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Biological Activities of Carbon Nanotubes

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1. Introduction

During the past several years, nanotechnology based on novel nanomaterials has gained considerable attention in various scientific disciplines such as biotechnology, medicine and material engineering (McCarthy and Weissleder 2008). According to British Standards Institute Report (2007), nanoparticles are those particles with at least one dimension of less than or equal to 100 nm ($1 \text{ nm} = 1 \times 10^{-6} \text{ m}$) in size. Since particle size is directly related to surface area and associated surface energy, nanoscaled materials relatively exhibit unique physicochemical, optical and electrical properties than micron-sized particles. Nanomaterials have exceptional properties and are beneficial in a wide range of applications. Nanotechnology based on these novel nanomaterials is fueling the modern industrial revolution which is already a multi-billion dollar market capitalization. Among the different types of nanomaterials, carbon nanoparticles have gained much attention in recent years due to their exceptional physicochemical properties. Some of the most popular carbon-based nanomaterials are fullerene (C_{60}), carbon nanohorn, single wall carbon nanotubes (SWCNT), and multi wall carbon nanotubes (MWCNT).

Carbon nanotubes (CNT) are one of the most commonly used nanomaterials possessing unique physicochemical properties such as high aspect ratio and a diameter of less than 100 nm (Iijima 1991). Due to their exceptional characteristics, CNT, if incorporated will enhance the efficiency of a number of applications including electronics (Bandaru 2007), biosensors (Le Goff, Holzinger et al. 2011), drug and biomolecule carriers (Prato, Kostarelos et al. 2007). Other potential biomedical applications of CNT include bone scaffold, dental tissue support, and neuronal cell growth scaffold (Li, Fan et al. 2010). Increasing evidence has shown that certain CNT properties such as nano-sized dimension, high surface energy, and large reactive surface area are directly correlated to their biological activities (Oberdorster, Ferin et al. 1994; Oberdorster, Oberdorster et al. 2005). The bioactivity of nanoparticles differs from micron-size particles of the same material. Although the underlying mechanism remains to be understood, small size, high surface area and chemical composition of nanomaterials play an important role. Recent studies have shown that CNT could be harmful to human health. Fiber morphology and high surface energy of CNT raise health concerns among scientists due to their structural similarities with asbestos fibers (Donaldson, Murphy et al. 2010). The biological properties of nanoparticles are currently under intense investigations and are the subject of this review.

2. Routes of nanoparticle exposure and associated pathologies

Nanomaterials such as CNT have very low specific weight and can be easily aerosolized and come in contact with humans during manufacturing, transportation or usage of the CNT-based products. Apart from unintentional exposures, for certain biomedical applications such as drug delivery, artificial tissues and diagnostic agents, CNT need to be introduced into the human body. Therefore, it is important to consider the potential adverse effects of nanoparticles. Most recent studies have focused on the adverse effects of nanoparticle exposure on pulmonary or dermal tissues.

2.1 Pulmonary exposure

Lung is the major target organ for nanoparticle exposure. Because of their low density and small size, CNT can be aerosolized and inadvertently inhaled during their manufacturing or handling. Therefore, respiratory exposure of nanomaterials including CNT has been the focus of intense research. Lung exposure to solid particles has been linked to asthma (Bonner 2010), fibrosis (Shvedova, Kisin et al. 2005), mesothelioma (Sakamoto, Nakae et al. 2009), and other inflammatory diseases (Li, Muralikrishnan et al. 2010). The region of lung affected by accidentally inhaled materials depends on the shape (fibrous, spherical), size (aerodynamic diameter), and other physical and chemical properties of the particles. Nano-sized particles are deposited deep inside the lung compared to micron-sized particles of similar chemical composition (Oberdorster, Ferin et al. 1994). As shown in Figure 1, a large fraction of inhaled particles with the size of less than 100 nm deposits mainly in the terminal alveolar region of the lung, whereas most of the micron-sized inhaled particles remain in the upper respiratory tract. Recent studies have shown that 80% of pulmonary exposed SWCNT reach the alveolar space of the lung in mice (Shvedova, Kisin et al. 2005; Mercer, Scabilloni et al. 2008). Pulmonary exposure of SWCNT and MWCNT has been shown to induce rapid interstitial lung fibrosis with non-persistent inflammatory response in rodents (Shvedova, Kisin et al. 2005; Porter, Hubbs et al. 2010). Inhaled CNT can also translocate to the surrounding regions of the lung such as pleural space (Mercer, Scabilloni et al. 2008; Wilson and Wynn 2009). In several *in vivo* studies, pulmonary exposure to CNT has been shown to induce granuloma formation in the terminal alveolar region of the lung (Lam, James et al. 2004; Warheit, Laurence et al. 2004; Shvedova, Kisin et al. 2005). Inflammatory granulomas are accumulation of epithelioid macrophages engulfing persistent and non-biodegradable particles. Neutrophil infiltration was also observed in these studies.

