for a focus on water contamination measurement and remediation. As arsenic, asbestos, and radon exert their carcinogenic effects through different exposure routes, they display similar, yet distinct mechanisms of genetic and epigenetic aberration, which may be useful in the identification and treatment of tumors caused by these agents.

In this chapter we highlight the molecular alterations induced by exposure to arsenic, asbestos, and radon in key lung cancer pathways, and finish with a discussion of the potential translational applications of environmentally-induced molecular damage.

2. Arsenic

2.1 Physiological and molecular impact of exposure

Arsenic exposure largely occurs through contaminated drinking-water sources, but this problem extends well beyond known arsenic-endemic areas. In fact, it is estimated that 200 million individuals are exposed worldwide to levels deemed non-toxic by the WHO, but shown to induce molecular damage [12].

The toxic effects of arsenic are prevalent from ingestion to excretion and are largely attributed to its various metabolites (**Figure 1**). Once ingested, arsenate

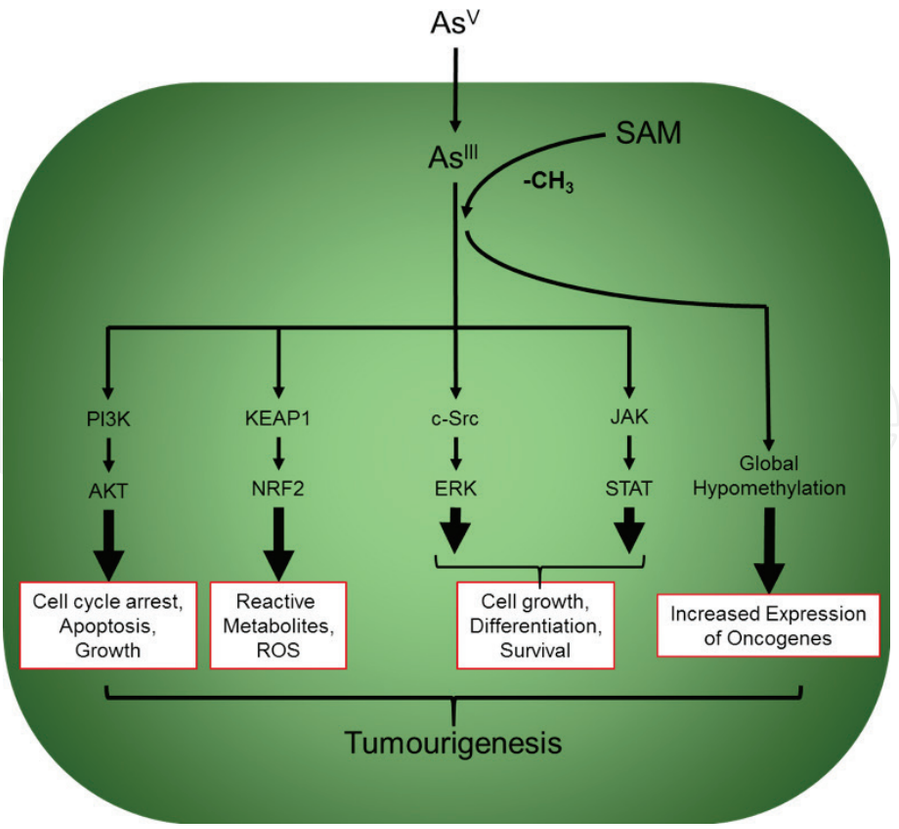


Figure 1.
Molecular mechanisms of arsenic-induced carcinogenesis.

(As^V)—the most common form of the compound in the environment—is taken into cells through membrane transporters, where it is quickly reduced to arsenite (As^{III}) by oxidoreductases including purine nucleotide phosphorylase (PNP) and glutathione-s-transferase omega (GSTO). As^{III} is the most toxic form of arsenic, largely due to its subsequent methylation by methyltransferase enzymes such as arsenic (+3) methyltransferase (As_3MT), a process exploited for promoting the excretion of arsenic [13]. However, methyl groups are provided by *S*-adenosylmethionine (SAM), a key cellular methyl group donor. Methylation of arsenic inside the cell can thus lead to the depletion of the cellular methyl pool through a high demand on SAM, which then promotes global DNA hypomethylation and aberrant histone modification [14–17]. Disruptions in the cellular methyl pool can lead to major disruptions in gene expression, which is known to contribute to malignant transformation [16].

The genomic instability and global changes in gene expression resulting from the exposure and biotransformation of arsenic is exacerbated by the widespread induction of DNA damage from toxic arsenic byproducts. In fact, arsenic has been demonstrated to cause distinct alterations in chromatin, gene expression (both coding and non-coding), as well as splicing, and transcription initiation [18]. In particular, one of the methylated species of arsenic, monomethylarsonic acid (MMA^{III}), can interrupt the electron transport chain in mitochondria, liberating electrons and inducing the formation of reactive oxygen species (ROS) [15, 19, 20]. ROS generated from arsenic exposure result in widespread DNA damage, including single- and double-stranded DNA breaks, DNA base oxidation leading to mutations (largely G>C → T>A transversions), adducts, deletions and even damage to mitochondrial DNA (mtDNA) [20–22]. Unsurprisingly, as oxidative stress is a known driver of tumorigenesis in multiple tissues, the DNA damage induced from arsenic exposure is thought to be a main mechanism of its carcinogenicity [23–25]. The disruption of the electron transport chain produces ROS such as hydroxyl

radicals (OH•), superoxide anion radicals (O_2•−), and hydrogen peroxide (H_2O_2), which can further damage cells through lipid oxidation, protein oxidation, and reduction of the mitochondrial membrane potential [26]. The subsequent liberation of cytochrome c can activate apoptotic pathways through caspases, leading to an abnormal rate of cell death. However in addition to faulty apoptotic signaling, exposure to arsenic can also lead to further aberrations in DNA-repair pathways. Here, arsenic affects the expression of genes involved in both nucleotide- (NER) and base-excision repair (BER) mechanisms, allowing the cell to continue through the cell cycle despite extensive damage and genomic instability [27–30]. Thus, arsenic exposure can induce an array of molecular damage across the genome and epigenome, culminating in malignant transformation.

2.2 Carcinogenic mechanisms

While it is exposure to the methylated metabolic byproducts that yields the largest toxic effects resulting from exposure to environmental arsenic, it is noteworthy that even at very low doses, arsenic may be able to act as a co-mutagen to other known carcinogens, such as ultraviolet light, X-rays, methyl methane sulfonate, and tobacco smoke [15]. ROS are perhaps more immediately damaging to cells, as they can lead to alterations in a variety of lung cancer-specific pathways. As stated previously, arsenic exposure can interfere with DNA damage repair pathways, which exacerbates the effects of ROS generation. In the NER pathway, arsenic can alter the expression of key damage-repair genes, such as XPC, in a process that may be mediated by the proteasome [31].

Collectively, aberrations in cellular DNA-damage repair pathways may not only highlight mechanisms of arsenic toxicity, but also its co-mutagenic effects. One of the most common pathways affected in lung cancer is the constitutive activation of the epidermal growth factor receptor (EGFR), especially in women and individuals who have never smoked [32]. Both amplification and mutation can lead to EGFR activation, which subsequently stimulates cell proliferation. As^{III} can activate proto-oncogene c-Src (c-Src) through vicinal sulfhydryl groups, which then promotes phosphorylation events in intracellular EGFR tyrosine residues (Tyr845) [32]. As tyrosine phosphorylation is a key event in EGFR activation, As^{III} thus promotes EGFR constitutive signaling. Alternatively, arsenic exposure may also indirectly affect downstream members of the EGFR pathway, through arsenic-induced oxidative stress and ROS, a common mechanism of environmentally-induced lung carcinogenesis. In a mechanism similar to that of EGFR activation, arsenic has been shown to induce the phosphorylation of several potential substrates of protein kinase B (Akt), a regulator of epithelial-to-mesenchymal transition (EMT) and metastasis, inducing cell migration [33]. Specifically, arsenic may affect c-Jun N-terminal kinase (JNK) activation and subsequent activation of signal transducer and activator of transcription 3 (STAT3), resulting in Akt growth and migration signaling [34]. Similarly, arsenic may increase the enzymatic activity of phosphoinositide 3-kinase (PI3K) and Akt phosphorylation, a key pathway in lung cancer tumorigenesis and progression [35]. The mechanism of PI3K/AKT activation has proven elusive, yet evidence suggests that ROS may play a mediating role, as well as alterations in histone modifications and activation of other related pathways, such as EGFR, mammalian target of rapamycin (mTOR), or polo-like kinase 1 (PLK1) signaling [35, 36]. Phenotypically, activation of the PI3K/Akt signaling axis by arsenic can result in a variety of changes, including cellular growth and angiogenesis [37]. There are many other lung cancer-specific pathways that may be altered upon exposure to arsenic and its toxic byproducts, including the nuclear

factor (erythroid-derived 2)-like 2/kelch-like ECH-associated protein 1 (NRF2/KEAP1) pathway, the nuclear factor kappa-light-chain-enhancer of activated B cells pathway (NF-κB), and various epigenetic pathways [35, 38]. Further experimental work is required to fully characterize and distinguish the molecular mechanisms of the pathways affected by chronic exposure to arsenic.