Usually inhalation mimics pulmonary exposure of non-soluble particles in animal models, while intratracheal instillation or pharyngeal aspiration have shown similar results (Li, Li et al. 2007; Shvedova, Kisin et al. 2008). Upon alveolar deposition, an unexpectedly rapid translocation of dispersed SWCNT into the alveolar interstitium (1 day post-exposure) has been observed (Shvedova 2005). Subsequent development of lung fibrosis occurs as early as 1 week post-exposure and progresses through 60 days post-exposure without persistent inflammation. The mechanism of nanoparticle-induced lung fibrosis is still under investigation. Data suggest oxidative stress, cytotoxicity and apoptosis induction via DNA damage (Nam, Kang et al. 2011; Ravichandran, Baluchamy et al. 2011) or direct stimulation of lung fibroblasts (Wang, Mercer et al. 2010). *In vitro* studies provide detailed information on the mechanism of the unusual CNT-induced lung fibrosis. Several key lung cells have been selected to determine the specific CNT-lung cell interactions. For example, SWCNT

directly stimulate fibroblasts to produce collagen (Wang, Mercer et al. 2010) or induce oxidative stress through ROS production in macrophages (Migliore, Saracino et al. 2010; Palomäki, Välimäki et al. 2011). A study using lung epithelial cells has shown that chronic exposure of low-dose SWCNT can induce cancer-like cell transformation (Wang, Luanpitpong et al. 2011). Several other studies have shown that CNT can induce toxicity of alveolar epithelial cells through a suppression of immune response or oxidative stress (Simon-Deckers, Gouget et al. 2008; Herzog, Byrne et al. 2009). Due to the large surface area and proximity to the circulatory system, inhaled nanoparticles can potentially translocate to other parts of the body and can cause toxic effects such as cardiovascular abnormality (Li, Hulderman et al. 2006).

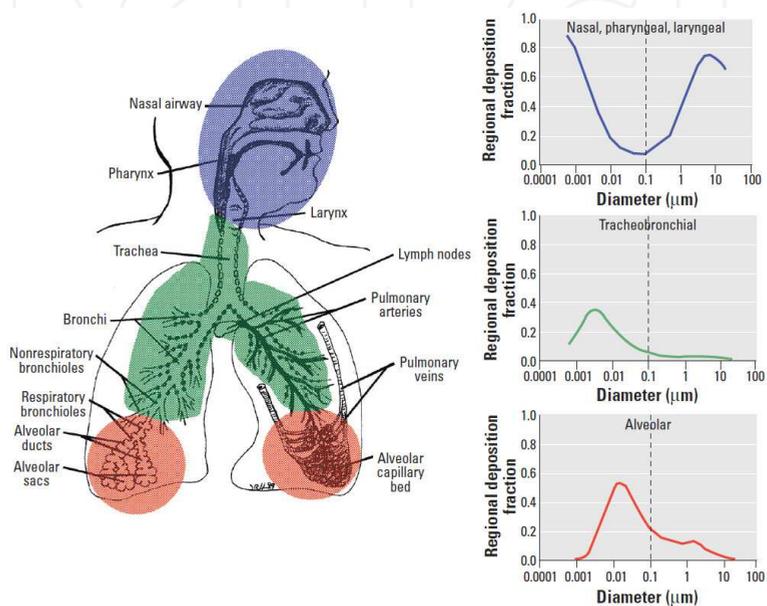


Fig. 1. Predicted fractional deposition of inhaled particles in the nasopharyngeal, tracheobronchial, and alveolar region of the human respiratory tract during nose breathing (Oberdorster, et al., 2005)

2.2 Skin exposure

Skin is the primary barrier preventing the entry of foreign particles into the body. Exposure of skin to nanoparticles can occur in the form of cosmetic formulations containing nanomaterials such as nano-sized titanium dioxide and accidental exposure of nanoparticles during manufacturing or handling. Recent *in vivo* and *in vitro* studies have shown that skin-exposed CNT can translocate to the deeper layers of skin such as dermis or subcutaneous layer. *In vivo* studies with dermal exposure of CNT have shown inflammation and inflammatory granuloma formation in dermal and subcutaneous tissues (Yokoyama, Sato et al. 2004; Koyama, Endo et al. 2006). Other studies have also shown that exposure to CNT can induce dermal granuloma formation, thickness of skin folding and neutrophil and macrophage-mediated inflammation (Sato, Yokoyama et al. 2005; Murray, Kisin et al. 2009).

A number of *in vitro* dermal studies has shown that SWCNT exposure can cause inflammation and oxidative stress in dermis and keratinocyte cells (Li, Hulderman et al. 2006; Poland, Duffin et al. 2008; Msiska, Pacurari et al. 2009). The inflammation and toxicity are less severe in skin exposure than lung exposure due to the stiffness and thick layer of the skin cutaneous tissue (Sato, Yokoyama et al. 2005).

2.3 Oral exposure

Oral exposure of nanoparticles could be through food packaging, contaminated food or water. In addition, ingestion of nano-drugs or nano-delivery systems can lead to gastrointestinal track (GIT) exposure to nanoparticles. Absorption from GIT depends on the physicochemical properties of nanomaterials. For example, Kolosnjaj-Tabi et al. (2010) reported that when SWCNT were administered orally (1000 mg/kg body weight), neither death nor growth or behavioral troubles were observed. However, intraperitoneal administration of SWCNT (50-1000 mg/kg body weight) can coalesce inside the body to form fiber-like structures. When SWCNT length exceeded 10 μm , they irretrievably induced granuloma formation compared to smaller aggregates which did not induce granuloma but persisted inside the cells for up to 5 months post-administration. Individualized SWCNT (< 300 nm) can escape the reticuloendothelial system to be excreted through the kidney and bile ducts (Kolosnjaj-Tabi, Hartman et al. 2010). Oral exposure of corn oil-suspended CNT induced oxidative and genotoxic changes in the lung and liver of rats (Folkmann, Risom et al. 2009). However, the risk of CNT ingestion is not clearly understood because of the short history of usage of this new nanomaterial and the limited knowledge/studies in the field.

2.4 Cardiovascular exposure

One of the applications of CNT is as a carrier for drugs and biomolecules into the body. This requires these materials to be able to get into the systemic circulation. Therefore, implication of CNT exposure in blood vessels and heart muscles should be thoroughly investigated. Apart from directly injected into the blood for medical applications, nanoparticles can also enter blood via translocation from the lung or skin. Intravenous exposure in mice to SWCNT induces inflammatory reactions and an up-regulation of pro-inflammatory cytokines such as tumor necrosis factor- α (Li, Hulderman et al. 2007; Yang, Wang et al. 2008). Another study reported that CNT exposure to the heart tissue induces cellular mitochondrial damage, oxidative stress and apoptosis (Li, Hulderman et al. 2007). Additionally, vascular thrombosis and platelet aggregation was observed in both *in vivo* and *in vitro* exposures to CNT (Radomski, Jurasz et al. 2005). These studies suggest that cardiovascular exposure of nanomaterials could be hazardous to normal cardiac function. However, studies on the dose, time, physicochemical properties and pharmacokinetic parameters of the administered CNT are limited.

2.5 Neuronal exposure

There are only a few studies on the effect of nanomaterial exposure on the nervous system. When exposed to neuroblast-glioma cells *in vitro*, SWCNT induced DNA damage and cytotoxicity (Belyanskaya, Weigel et al. 2009). Also SWCNT induced oxidative stress, cell membrane damage and DNA damage in neuronal pc12 cells (Zhang, Ali et al. 2010). *In vivo*

systemic exposure studies did not find distribution or translocation of CNT to neuronal tissues or brain (Wang, Wang et al. 2004). However, another *in vivo* study showed the translocation of CNT across blood brain barrier (Yang, Guo et al. 2007)