2.3 Prominent cancer genes affected by arsenic

As evidenced by its genome-wide effects on cellular physiology and molecular pathways, gene expression alterations cause by arsenic exposure can potentiate negative health outcomes. In fact, there are a growing number of genes that have been observed to have abnormal expression resulting from arsenic exposure, in cell lines, mouse, and human samples. Many of these genes have accepted roles in cancer, both as tumor-suppressors and oncogenes. Most notably, the tumor suppressor gene *TP53* has been shown to be epigenetically inactivated in arsenic-exposed cell lines [39]. Similarly, other cell line studies have suggested that low concentrations of arsenic may upregulate the known lung oncogene *Myc* (also related to the cell cycle) through aberrant expression of miRNAs targeting upstream regulators of its transcription [40].

As previously discussed, the frequent disruption of DNA damage repair and stress response pathways is a common feature of arsenic-induced lung tumors. Notably, arsenic has been associated with stimulation of the DNA damage response through the upregulation of critical genes, such as the gene encoding DNA excision repair protein ERCC1 (*ERCC1*) [41], confirming that DNA damage is prevalent in arsenic-exposed individuals. Alternatively, arsenic may induce repression and decreased activity of main DNA repair enzymes, including poly [ADP-ribose] polymerase 1 (PARP1) inhibition (through ROS) [42], proteasomal degradation of xeroderma pigmentosum, complementation group C (XPC) [31], and widespread hypermethylation of NER genes [43]. Additional lung cancer-related genes affected by arsenic include: *EGFR* [44], *cyclin-dependent kinase inhibitor 1A* (*CDKN1A*) [45], and *B-cell lymphoma 2 (BCL2)* [46]. Despite the mounting evidence of the toxic effects of arsenic, the concentration and identity of key damage-related arsenic compounds varies widely between studies. While different arsenic-based compounds affect similar pathways, specific physiological responses may vary greatly depending on compound type and dose response, necessitating closer examination of these factors in future studies.

However, it is important to note that variations in these genes may exist within individuals prior to arsenic exposure, and that certain genetic polymorphisms may make some individuals more susceptible to the genotoxic effects of arsenic. For instance, a single nucleotide polymorphism (rs238406; C > A) in *ERCC2* (part of the DNA-damage response) leads to the inclusion of an alanine residue in the place of a cysteine in the complete protein, increasing an individual's odds ratio for skin cancer to 2.04 [47]. Additionally, polymorphisms in many of the genes involved in the metabolism and biotransformation of arsenic may result in the production of different metabolic byproducts, conferring differential susceptibility and cancer risk [48]. This is exemplified by the rs1191439 polymorphism of As_3MT, which is correlated with elevated MMA levels in urine [49]. Thus, the landscape of arsenic-induced carcinogenesis is quite complex, with multiple types and outcomes of the molecular aberrations that can result from chronic exposure. A more comprehensive understanding of the mechanisms at play may result in the identification of the underlying causes of lung cancer in never-smokers, and may help to direct the development of novel treatment strategies for these affected individuals.

3. Asbestos

3.1 Physiological and molecular impact of exposure

Asbestos is a term used to define a group of mineral fibers incorporated in a wide variety of products, including talcum powder, brake pads, and construction materials. While more than 50 countries have banned the use of asbestos-containing materials, more than 2 million metric tonnes are still produced every year, which still poses a great public health risk for asbestos-related diseases [50, 51]. There are two main classes of asbestos: chrysotile (spiral-shaped, the most common form) and amphibole (needle-shaped). Other elements such as iron (which can constitute up to 30% of the weight of asbestos fibers) embedded in the surface of fibers can potentiate asbestos-related pathogenic effects [52, 53]. Importantly, all identified forms of asbestos have been classified as carcinogens to humans (Group 1) by the IARC [54].

Exposure to asbestos fibers has been strongly linked to the development of malignant mesothelioma, but it is also a known contributor to the development of lung cancer [55–57]. Between 5 and 7% of all lung cancer cases worldwide have records of high levels of asbestos, mostly derived from occupational exposure (e.g., mining) [10]. Exposure is usually determined by the presence of pleural plaques (areas of fibrosis associated with past exposure to asbestos), or by detection of asbestos fibers in bronchoalveolar lavage (BAL) and lung tissue [58]. The primary source of asbestos exposure comes from inhaled fibers [54]. However, the mechanism of disruption that occurs as a result of asbestos exposure is determined by the efficiency of fiber clearance from airway cells. Longer fibers are cleared at a slower rate than short fibers, and are associated with higher carcinogenic potential [59]. Similarly, thin fibers (width <0.25 μm) are more carcinogenic than thicker ones [60], likely because they can penetrate deeper in airways. Accumulation of asbestos fibers in the lung leads to fibrosis, inflammation, and carcinogenesis, although specific effects depend on the cumulative dose and the type of fiber inhaled [61, 62].

Asbestos-related carcinogenesis is thought to primarily result from the ability of the fibers to induce oxidative stress (**Figure 2**), although the specific mechanisms are not yet fully understood [63]. Asbestos induces the recruitment of alveolar macrophages, followed by an inflammatory reaction [64–66]. Failed phagocytosis of these fibers by macrophages results in the generation of ROS, together with the release of cytokines, chemokines, proteases, and growth factors further amplifying deleterious effects of asbestos [10, 56, 67]. Additionally, the iron contained in asbestos fibers deposits in the lungs and cycles between the reduced and oxidized forms, potentially inducing further oxidative DNA damage in nearby cells via the Fenton reaction which converts H_2O_2 into more reactive ROS [10, 56, 68, 69].

In lungs, oxidative stress following asbestos exposure can activate several signaling pathways including mitogen-activated protein kinases (MAPK), NF-κB, and activator protein 1 (AP1). All of these pathways have been linked to increases in early response genes (e.g., *JUN* and *FOS*) that govern cell proliferation, apoptosis, and inflammatory signaling [55, 56].

3.2 Carcinogenic mechanisms

The most frequent asbestos-induced alterations in cancer-related genes have been reported in tumor suppressor genes (TSGs). Activation of p53 and p21 are frequently described, both in animal models and lung cancer patients with asbestosis (reviewed in [63]). This likely represents the initial DNA-damage response following exposure to asbestos-induced oxidative stress. In lung cancer patients, the frequency of *TP53* gene mutations is similar between asbestos-exposed and

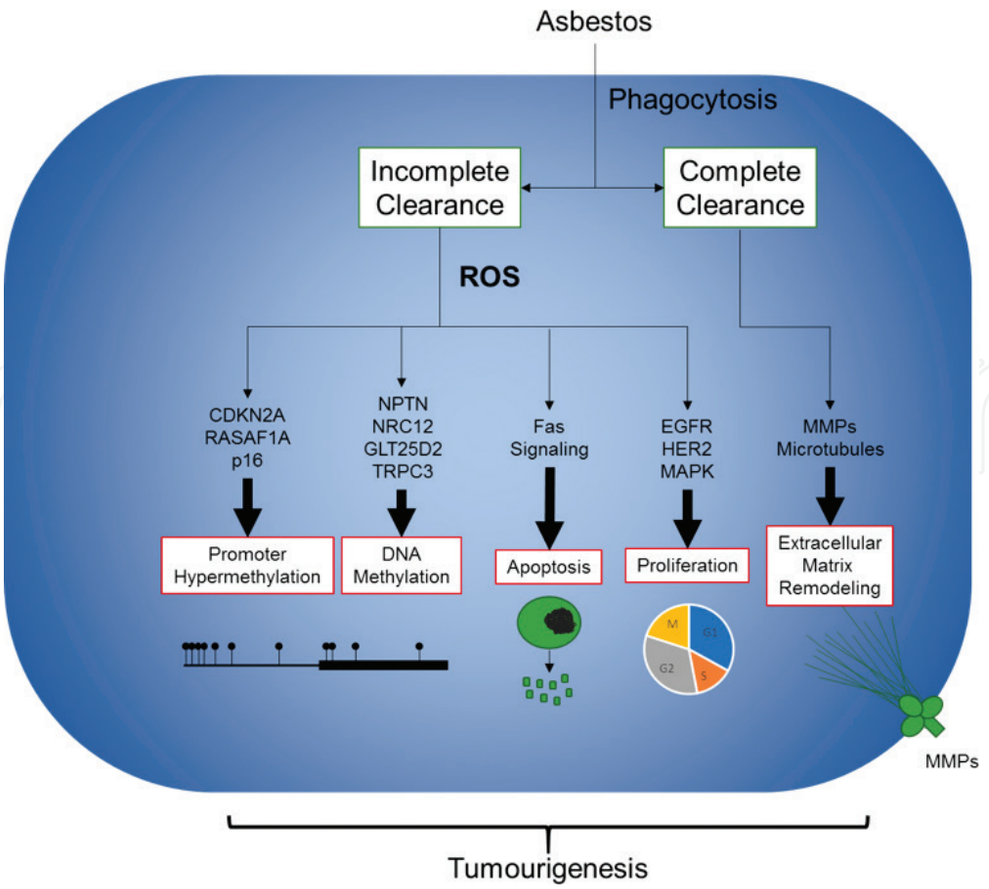


Figure 2.
Molecular mechanisms of asbestos-induced carcinogenesis.

unexposed NSCLC cases; however, a higher frequency of G:C to T:A transversions in the sequence of *TP53* is observed in asbestos-exposed cases [70, 71]. Contrarily, other tumor suppressor genes such as *CDKN2A* are inactivated in asbestos-exposed lung cancer cases, mostly via segmental copy-number losses [72]. In murine models, chrysotile fibers are able to induce the activity of the c-Jun and c-Fos oncogenes and inactivate p53 and p16 tumor suppressors, both at the mRNA and protein levels [73].