3. Absorption, distribution and metabolism of carbon nanotubes *in vivo*

Biodegradation of nanoparticles after exposure depends on the nature of nanomaterial and its chemical constituents. It also depends on the bio-distribution and persistence of nanoparticles in the body. Much of the absorption of CNT depends on the translocation of CNT from the site of exposure (lung, skin, etc.) to the systemic circulation (Yang, Wang et al. 2008). Only a few studies have shown the translocation and distribution of systemically exposed CNT into organs such as liver, lung, spleen and kidney where a high level of CNT accumulation was observed (Wang, Wang et al. 2004; Rotoli, Bussolati et al. 2008). Usually biodegradable nanomaterials are broken down into constituent molecules. However, some nanomaterials including SWCNT and MWCNT are bio-persistent and difficult to excrete, which become a safety concern and deter their biomedical applications. Studies have shown that these CNT can stay in the lung tissue for months after exposure and lead to granuloma or progressive interstitial fibrosis (Shvedova, Kisin et al. 2005; Mercer, Hubbs et al. 2011). Bio-persistence of CNT increases their interaction with body's cells which can lead to harmful effects to specific tissues and organs. Contaminants, mainly metal ions which are used as catalysts of CNT synthesis, can induce reactive oxygen species (ROS) generation which can cause tissue inflammation, cell damage and even carcinogenesis.

4. Physicochemical properties of nanomaterials affecting their biological activities

Physicochemical properties of nanomaterials can have a great influence on the biological activities of the materials. Some key physicochemical properties affecting their bioactivities include size, shape, surface activity, dispersion status, and metal contaminants.

4.1 Size

Studies with micron- and nano-sized particles of the same material, e.g., silica and CNT, have shown that the nano-sized particles have a deeper lung deposition and are more toxic than large particles. As the particle size reduces, the surface atom increases. As the particles size reduces to less than 100 nm, the surface atom increases exponentially (Figure 2). Properties such as surface energy and electrical force also change accordingly (Garg and Sinnott 1998; Folkmann, Risom et al. 2009). These properties have been shown to influence the translocation and distribution of nanoparticles in the body.

4.2 Shape

High aspect-ratio fibers like asbestos are historically known to be cytotoxic (Jaurand, Renier et al. 2009). Compared to asbestos fibers, the aspect ratio of MWCNT is similar but larger. Recent animal studies have shown that the toxicity of CNT is several times higher than that of asbestos. Pulmonary exposed long fibers like CNT (> 20 μm) are difficult to be cleared by macrophages (Lam, James et al. 2004). Other studies have also reported that short CNT

evade phagocytosis by macrophages when compared to larger micron-sized particles of similar composition (Muller, Huaux et al. 2005; Mercer, Scabilloni et al. 2008; Zhang, Bai et al. 2010; Palomäki, Välimäki et al. 2011)

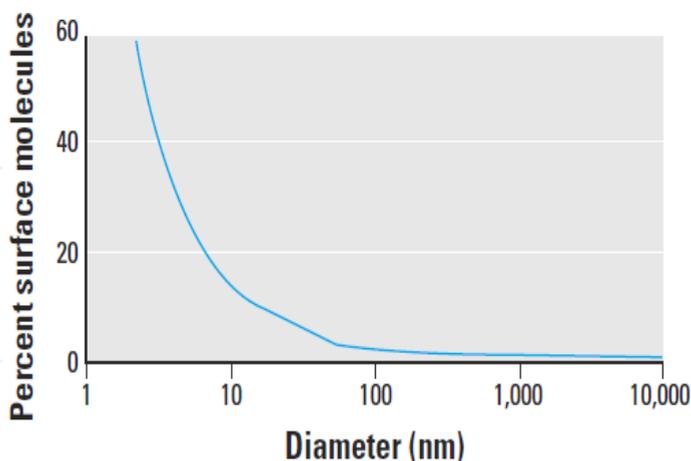


Fig. 2. Surface molecules as a function of particle size. Surface molecules increase exponentially when particle size decreases to less than 100 nm (Oberdorster et al. 2005).

4.3 Surface activity

The biological activity of CNT is directly related to its surface activity. CNT have a large surface area and high surface energy. Studies have shown that surface modifications can lead to changes in biological activity and toxicity. Surface modification with different chemical functionalities can affect the overall biological activity of nanoparticles. For example, acid treatment of CNT introduces carboxyl groups onto the surface of particles leading to an increase in dispersion and water solubility. Functionalization of CNT with COOH reduces the attractive electrical force between CNT surfaces and affects the biological response. COOH-functionalized MWCNT are more water soluble and dispersed than non-functionalized MWCNT (Upadhyayula and Gadhamshetty; Cao, Chen et al. 2011; Jacobs, Vickrey et al. 2011)

4.4 Dispersion status

Particle agglomeration and aggregation is a common phenomenon for CNT. High surface energy and surface area of nanoparticles result in Van der Waals interactions leading to agglomeration. For full exploitation of CNT, they should be used as well dispersed particles such as those observed with aerosolized particles. Dispersion results in an increase in particle number per unit mass and an associated increase in contact surface area with exposed cells, thus affecting their biological activities. Published data have shown that dispersed CNT exhibit more pronounced effects on cell proliferation and cytotoxicity than their non-dispersed counterpart. Several methods of nanoparticle dispersion have been investigated including the use of natural lung surfactants such as Survanta® (Wang et al. 2010), phospholipids such as dipalmitoylphosphatidylcholine (Sager, Porter et al. 2007),

organic solvents such as acetone and dimethyl sulphoxide (Soto, Carrasco et al. 2005) and biomolecules such as single-stranded DNA, albumin, and cell culture serum (Cherukuri, Bachilo et al. 2004; Jia, Wang et al. 2005; Muller, Huaux et al. 2005)

4.4.1 Dispersion of CNT using natural lung surfactants

Survanta® is a surfactant replacement used in clinic which provides some advantages as a dispersing agent for CNT, i.e., it is commercially available, biocompatible and safe. Previous study has also shown that it is effective in dispersing CNT into fine particles comparable in size to that of aerosolized CNT (Figure 3). It has no apparent cytotoxic effect and does not mask the biological effect of CNT (Wang et al. 2010).

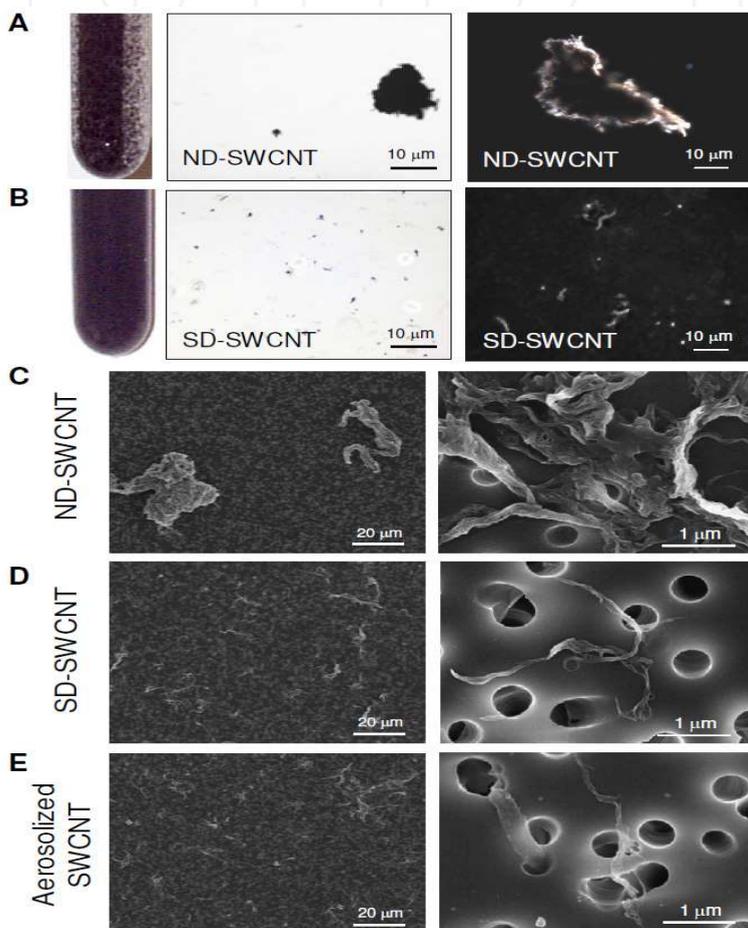


Fig. 3. Comparison of Survanta®-dispersed and non-dispersed SWCNT. (A) Non-dispersed SWCNT suspension showing visible clumping of SWCNT (left panel) with corresponding light microscopy (middle panel, 100x) and hyperspectral imaging of an individual clump (right panel, 400x). (B) Survanta®-dispersed SWCNT suspension showing much improved

dispersion with no visible large clumps (left panel) observed in the corresponding light microscopy and hyperspectral imaging. (C-E) Scanning electron microscopy of non-dispersed, Survanta®-dispersed and aerosolized SWCNT at low magnification (400x, left panel) and high magnification (30,000x, right panel)(Wang, Castranova et al. 2010)