Additionally, other well-known lung cancer genes and pathways have been shown to display aberrant functions in response to asbestos exposure. Different mechanisms of asbestos-mediated activation of the EGFR pathway have been described. Asbestos-induced chronic inflammation has been associated with activation of the EGFR-related and extracellular signal-regulated kinase (ERK) signaling pathway that promote lung epithelial cell and fibroblast proliferation [55, 56, 74]. Also, asbestos fibers can induce over-expression of EGFR mRNA and induce protein dimerization, phosphorylation, and subsequent pathway activation by directly interacting with the surface portion of the receptor [63, 75, 76]. On the other hand, DNA mutations affecting EGFR do not seem to be main mechanisms of asbestos-induced EGFR activation. Asbestos-exposed patients displayed a significantly lower rate of *EGFR* mutations compared to non-exposed patients [77]. Moreover, it is unclear if there is a causal relationship between the mutations found in *EGFR* and exposure to asbestos fibers [78, 79].

Other genes, such as *MAP4K3, CEBPZ, QPCT, FANCG, IGFBPL1, CCL19, MELK, FANCM*, and *CDKL1* have shown aberrant gene expression in human epithelial bronchial cell lines (Beas-2B), following asbestos exposure [80]. Asbestos inhalation also causes up-regulation of mRNA levels of matrix metalloproteinase family members in rat lungs, suggesting induction of extracellular matrix remodeling [81].

At the epigenetic level, alterations affecting tumor suppressor genes have been observed in lung cancer cases associated with asbestos exposure, including those in the promoter regions of *RASSF1A* and *CDKN2A* (p16) [82]. Additionally, a genome-wide DNA methylation study identified differentially methylated CpGs in regions nearby the transcription start site of genes such as *NPTN, NRG2, GLT25D2* and *TRPC3* to be significantly associated with asbestos exposure [83].

The effect of asbestos on micro RNA (miRNA) expression has been also investigated. miRNAs are short (~22 nucleotide) RNA transcripts that negatively regulate gene expression through direct interaction with mRNAs. Interestingly, the overexpression of miR-148b has been described in multiple independent studies. This miRNA was part of an asbestos-related signature in lung tumors, also composed of seven other overexpressed (miR-374a, miR-24-1*, let-7d, Let-7e, miR-199b-5p, miR-331-3p, and miR-96) and five miRNAs with decreased expression in tumors (miR-939, miR-671-5p, miR-605, miR-1224-5p, and miR-20) [84]. Additionally, miR-148b was found to be overexpressed in asbestos-related lung cancer compared to tumors in non-exposed individuals, and three of its targets (*GADD45A, LTBP1* and *FOSB*) were down-regulated in asbestos-exposed patients [84].

Despite the known genetic and epigenetic abnormalities resulting from asbestos exposure, a relatively small proportion of exposed individuals develop thoracic malignancies (mesothelioma or lung cancer). It has been hypothesized that specific genetic variants may confer increased risk of developing asbestos-related diseases [85]. Thus, recent studies have investigated the association between genomic variants and risk of lung cancer following asbestos exposure. In a genome-wide association study (GWAS) performed in the Texas lung cancer GWAS dataset, the authors did not find statistical evidence for gene-asbestos interaction in the etiology of lung cancer [86]. However, the Fas signaling pathway (regulation of tissue homeostasis in the immune system by inducing apoptosis) was identified as the most significant pathway associated with asbestos exposure in the etiology of lung cancer. Another study identified three single nucleotide polymorphisms (SNPs) in the *MIRLET7BHG* (*MIRLET7B* host gene located at 22q13.31) significantly associated with increased lung cancer risk among individuals exposed to asbestos [36].

The identification of risk variants linked with asbestos-related lung cancer is a challenging task. Sample sizes for asbestos-related lung cancer cohorts are particularly limited by the number of cases that can be unequivocally attributed to asbestos exposure despite other well-known factors (e.g., smoking). Thus, focusing on the genes and chromosomal regions found by these preliminary studies might be useful for more targeted strategies aiming to validate these results.

3.3 Carcinogenic potential of other fibers

While the oncogenic effects of asbestos have been extensively established, recent evidence indicates that non-asbestos fibers, both natural and synthetic in nature can also cause thoracic cancers. Non-asbestos mineral (natural) fibers include erionite and fluoro-edenite, among others. Erionite is a naturally occurring fibrous mineral that shares some physical properties with asbestos, although it is less widespread. In fact, it has been shown that erionite is a more potent carcinogen in causing malignant mesothelioma [87, 88]. Erionite activates the NLR family pyrin domain containing 3 (*NLRP3, NALP3*) inflammasome, inducing the transcription and production of cytokines critical to cancer initiation [89]. On the other hand, Fluoro-edenite (originating from volcanic activity) can induce ROS that result in DNA damage and increase in lactic dehydrogenase release (a damage and toxicity marker) in human lung adenocarcinoma (A549) and monocyte-macrophage (J774) cell lines [90].

Synthetic graphene-based fibers are widely used in several industries. They have also been explored as a drug delivery system for cancer treatments. Physical similarities to asbestos, particularly its high length-to-width ratio, have raised some concerns about the potential carcinogenicity effects of these fibers [91]. Exposure to carbon nanotubules has been shown to induce oncogenic pathways, such as TGF-β and Akt/GSK-3β, resulting in activation of the SNAIL-1 signaling pathway and epithelial-mesenchymal transition [92]. Additionally, carbon nanotubules can generate ROS, activating MAPKs, AP-1, NF-κB, and Akt in normal and malignant human mesothelial cells [93]. Other genetic alterations, including micronuclei formation, disruption of mitotic spindles, and polyploidy have also been observed in response to carbon nanotubule exposure [94–96]. Moreover, it has been shown that exposure to carbon nanotubules can induce specific methylation changes at the promoter regions several genes, including *DNMT1*, *ATM*, *SKI*, and *HDAC4*, while they seem to have only a marginal effect on miRNA expression [97]. Thus, the oncogenetic factors of natural and synthetic fibers, while similar in morphology, are distinct entities that may collectively culminate in tumor development.

4. Radon

4.1 Physiological and molecular impact of exposure

Radon is the second most common cause of lung cancer in many countries; however, the intricacies of its mechanism of action remain underappreciated. The genotoxicity of radon is largely the result of alpha particle emission during its spontaneous decay into short-lived radioactive progeny (^{218}Po and ^{214}Po) and comparably long-lived radioactive ^{210}Pb, which also induces cellular damage through alpha decay (**Figure 3**) [98].

Alpha decay is the emission of a 4 atomic mass unit helium ion (two protons and two neutrons), which can liberate electrons from water molecules and result in the generation of several types of ROS [15]. Much like the mechanisms of arsenic and asbestos toxicity, ROS generated as a consequence of radon exposure can lead to widespread molecular aberrations, especially base oxidation (leading to mismatches and mutagenesis), DNA strand breaks, chromosomal aberrations, and deletions. For example, chromatid deletions in blood lymphocytes may be a result of radon exposure, which may in part explain the associations between radon exposure and blood malignancies [8]. These events may occur at levels well below those currently deemed safe in many countries, exemplified by the observation of chromosomal abnormalities in lymphocytes at very low doses of polonium-214, a radioactive progeny of radon [99].

Beyond the molecular events resulting from ROS generation, alpha radiation from radon exposure can induce bystander responses in cells that have not been directly affected by alpha particles [100]. The bystander effect of radiation exposure can occur through the release of signals from nearby irradiated cells, generating a physiological response in non-irradiated cells, even at relatively low doses of radiation [101]. The effect requires direct contact between adjacent cells, such as through gap junctions, as well as compounds in the surrounding medium, including cytokines [102]. One of these compounds, nitric oxide (NO), has been shown to be an important factor for the cell-killing effects of the bystander response, largely through the direct interaction with and damage of DNA [103]. Moreover, NO byproducts such as dinitrogen trioxide (N_2O_3) can promote nitrosation of other amines, such as those of DNA bases, leading to cross-linking and DNA alkylation [102]. Another compound that may be relevant to the bystander effect of cellular

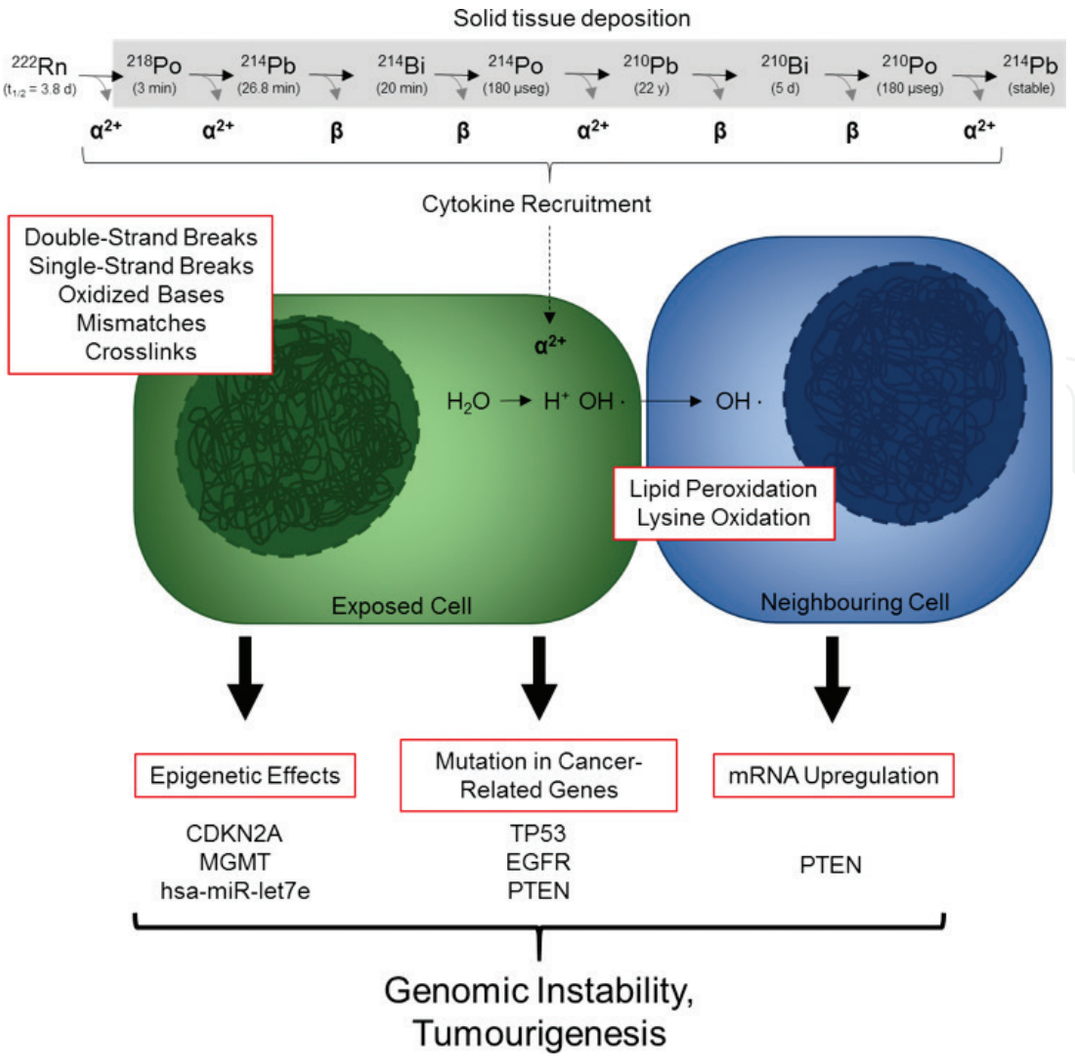


Figure 3.
Molecular mechanisms of radon-induced carcinogenesis.

radiation exposure is cyclooxygenase 2 (COX-2), which is related to the NF-κB pathway, an effect that is attenuated upon COX-2 inhibition [103, 104]. Finally, this response may be dependent on *TP53* status, which will be discussed in Section 4.3.

4.2 Carcinogenic mechanisms

Despite differences in the details of exposure, the molecular mechanisms contributing to carcinogenesis in individuals exposed to arsenic, asbestos, and radon converge in that they all produce ROS. Radon has a half-life of 3.8 days, and as previously mentioned, commonly generates alpha particles and polonium decay products, which themselves emit further alpha radiation [105]. Alpha particles have a high linear energy transfer (LET) despite having relatively low penetration capability, meaning that they interact readily with DNA, especially in regions close to their site of exposure, such as the bronchial epithelium [105]. Thus, it is not surprising that lung malignancies are the most common type of radon-induced cancer. High LET radiation is distinct from low LET radiation (such as x-rays or gamma rays) in that it produces a substantially greater proportion of clustered damage, meaning the occurrence of ≥2 lesions of ≥1 different types within 1–2 helical turns of DNA. Clustered DNA damage is typically repaired with slower kinetics and has a greater likelihood of producing sequence alterations, as repair pathways converge and conflict with one another [106–108].

The largest radon-induced mechanisms of carcinogenesis include DNA damage, ROS, and alpha particle generation; likewise, pathways associated with these functions are also known to be associated with lung cancer. In fact, patients positive for rearrangements in the gene encoding anaplastic lymphoma kinase (*ALK*)—an event frequently found to drive lung tumorigenesis—were found to have two-fold increases in residential radon levels than those without these rearrangements [109, 110]. While a synergistic effect between radon and smoking has been suggested [11], the G:C to T:A transversions associated with tobacco-related molecular damage are not as commonly observed in individuals exposed to radon, suggesting a unique molecular signature in radon-associated lung tumors [15]. Again, it is important to note that a number of the pathways affected by radon exposure, including gene expression alterations and apoptotic disturbances, may actually be from cells neighboring those that are irradiated [104]. In fact, pro-inflammatory and ROS-generating cytokines such as tumor necrosis factor alpha (TNF-α) may be released upon radiation exposure, which may perpetuate the damage enacted by ROS [111]. Thus, key pathways such as DNA repair, proliferation, and cell death can be altered in cells beyond those that are irradiated [111].

4.3 Prominent cancer genes affected by radon

ROS-induced DNA damage is a large factor in radon-induced carcinogenesis, thus, many of the examinations into genes affected by radon are relevant to DNA-repair and apoptotic pathways. Naturally, a heavy focus is placed on *TP53.* Many investigations into *TP53* examine whether hotspot mutations in *TP53* can act as a molecular signal for radon-induced genotoxicity in at-risk populations. Although *TP53* is observed to be altered in high exposure populations, there are limited observations available to suggest a consistent mutational landscape [112]. However, the role of *TP53* in the molecular response to radon exposure may be relevant to the bystander effect, wherein *TP53* may mediate the inhibition of response signals coming from irradiated cells [103]. Additionally, other key lung cancer-related genes may also be mutated by radon exposure, including *EGFR* and phosphatase and tensin homolog (*PTEN*), but the exact mechanisms remain to be characterized [113].

As previously discussed, radon may also exhibit its carcinogenic effects epigenetically, as evidenced by the promoter hypermethylation of the tumor suppressor genes *CDKN2A* and *MGMT.* In normal human lung cell lines, miRNAs shown to be primarily involved in cell proliferation, differentiation, and adhesion displayed aberrant expression upon radon exposure [114]. Moreover, the miRNA *let-7e*—an epigenetic regulator of the RAS oncogene—was found to be upregulated upon low radon exposure [115]. In this study, the upregulation of miRNAs targeting tumor suppressor genes was also noted, including *PTEN*, which may present an alternative mechanism of radon-induced carcinogenesis.

Finally, a number of studies have examined the effect of genetic polymorphisms of DNA damage repair genes in the outcome of individuals exposed to radon. For instance, individuals with a polymorphism leading to the Asp1104His substitution of DNA repair gene *ERCC5* (XpG) displayed a higher frequency of micronuclei in their lymphocytes, representative of elevated cytogenetic damage and decreased radiosensitivity [116]. Alternatively, the absence of *GSTM1* and *GSTT1*, members of the glutathione-s-transferase enzyme family—critical to detoxification and excretion—is associated with an increased risk of lung cancer development [117, 118]. When radon exposure is considered, individuals with null alleles show a doubly increased odds ratio of lung cancer development [118]. Notably, this enzyme is relevant in the biotransformation and excretion of arsenic, suggesting similar carcinogenic pathways between these two environmental agents.

Taken together, the molecular landscape of radon-induced carcinogenesis is complex and diverse, with effects being observed at the genetic, epigenetic and extracellular level. Future studies may examine the underlying molecular events common to radon-induced lung cancer, to aid in diagnosis and perhaps novel treatment strategies.

5. Common oncogenic features exhibited by environmental carcinogens

The landscape of the genomic disruptions induced by environmental carcinogens is extensive. It has been demonstrated that these compounds can induce alterations such as chromosomal abnormalities, DNA double-strand breaks, gene expression dysregulation, and epigenetic aberrations. While each agent presents a unique mechanism and clinical challenge, a number of parallels can be seen. The molecular effects of exposure to arsenic, asbestos, and radon converge in that each compound can result in DNA damage induced by ROS and inflammation. As these events occur early during tumor development, the identification of the underlying genomic and epigenomic abnormalities caused by these compounds is extremely relevant in identifying early oncogenic events and individual susceptibility differences.