4.4.2 Effect of dispersed CNT on fibrogenesis

Well dispersed SWCNT and MWCNT can deposit deep in the interstitial area of the alveoli, where it can enhance the fibrotic process by directly stimulating interstitial lung fibroblasts (Mercer, Scabilloni et al. 2008; Monteiro-Riviere, Inman et al. 2009). Dispersed SWCNT have been shown to evade engulfment by lung macrophages where 80% of pulmonary exposed SWCNT reach the alveolar interstitial space (Shvedova, Kisin et al. 2005; Mercer, Scabilloni et al. 2008). In case of exposure to micron-sized particles, most of these particles are engulfed by macrophages which induce a robust inflammatory response. Dispersed SWCNT bypass the inflammatory response which might be due to evading macrophage engulfment. Dispersed SWCNT can stimulate resident fibroblasts in the interstitial space to produce collagen. Ongoing research suggests that dispersed nano-sized SWCNT can induce lung fibrosis without persistent inflammation. Usually micron-sized particles induce robust inflammation followed by slow developing fibrosis in contrast to nano-sized particles like CNT which induce rapid fibrosis. The mechanism of this unusual fibrosis is unclear and is under investigation.

4.5 Metal contaminants

Metals are routinely used as catalysts in nanomaterial production. These metal ions are usually incorporated into the nanomaterials during the manufacturing process and contribute towards metal contaminants. Generally metal ions present in CNT as impurities are Fe, Ni, Co, etc. During the purification process, manufactured CNT are thoroughly washed in acid to remove these metal ions or any amorphous carbon. The metal ion concentration depends on the method used to manufacture CNT and the purification process. In some cases, metal ion contamination can reach 30% by weight in unpurified CNT. Metal impurities such as Fe in CNT are known to induce oxidative stress in cells (Warheit, Laurence et al. 2004; Le Goff, Holzinger et al. 2011). These ions can influence redox reactions by inducing ROS or inhibiting antioxidant enzymes. Formation of ROS leads to oxidative stress, inflammation and apoptosis.

5. Mechanisms of CNT toxicity

5.1 Oxidative stress

ROS are generated by distressed cells leading to oxidative stress and apoptosis. It is an imbalance between antioxidant proteins and ROS produced in cells and induced by toxic substances such as asbestos (Liu, Ernst et al. 2000). CNT have been found to induce oxidative stress and ROS in the lung (Manna, Sarkar et al. 2005; Shvedova, Kisin et al. 2005; Pacurari, Yin et al. 2008), skin (Murray, Kisin et al. 2009), and heart (Li, Hulderman et al. 2007). Metal contaminants such as Fe are the major source of ROS generation induced by CNT. Studies have shown that SWCNT containing up to 30% of Fe (%wt) are more toxic than SWCNT with 0.23% iron content (Shvedova, Castranova et al. 2003). Iron ion can

initiate Fenton reaction with hydrogen peroxide in cells to produce highly oxidative species such as hydroxyl radicals.



As mentioned above, metal ions are key contributor to nanomaterial-induced ROS generation. Since many nanoparticles are prepared by using metal ions, exposure to raw or as manufactured materials in occupational workers can exacerbate the toxic response due to these impurities. Oxidative stress further leads to inflammation and toxicity which ultimately results in cell death. Other studies have also suggested that oxidative stress plays an important role in nanoparticle-induced toxicities (Warheit, Laurence et al. 2004; Li, Muralikrishnan et al. 2010). The damage caused by nanoparticle-induced oxidative stress can be reduced by pretreatment with antioxidants (Shvedova, Kisin et al. 2007).

5.2 Inflammation

CNT have been shown to induce inflammatory response in a number of *in vivo* studies (Shvedova, Kisin et al. 2005; Poland, Duffin et al. 2008). Macrophages engulf inhaled particles and produce various inflammatory cytokines and chemokines, which attract and amplify inflammatory responses in the body. Pulmonary exposed CNT induce transient inflammation whereas micro-sized particles usually induce persistent inflammation. Previous study has shown that alveolar macrophages ignore certain small-sized CNT (Shvedova, Kisin et al. 2005), which may explain the less inflammation induced by the nanoparticles. Some studies suggest that CNT suppress the immune response by reducing the inflammatory signal and preventing macrophage activation (Mitchell, Gao et al. 2007). *In vitro* studies using keratinocytes and macrophages showed that these cells secrete pro-inflammatory cytokines such as interleukin-8 and tumor necrosis factor- α in response to CNT stimulation (Monteiro-Riviere, Inman et al. 2005; Brown, Kinloch et al. 2007).