Although the intricacies of the molecular mechanisms of alteration may differ between the various toxic agents, ROS generation is a common outcome of exposure that can lead to extensive DNA damage and further perturbations in various cellular compartments and processes [119]. As mitochondria are one of the primary sources of ROS, they are also key targets of oxidative toxicity [120]. Arsenic exposure is associated with dysfunction of the mitochondria, through the ability of its metabolites to disrupt the mitochondrial membrane potential and reduce mitochondrial ATP levels, as well as ROS-induced mitochondrial damage [121, 122]. Mitochondrial damage induced by arsenic can then lead to numerous alterations in key signaling pathways, such as the decreased expression of apoptotic regulator protein Bcl-2 [122]. Regardless of the molecular mechanism, mitochondrial insult culminates in apoptosis and increased inflammation, in addition to the exacerbation of reactive species generation; events that commonly precede tumorigenesis [121, 123].

Another frequently observed early consequence of exposure to environmental carcinogens is an inflammatory response. Indeed, inflammation caused by infiltrating immune cells underlies numerous hallmarks of cancer biology by providing key molecules for tumor survival and growth, as well as the promotion of genomic aberrations, again through the generation of ROS [124]. Asbestos-induced carcinogenesis is thought to rely heavily on the inflammatory response, where the macrophages of the innate immune system attempt to clear the carcinogenic fibers through phagocytosis [125]. However, these fibers are inherently difficult to digest, leading to the eventual death of the macrophage and subsequent release of pro-inflammatory cytokines, ROS, and other growth factors [126]. Interestingly, many malignancies have noticeable local immune responses prior to tumor development, highlighting the complex and dichotomous role of host immune cells in both pro- and anti-tumor functions [127]. Thus, exposure to environmental carcinogens threatens the genetic and epigenetic landscape of oncogene expression in the development of malignancies, and subsequently changes cellular and systemic processes.

The intertwined role of genetic and epigenetic aberrations resulting from exposure to these compounds highlights the complexity of environmentally-induced lung cancer. However, the carcinogenic mechanisms associated with exposure to these agents have been mainly identified using a “one-agent-at-a-time” approach. Further, we have yet to understand how these factors interplay with one another in cases of

combined exposure and how individual genomes modulate the molecular events that arise following exposure. For example, it is difficult to accurately assess the relative risk of lung cancer in an individual who is exposed to occupational asbestos, arsenic-contaminated water, and high levels of domestic indoor air radon. Whether these factors synergize in terms of their molecular effects is not clearly understood and has critical implications to patient monitoring and disease management.

Recently, the idea of the human exposome has sought to provide a method for analyzing individual risk factors by integrating the effects of factors ranging from DNA-level alterations to geographic location. The human exposome is defined as the sum of every exposure to which an individual is subjected to from conception to death [128]. The exposome is dynamic: the nature, amount, and conditions of exposure change over time. It also includes exposure from internal (e.g., metabolism, endogenous hormones, gut microflora, inflammation, oxidative stress, etc.) and external (e.g., radiation, infectious agents, chemical contaminants and environmental pollutants, among others) sources [129]. The lungs are one of the organs at the highest risk of disease development from environmental exposures as the lung exposome can be comprised of an array of molecules and environmental insults. Arsenic, asbestos, and radon, together with air pollution and tobacco smoke, constitute a fraction of the complex mix of environmental carcinogens posing risks for developing thoracic malignancies in humans. However, understanding the oncogenic events following exposure to these agents may allow for the identification of key intervention points to minimize environmentally-induced lung cancer in at-risk populations.

6. Translational outlook for environmentally-induced cancer

As the molecular mechanisms of environmentally-induced carcinogenesis continue to emerge, a need to characterize the clinical utility of these findings should be underscored. This need is further emphasized by the complex interplay between the numerous features of the lung exposome. Many of the single cancer-associated genes that are affected by exposure to these environmental agents are promising therapeutic intervention points. For instance, targeted inhibitors of EGFR (e.g., erlotinib, afatinib)—a protein transcribed from a gene commonly up-regulated upon exposure to arsenic—are used in lung cancer treatment to interfere with the aberrant growth pathways activated by the upregulation of this signaling receptor [130]. Additionally, the association between radon exposure and *ALK* gene rearrangements in lung cancer patients may be amenable to therapy with inhibitors of the ALK protein (e.g., crizotinib, ceritinib) [131]. However, patients that do not present with alterations in genes that are clinically actionable remain extremely difficult to treat beyond standard regimes. Thus, it is critical to analyze the oncogenetic alterations induced by environmental carcinogens, to not only identify the contribution of each of these widely-distributed agents to tumorigenesis, but also to direct the development of novel treatment and risk-management strategies. Concurrent analysis of altered genes, transcripts, and proteins may help to parse out the risk associated with the varying molecular aberrations that have been observed to be induced by these compounds [132]. This approach, while difficult in terms of scale, necessitates the use of geographic, demographic, and exposome level data, which can be scarce in areas where environmental carcinogen levels are especially concerning. **Table 1** summarizes the currently available sources of information for carcinogens found in the environment that are associated with lung cancer. Overall, future mitigation of the environmental risk factors that lead to lung cancer will rely on the integration of information from the genomic to epidemiological levels.

Name	Website	Description
The IARC Monographs, International Agency for Research on Cancer	http://monographs.iarc.fr/	Compilation of factors that increase the risk of human cancer: occupational exposures, physical agents, biological agents, and lifestyle
Carcinogens, American Cancer Society	http://www.cancer.org/Cancer/CancerCauses/OtherCarcinogens/index	Environmental carcinogens from different sources (e.g., indoor, pollution, medical tests)
Cancer-Causing Substances in the Environment, National Cancer Institute	https://www.cancer.gov/about-cancer/causes-prevention/risk/substances	Information of environmental carcinogens to affect human health.
Chemicals of Public Health Concern, World Health Organization (WHO)	http://www.who.int/ipcs/assessment/public_health/chemicals_phc/en/index.html	Information on the 10 chemicals or groups of chemicals of major public health concern
Radon and Health, WHO	http://www.who.int/mediacentre/factsheets/fs291/en/	Health effects and guide line of Radon.
Arsenic Fact Sheet, WHO	http://www.who.int/mediacentre/factsheets/fs372/en/	Contents include health effects, prevention, and control on Arsenic.
Elimination of asbestos-related diseases, WHO	http://www.who.int/mediacentre/factsheets/fs343/en/	Information about asbestos related diseases.
Science and Technology: Health, Environmental Protection Agency (EPA)	http://www.epa.gov/gateway/science/humanhealth.html	Information on human health impacts associated with environmental exposures
Work-Related Lung Disease (WoRLD) Surveillance System, National Institute for Occupational Safety and Health (NIOSH)	http://www2.cdc.gov/drds/WorldReportData/	Contents on occupationally-related respiratory disease surveillance data.
U.S. Geological Survey (USGS)	http://www.usgs.gov/	Organization that provides impartial information on the health of U.S. environment and the natural hazards
CARcinogen EXposure Canadian Surveillance Project (CAREX)	http://www.carexcanada.ca/	Project that combines academic expertise and government resources to generate an evidence-based carcinogen surveillance program
Lung Cancer and the Environment, Centers for Disease Control and Prevention (CDC)	https://ephtracking.cdc.gov/showCancerLcEnv.action	Information about exposure to environmental carcinogen and the risk for lung cancer.

Table 1.
Sources of information on environmental carcinogens associated with lung cancer.

7. Conclusions and future directions

The geographical conditions facilitating human exposure to environmental lung carcinogens such as arsenic, asbestos and radon occur commonly across the globe. While millions of individuals are known to be exposed to potentially damaging doses of these carcinogens, another significant part of the population is unaware of its exposure. Despite the worldwide impact of the public health risk posed by these compounds, the genomic and epigenetic consequences of these exposures are drastically understudied. Barriers such as: (i) availability of individual-level exposure data; (ii) collection of genomic, epigenomic, and transcriptomic readouts following acute and chronic exposure to carcinogens; and (iii) obtaining enough samples to reach statistical power; impose even further challenges to determining the true extent of environmentally-induced health effects.

Understanding these mechanisms could have a significant impact on the establishment of safe exposure limits for each of these agents. For instance, most of the current frameworks used to regulate arsenic exposure in drinking water have been derived from studies performed in specific populations exposed to high levels of arsenic, such as Bangladesh, Chile, and China [9, 133, 134]. However, an increased risk of arsenic-related health effects (including cancer) has been documented at levels below current safety thresholds that are commonly found in water sources throughout North America and Europe [7]. Thus, characterizing the effects of these agents at the genomic/epigenomic level will not only aid in determining the oncogenes that are perturbed in environmentally-induced lung cancers, but may also uncover early molecular events that can be used as diagnostic and prognostic markers.

The fraction of lung cancer patients who have never smoked or have ceased smoking is likely to increase in the coming years. Exposure to environmental carcinogens, such as arsenic, asbestos, and radon will play a key role in their etiology. Further elucidation of the detailed mechanisms driving environmentally-induced lung tumors will provide the much-needed insight to define specific detection methods and intervention strategies. Collectively, uncovering these carcinogen-specific mechanisms, as well as the affected genes driving malignant transformation, will greatly contribute to the development of personalized approaches to provide better support to lung cancer patients.

Acknowledgements

This work was supported by grants from the Canadian Institutes for Health Research (CIHR FDN-143345). VDM, APS, and EAM are supported by scholarships from the University of British Columbia. APS is further supported by the Frederick Banting and Charles Best Scholarship from CIHR. EAM is also supported by the Vanier Canada Graduate Scholarship from CIHR. AAG is the Canada Research Chair for Radiation Exposure Disease and this work was undertaken, in part, thanks to funding from the Canada Research Chairs program. The AAG laboratory is supported by the Canadian Institutes of Health Research.

Conflict of interest

Authors declare no conflict of interest.

IntechOpen

Author details

Victor D. Martinez[1,6,†*], Adam P. Sage[1,6,†], Erin A. Marshall[1,6], Miwa Suzuki[1], Aaron A. Goodarzi[2,3,6], Graham Dellaire[4,5,6] and Wan L. Lam[1,6]

1 Department of Integrative Oncology, British Columbia Cancer Research Centre, Vancouver, British Columbia, Canada

2 Department of Biochemistry & Molecular Biology, Robson DNA Science Centre, Arnie Charbonneau Cancer Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

3 Department Oncology, Robson DNA Science Centre, Arnie Charbonneau Cancer Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

4 Department of Pathology, University of Dalhousie, Halifax, Nova Scotia, Canada

5 Department of Biochemistry & Molecular Biology, University of Dalhousie, Halifax, Nova Scotia, Canada

6 Canadian Environmental Exposures in Cancer (CE2C) Network, Dalhousie University, Halifax, Nova Scotia, Canada

† These authors contributed equally to this work.

*Address all correspondence to: vmartinez@bccrc.ca

IntechOpen

© 2018 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

References

[1] Global Burden of Disease Cancer. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A systematic analysis for the global burden of disease study. JAMA Oncology. 2017;**3**(4):524-548

[2] Pallis AG, Syrigos KN. Lung cancer in never smokers: Disease characteristics and risk factors. Critical Reviews in Oncology/Hematology. 2013;**88**(3):494-503

[3] Shahadin MS et al. Challenges and future direction of molecular research in air pollution-related lung cancers. Lung Cancer. 2018;**118**:69-75

[4] Hubaux R et al. Arsenic, asbestos and radon: Emerging players in lung tumorigenesis. Environmental Health. 2012;**11**:89

[5] Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers—A different disease. Nature Reviews. Cancer. 2007;**7**(10):778-790

[6] Stanley FK et al. Comprehensive survey of household radon gas levels and risk factors in southern Alberta. CMAJ Open. 2017;**5**(1):E255-E264

[7] Saint-Jacques N et al. Estimating the risk of bladder and kidney cancer from exposure to low-levels of arsenic in drinking water, Nova Scotia, Canada. Environment International. 2018;**110**:95-104

[8] Teras LR et al. Residential radon exposure and risk of incident hematologic malignancies in the cancer prevention study-II nutrition cohort. Environmental Research. 2016;**148**:46-54

[9] World Health Organization Arsenic. 2016. Available from: http://www.who.int/mediacentre/factsheets/fs372/en/ [Accessed: Feb 15, 2017]

[10] Huang SX et al. Role of mutagenicity in asbestos fiber-induced carcinogenicity and other diseases. Journal of Toxicology and Environmental Health. Part B, Critical Reviews. 2011;**14**(1-4):179-245

[11] World Health Organization. Radon and Health. Geneva, Switzerland: WHO; 2016. Available from: http://www.who.int/mediacentre/factsheets/fs291/en/ [cited 2018]

[12] Naujokas MF et al. The broad scope of health effects from chronic arsenic exposure: Update on a worldwide public health problem. Environmental Health Perspectives. 2013;**121**(3):295-302

[13] Lin S et al. A novel S-adenosyl-L-methionine: Arsenic(III) methyltransferase from rat liver cytosol. The Journal of Biological Chemistry. 2002;**277**(13):10795-10803

[14] Ren X et al. An emerging role for epigenetic dysregulation in arsenic toxicity and carcinogenesis. Environmental Health Perspectives. 2011;**119**(1):11-19

[15] Hubaux R et al. Molecular features in arsenic-induced lung tumors. Molecular Cancer. 2013;**12**:20

[16] Reichard JF, Puga A. Effects of arsenic exposure on DNA methylation and epigenetic gene regulation. Epigenomics. 2010;**2**(1):87-104

[17] Howe CG et al. Sex-specific associations between one-carbon metabolism indices and posttranslational histone modifications in arsenic-exposed Bangladeshi adults. Cancer Epidemiology, Biomarkers & Prevention. 2017;**26**(2):261-269

[18] Riedmann C et al. Inorganic arsenic-induced cellular transformation is coupled with genome wide changes in

chromatin structure, transcriptome and splicing patterns. BMC Genomics. 2015;**16**:212

[19] Naranmandura H et al. Mitochondria are the main target organelle for trivalent monomethylarsonous acid (MMA(III))-induced cytotoxicity. Chemical Research in Toxicology. 2011;**24**(7):1094-1103

[20] Kligerman AD, Malik SI, Campbell JA. Cytogenetic insights into DNA damage and repair of lesions induced by a monomethylated trivalent arsenical. Mutation Research. 2010;**695**(1-2):2-8

[21] Martinez VD et al. Whole-genome sequencing analysis identifies a distinctive mutational spectrum in an arsenic-related lung tumor. Journal of Thoracic Oncology. 2013;**8**(11):1451-1455

[22] Zhao CQ et al. Association of arsenic-induced malignant transformation with DNA hypomethylation and aberrant gene expression. Proceedings of the National Academy of Sciences of the United States of America. 1997;**94**:10907-10912

[23] Bhattacharjee P, Banerjee M, Giri AK. Role of genomic instability in arsenic-induced carcinogenicity. A review. Environment International. 2013;**53**:29-40

[24] Kessel M et al. Arsenic induces oxidative DNA damage in mammalian cells. Molecular and Cellular Biochemistry. 2002;**234-235**(1-2):301-308

[25] Matsui M et al. The role of oxidative DNA damage in human arsenic carcinogenesis: Detection of 8-hydroxy-2′-deoxyguanosine in arsenic-related Bowen's disease. The Journal of Investigative Dermatology. 1999;**113**(1):26-31

[26] Turrens JF. Mitochondrial formation of reactive oxygen species. The Journal of Physiology. 2003;**552**(Pt 2):335-344

[27] Melis JP, van Steeg H, Luijten M. Oxidative DNA damage and nucleotide excision repair. Antioxidants & Redox Signaling. 2013;**18**(18):2409-2419

[28] Hanawalt PC, Spivak G. Transcription-coupled DNA repair: Two decades of progress and surprises. Nature Reviews. Molecular Cell Biology. 2008;**9**(12):958-970

[29] Banerjee M et al. Polymorphism in the ERCC2 codon 751 is associated with arsenic-induced premalignant hyperkeratosis and significant chromosome aberrations. Carcinogenesis. 2007;**28**(3):672-676

[30] Ahsan H et al. DNA repair gene XPD and susceptibility to arsenic-induced hyperkeratosis. Toxicology Letters. 2003;**143**(2):123-131

[31] Holcomb N et al. Inorganic arsenic inhibits the nucleotide excision repair pathway and reduces the expression of XPC. DNA Repair (Amst). 2017;**52**:70-80

[32] Andrew AS et al. Arsenic activates EGFR pathway signaling in the lung. Toxicological Sciences: An Official Journal of the Society of Toxicology. Oxford UK: Oxford University Press; 2009:**109**

[33] Li L et al. Filamin A phosphorylation by Akt promotes cell migration in response to arsenic. Oncotarget. 2015;**6**(14):12009-12019

[34] Liu J et al. JNK-dependent Stat3 phosphorylation contributes to Akt activation in response to arsenic exposure. Toxicological Sciences. 2012;**129**(2):363-371

[35] Carpenter RL, Jiang BH. Roles of EGFR, PI3K, AKT, and mTOR in heavy metal-induced cancer. Current Cancer Drug Targets. 2013;**13**(3):252-266

[36] Li Z et al. Low-dose arsenic-mediated metabolic shift is associated with activation of polo-like kinase 1 (Plk1). Cell Cycle. 2015;**14**(19):3030-3039

[37] Ersahin T, Tuncbag N, Cetin-Atalay R. The PI3K/AKT/mTOR interactive pathway. Molecular BioSystems. 2015;**11**(7):1946-1954

[38] Chen C et al. MicroRNA-155 regulates arsenite-induced malignant transformation by targeting Nrf2-mediated oxidative damage in human bronchial epithelial cells. Toxicology Letters. 2017;**278**:38-47

[39] Al-Eryani L et al. Differentially expressed mRNA targets of differentially expressed miRNAs predict changes in the TP53 axis and carcinogenesis related pathways in human keratinocytes chronically exposed to arsenic. Toxicological Sciences. 2018;**162**:645-654