5.3 Fibrosis

Unlike micron-sized particles, nanoparticles induce an unusual rapid fibrosis. For example, inhaled CNT can quickly penetrate the alveolar epithelial barrier into the interstitial tissue to form a matrix which stimulates resident fibroblasts to produce collagen (Mercer, Scabilloni et al. 2008; Monteiro-Riviere, Inman et al. 2009). Persistent stimulation of fibroblasts has been shown to result in interstitial lung fibrosis *in vivo* and collagen production by lung fibroblasts *in vitro* (Wang, Mercer et al. 2010). Data have also shown that CNT induce fibrogenic cytokines and growth factors such as transforming growth factor- β 1, matrix metalloproteinase-9, and fibroblast growth factor-2 in human lung cells both *in vitro* and *in vivo* (Shvedova, Kisin et al. 2008; Wang, Mercer et al. 2010).

5.4 DNA damage

CNT can interfere with the genetic constituents of the cells such as DNA and RNA (Zhu, Chang et al. 2007; Pacurari, Yin et al. 2008; Bonner 2010). These changes in nucleic acid structures can affect cell survival and genomic integrity. MWCNT induce clastogenic (DNA break) and aneugenic response (chromosomal loss) raising the possibility of mutational changes in the genetic materials of the cell (Muller, Decordier et al. 2008). Mutational

changes in K-ras have been observed in the lung of mice after CNT exposure (Shvedova, Kisin et al. 2008). A recent study showed that chronic exposure of SWCNT to lung epithelial cells causes malignant transformation of the cells and tumorigenesis in nude mice (Wang, Luanpitpong et al. 2011). Changes in p53 protein phosphorylation in embryonic stem cells after SWCNT exposure further support the potential genotoxicity and tumorigenicity of the nanomaterial (Zhu, Chang et al. 2007). Genotoxic damage due to CNT exposure has also reported in lung fibroblasts (Kisin, Murray et al. 2007).

6. Conclusion

The unique characteristics of nanomaterials offer potential novel applications as well as potential toxicities. A number of factors including the route of exposure and physico-chemical properties of nanoparticles can affect the biological activities of CNT and their toxic responses. Among the various exposure routes, the pulmonary route is the most common route of exposure to airborne nanoparticles, which have been shown to induce fibrotic and toxicological responses. Properties of nanoparticles such as dispersion status, size and shape, chemical composition and surface functionalization play an important role in the biological activities of nanoparticles. Mechanistic understanding of nanoparticle interactions with cells and tissues is still lacking. Most of the reported toxic effects of nanoparticles are caused by tissue penetration and induction of oxidative stress, DNA damage, inflammation and fibrosis. Careful evaluations of the toxic and fibrogenic effects of nanomaterials are critically needed for the safe and effective use of nanomaterials.

7. Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

8. References

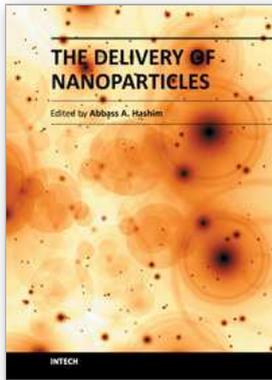
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The Delivery of Nanoparticles

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Nanoparticle is a general challenge for today's technology and the near future observations of science. Nanoparticles cover mostly all types of sciences and manufacturing technologies. The properties of this particle are flying over today scientific barriers and have passed the limitations of conventional sciences. This is the reason why nanoparticles have been evaluated for the use in many fields. InTech publisher and the contributing authors of this book in nanoparticles are all overconfident to invite all scientists to read this new book. The book's potential was held until it was approached by the art of exploring the most advanced research in the field of nano-scale particles, preparation techniques and the way of reaching their destination. 25 reputable chapters were framed in this book and there were alienated into four altered sections; Toxic Nanoparticles, Drug Nanoparticles, Biological Activities and Nano-Technology.

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