[40] Pratheeshkumar P et al. Oncogenic transformation of human lung bronchial epithelial cells induced by arsenic involves ROS-dependent activation of STAT3-miR-21-PDCD4 mechanism. Scientific Reports. 2016;**6**:37227

[41] Mo J et al. Elevated ERCC1 gene expression in blood cells associated with exposure to arsenic from drinking water in Inner Mongolia. Anticancer Research. 2009;**29**(8):3253-3259

[42] Zhou X et al. S-nitrosation on zinc finger motif of PARP-1 as a mechanism of DNA repair inhibition by arsenite. Oncotarget. 2016;**7**(49):80482-80492

[43] Zhang A et al. Aberrant methylation of nucleotide excision repair genes is associated with chronic arsenic poisoning. Biomarkers. 2017;**22**(5):429-438

[44] Michailidi C et al. Involvement of epigenetics and EMT-related miRNA in arsenic-induced neoplastic transformation and their potential clinical use. Cancer Prevention Research (Philadelphia, PA). 2015;**8**(3):208-221

[45] Komissarova EV, Rossman TG. Arsenite induced poly(ADP-ribosyl)ation of tumor suppressor P53 in human skin keratinocytes as a possible mechanism for carcinogenesis associated with arsenic exposure. Toxicology and Applied Pharmacology. 2010;**243**(3):399-404

[46] Lee HY et al. Formation of biofilm by listeria monocytogenes ATCC 19112 at different incubation temperatures and concentrations of sodium chloride. Brazilian Journal of Microbiology. 2013;**44**(1):51-55

[47] Hsu LI et al. Association of environmental arsenic exposure, genetic polymorphisms of susceptible genes, and skin cancers in Taiwan. BioMed Research International. 2015;**2015**:892579

[48] Minatel BC et al. Environmental arsenic exposure: From genetic susceptibility to pathogenesis. Environment International. 2017;**112**:183-197

[49] Antonelli R et al. AS3MT, GSTO, and PNP polymorphisms: Impact on arsenic methylation and implications for disease susceptibility. Environmental Research. 2014;**132**:156-167

[50] The International Ban Asbestos Secretariat. Current Asbestos Bans. 2018. Available from: http://www.ibasecretariat.org/alpha_ban_list.php [cited Apr 1, 2018]

[51] Virta RL. Worldwide Asbestos Supply and Consumption Trends from 1900 through 2003 Circular 1298. Reston, Virginia: U.S. Geological Survey; 2006. p. 80. Available from: http://pubs.usgs.gov/circ/2006/1298/c1298.pdf

[52] Ghio AJ, Churg A, Roggli VL. Ferruginous bodies: Implications in the mechanism of fiber and particle toxicity. Toxicologic Pathology. 2004;**32**(6):643-649

[53] Fubini B, Barcelo F, Otero Arean C. Ferritin adsorption on amosite fibers: Possible implications in the formation and toxicity of asbestos bodies. Journal of Toxicology and Environmental Health. 1997;**52**(4):343-352

[54] Global Burden of Disease Cancer Collaboration et al. The global burden of cancer 2013. JAMA Oncology. 2015;**1**(4):505-527

[55] Heintz NH, Janssen-Heininger YM, Mossman BT. Asbestos, lung cancers, and mesotheliomas: From molecular approaches to targeting tumor survival pathways. American Journal of Respiratory Cell and Molecular Biology. 2010;**42**(2):133-139

[56] Mossman BT et al. Pulmonary endpoints (lung carcinomas and asbestosis) following inhalation exposure to asbestos. Journal of Toxicology and Environmental Health. Part B, Critical Reviews. 2011;**14**(1-4):76-121

[57] Sankpal UT et al. Environmental factors in causing human cancers: Emphasis on tumorigenesis. Tumour Biology. 2012;**33**(5):1265-1274

[58] American Thoracic S. Diagnosis and initial management of nonmalignant diseases related to asbestos. American Journal of Respiratory and Critical Care Medicine. 2004;**170**(6):691-715

[59] Loomis D et al. Increased lung cancer mortality among chrysotile asbestos textile workers is more strongly associated with exposure to long thin fibres. Occupational and Environmental Medicine. 2012;**69**(8):564-568

[60] Stayner L et al. An epidemiological study of the role of chrysotile asbestos fibre dimensions in determining respiratory disease risk in exposed workers. Occupational and Environmental Medicine. 2008;**65**(9):613-619

[61] Xu A et al. Genotoxic mechanisms of asbestos fibers: Role of extranuclear targets. Chemical Research in Toxicology. 2007;**20**:724-733

[62] Choe N, Tanaka S, Kagan E. Asbestos fibers and interleukin-1 upregulate the formation of reactive nitrogen species in rat pleural mesothelial cells. American Journal of Respiratory Cell and Molecular Biology. 1998;**19**:226-236

[63] Liu G, Cheresh P, Kamp DW. Molecular basis of asbestos-induced lung disease. Annual Review of Pathology. 2013;**8**:161-187

[64] Pinkerton KE et al. Alveolar type II cell responses to chronic inhalation of chrysotile asbestos in rats. American Journal of Respiratory Cell and Molecular Biology. 1990;**3**(6):543-552

[65] Mossman BT et al. Asbestos: Scientific developments and implications for public policy. Science. 1990;**247**(4940):294-301

[66] Brody AR, Overby LH. Incorporation of tritiated thymidine by epithelial and interstitial cells in bronchiolar-alveolar regions of asbestos-exposed rats. The American Journal of Pathology. 1989;**134**(1):133-140

[67] Kamp DW et al. The role of free radicals in asbestos-induced diseases. Free Radical Biology & Medicine. 1992;**12**(4):293-315

[68] Shukla A et al. Multiple roles of oxidants in the pathogenesis of asbestos-induced diseases. Free Radical Biology & Medicine. 2003;**34**(9):1117-1129

[69] Pascolo L et al. The interaction of asbestos and iron in lung tissue

revealed by synchrotron-based scanning X-ray microscopy. Scientific Reports. 2013;**3**:1123

[70] Andujar P et al. Differential mutation profiles and similar intronic TP53 polymorphisms in asbestos-related lung cancer and pleural mesothelioma. Mutagenesis. 2013;**28**(3):323-331

[71] Wang X et al. Mutations in the p53 gene in lung cancer are associated with cigarette smoking and asbestos exposure. Cancer Epidemiology, Biomarkers & Prevention. 1995;**4**(5):543-548

[72] Andujar P et al. p16INK4A inactivation mechanisms in non-small-cell lung cancer patients occupationally exposed to asbestos. Lung Cancer. 2010;**67**(1):23-30

[73] Cui Y et al. Chrysotile effects on the expression of anti-oncogene P53 and P16 and oncogene C-jun and C-fos in Wistar rats' lung tissues. Environmental Science and Pollution Research International. 2017;**25**:22378-22388

[74] Shukla A et al. ERK2 is essential for the growth of human epithelioid malignant mesotheliomas. International Journal of Cancer. 2011;**129**(5):1075-1086

[75] Shukla A et al. The gamma-glutamylcysteine synthetase and glutathione regulate asbestos-induced expression of activator protein-1 family members and activity. Cancer Research. 2004;**64**(21):7780-7786

[76] Zanella CL et al. Asbestos-induced phosphorylation of epidermal growth factor receptor is linked to c-fos and apoptosis. The American Journal of Physiology. 1999;**277**(4 Pt 1):L684-L693

[77] Paris C et al. Association between lung cancer somatic mutations and occupational exposure in never-smokers. The European Respiratory Journal. 2017;**50**(4)

[78] Kradin RL, Iafrate J, Christiani DC. Pulmonary adenocarcinoma with epidermal growth factor receptor-mutations in asbestos exposed non-smokers: A case series. American Journal of Industrial Medicine. 2017;**60**(3):306-309

[79] Maki-Nevala S et al. Epidermal growth factor receptor mutations in 510 Finnish non-small-cell lung cancer patients. Journal of Thoracic Oncology. 2014;**9**(6):886-891

[80] Nymark P et al. Gene expression profiles in asbestos-exposed epithelial and mesothelial lung cell lines. BMC Genomics. 2007;**8**:62

[81] Shukla A et al. Transcriptional up-regulation of MMP12 and MMP13 by asbestos occurs via a PKCdelta-dependent pathway in murine lung. The FASEB Journal. 2006;**20**(7):997-999

[82] Dammann R et al. CpG island methylation and expression of tumour-associated genes in lung carcinoma. European Journal of Cancer. 2005;**41**(8):1223-1236

[83] Kettunen E et al. Asbestos-associated genome-wide DNA methylation changes in lung cancer. International Journal of Cancer. 2017;**141**(10):2014-2029

[84] Nymark P et al. Integrative analysis of microRNA, mRNA and aCGH data reveals asbestos- and histology-related changes in lung cancer. Genes, Chromosomes & Cancer. 2011;**50**(8):585-597

[85] Tunesi S et al. Gene-asbestos interaction in malignant pleural mesothelioma susceptibility. Carcinogenesis. 2015;**36**(10):1129-1135

[86] Wei S et al. Genome-wide gene-environment interaction analysis for asbestos exposure in lung cancer susceptibility. Carcinogenesis. 2012;**33**(8):1531-1537

[87] Carbone M et al. A mesothelioma epidemic in Cappadocia: Scientific developments and unexpected social outcomes. Nature Reviews. Cancer. 2007;**7**(2):147-154

[88] Carbone M, Yang H. Molecular pathways: Targeting mechanisms of asbestos and erionite carcinogenesis in mesothelioma. Clinical Cancer Research. 2012;**18**(3):598-604

[89] Hillegass JM et al. Asbestos and erionite prime and activate the NLRP3 inflammasome that stimulates autocrine cytokine release in human mesothelial cells. Particle and Fibre Toxicology. 2013;**10**:39

[90] Cardile V et al. Behaviour of the new asbestos amphibole fluor-edenite in different lung cell systems. The International Journal of Biochemistry & Cell Biology. 2004;**36**(5):849-860

[91] Shvedova AA et al. Long-term effects of carbon containing engineered nanomaterials and asbestos in the lung: One year postexposure comparisons. American Journal of Physiology. Lung Cellular and Molecular Physiology. 2014;**306**(2):L170-L182

[92] Polimeni M et al. Multi-walled carbon nanotubes directly induce epithelial-mesenchymal transition in human bronchial epithelial cells via the TGF-beta-mediated Akt/GSK-3beta/SNAIL-1 signalling pathway. Particle and Fibre Toxicology. 2016;**13**(1):27

[93] Pacurari M et al. Raw single-wall carbon nanotubes induce oxidative stress and activate MAPKs, AP-1, NF-kappaB, and Akt in normal and malignant human mesothelial cells. Environmental Health Perspectives. 2008;**116**(9):1211-1217

[94] Asakura M et al. Genotoxicity and cytotoxicity of multi-wall carbon nanotubes in cultured Chinese hamster lung cells in comparison with chrysotile A fibers. Journal of Occupational Health. 2010;**52**(3):155-166

[95] Yamashita K et al. Carbon nanotubes elicit DNA damage and inflammatory response relative to their size and shape. Inflammation. 2010;**33**(4):276-280

[96] Kisin ER et al. Single-walled carbon nanotubes: Geno- and cytotoxic effects in lung fibroblast V79 cells. Journal of Toxicology and Environmental Health. Part A. 2007;**70**(24):2071-2079

[97] Ghosh M et al. Single-walled and multi-walled carbon nanotubes induce sequence-specific epigenetic alterations in 16 HBE cells. Oncotarget. 2018;**9**(29):20351-20365

[98] Mohery M et al. Radon decay products in realistic living rooms and their activity distributions in human respiratory system. Radiation Protection Dosimetry. 2014;**162**(3):394-399

[99] Pohl-Ruling J et al. Chromosomal aberrations of blood lymphocytes induced in vitro by radon-222 daughter alpha-irradiation. Mutation Research. 2000;**449**(1-2):7-19

[100] Jovanovic B, Nikezic D. Probability of bystander effect induced by alpha-particles emitted by radon progeny using the analytical model of tracheobronchial tree. Radiation Protection Dosimetry. 2010;**142**(2-4):168-173

[101] Jalal N et al. Radiation induced bystander effect and DNA damage. Journal of Cancer Research and Therapeutics. 2014;**10**(4):819-833

[102] Tomita M, Maeda M. Mechanisms and biological importance of photon-induced bystander responses: Do they

have an impact on low-dose radiation responses. Journal of Radiation Research. 2015;**56**(2):205-219

[103] Tomita M et al. Dose response of soft X-ray-induced bystander cell killing affected by p53 status. Radiation Research. 2013;**179**(2):200-207

[104] Hei TK et al. Radiation induced non-targeted response: Mechanism and potential clinical implications. Current Molecular Pharmacology. 2011;**4**(2):96-105

[105] Robertson A et al. The cellular and molecular carcinogenic effects of radon exposure: A review. International Journal of Molecular Sciences. 2013;**14**(7):14024-14063

[106] Moore S, Stanley FK, Goodarzi AA. The repair of environmentally relevant DNA double strand breaks caused by high linear energy transfer irradiation—No simple task. DNA Repair (Amst). 2014;**17**:64-73

[107] Rothkamm K et al. Radiation-induced HPRT mutations resulting from misrejoined DNA double-strand breaks. Radiation Research. 2008;**169**(6):639-648

[108] Kuhne M, Rothkamm K, Lobrich M. No dose-dependence of DNA double-strand break misrejoining following alpha-particle irradiation. International Journal of Radiation Biology. 2000;**76**(7):891-900

[109] Tsao MS, Hirsch FR, Yatabe Y, editors. IASLC Atlas of ALK and ROS1 Testing in Lung Cancer. 2nd ed. Aurora, CO, USA: IASLC; 2016

[110] Ruano-Ravina A et al. Residential radon, EGFR mutations and ALK alterations in never-smoking lung cancer cases. The European Respiratory Journal. 2016;**48**(5):1462-1470

[111] Schaue D, Kachikwu EL, McBride WH. Cytokines in radiobiological responses: A review. Radiation Research. 2012;**178**(6):505-523

[112] Ruano-Ravina A, Faraldo-Valles MJ, Barros-Dios JM. Is there a specific mutation of p53 gene due to radon exposure? A systematic review. International Journal of Radiation Biology. 2009;**85**(7):614-621

[113] Choi JR et al. Novel genetic associations between lung cancer and indoor radon exposure. Journal of Cancer Prevention. 2017;**22**(4):234-240

[114] Cui FM et al. Radon-induced alterations in micro-RNA expression profiles in transformed BEAS2B cells. Journal of Toxicology and Environmental Health. Part A. 2013;**76**(2):107-119

[115] Chaudhry MA et al. Micro RNA responses to chronic or acute exposures to low dose ionizing radiation. Molecular Biology Reports. 2012;**39**(7):7549-7558

[116] Sinitsky MY et al. Associations of DNA-repair gene polymorphisms with a genetic susceptibility to ionizing radiation in residents of areas with high radon (222Rn) concentration. International Journal of Radiation Biology. 2015;**91**(6):486-494

[117] Bonner MR et al. Radon, secondhand smoke, glutathione-S-transferase M1 and lung cancer among women. International Journal of Cancer. 2006;**119**(6):1462-1467

[118] Ruano-Ravina A et al. Genetic susceptibility, residential radon, and lung cancer in a radon prone area. Journal of Thoracic Oncology. 2014;**9**(8):1073-1080

[119] Sabharwal SS, Schumacker PT. Mitochondrial ROS in cancer: Initiators, amplifiers or an Achilles' heel? Nature Reviews. Cancer. 2014;**14**(11):709-721

[120] Yang Y et al. Mitochondria and mitochondrial ROS in cancer: Novel targets for anticancer therapy. Journal of Cellular Physiology. 2016;**231**(12):2570-2581

[121] Pace C et al. Monomethylarsonous acid, but not inorganic arsenic, is a mitochondria-specific toxicant in vascular smooth muscle cells. Toxicology In Vitro. 2016;**35**:188-201

[122] Flora SJ. Arsenic-induced oxidative stress and its reversibility. Free Radical Biology & Medicine. 2011;**51**(2):257-281

[123] Pulido MD, Parrish AR. Metal-induced apoptosis: Mechanisms. Mutation Research. 2003;**533**(1-2):227-241

[124] Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell. 2011;**144**(5):646-674

[125] Murphy FA et al. The mechanism of pleural inflammation by long carbon nanotubes: Interaction of long fibres with macrophages stimulates them to amplify pro-inflammatory responses in mesothelial cells. Particle and Fibre Toxicology. 2012;**9**:8

[126] Matsuzaki H et al. Asbestos-induced cellular and molecular alteration of immunocompetent cells and their relationship with chronic inflammation and carcinogenesis. Journal of Biomedicine & Biotechnology. 2012;**2012**:492608

[127] Diakos CI et al. Cancer-related inflammation and treatment effectiveness. The Lancet Oncology. 2014;**15**(11):e493-e503

[128] Wild CP. Complementing the genome with an "exposome": The outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiology, Biomarkers & Prevention. 2005;**14**(8):1847-1850

[129] Wild CP. The exposome: From concept to utility. International Journal of Epidemiology. 2012;**41**(1):24-32

[130] Bartholomew C et al. EGFR targeted therapy in lung cancer: An evolving story. Respiratory Medicine Case Reports. 2017;**20**:137-140

[131] Sullivan I, Planchard D. ALK inhibitors in non-small cell lung cancer: The latest evidence and developments. Therapeutic Advances in Medical Oncology. 2016;**8**(1):32-47

[132] Vargas AJ, Harris CC. Biomarker development in the precision medicine era: Lung cancer as a case study. Nature Reviews. Cancer. 2016;**16**(8):525-537

[133] Martinez VD et al. Emerging arsenic threat in Canada. Science. 2013;**342**(6158):559

[134] Martinez VD et al. Arsenic-related DNA copy-number alterations in lung squamous cell carcinomas. British Journal of Cancer. 2010;**103**(8):1277-1283