

Impact of single-walled carbon nanotubes on the embryo: a brief review

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Abstract: Carbon nanotubes (CNTs) are considered one of the most interesting materials in the 21st century due to their unique physiochemical characteristics and applicability to various industrial products and medical applications. However, in the last few years, questions have been raised regarding the potential toxicity of CNTs to humans and the environment; it is believed that the physiochemical characteristics of these materials are key determinants of CNT interaction with living cells and hence determine their toxicity in humans and other organisms as well as their embryos. Thus, several recent studies, including ours, pointed out that CNTs have cytotoxic effects on human and animal cells, which occur via the alteration of key regulator genes of cell proliferation, apoptosis, survival, cell–cell adhesion, and angiogenesis. Meanwhile, few investigations revealed that CNTs could also be harmful to the normal development of the embryo. In this review, we will discuss the toxic role of single-walled CNTs in the embryo, which was recently explored by several groups including ours.

Keywords: single-walled carbon nanotubes, embryo, toxicity

Introduction

The 21st century has seen an emergence of nanotechnology, which has been applied to a wide range of scientific disciplines including agri-food industry, electrical and electronic equipment, and construction.¹⁻⁸ Another area of application is in the realm of nanoparticles (NPs) use in medicine, giving rise to the field of nanomedicine. This field holds the promise of providing great benefits for society in the future,⁹⁻¹¹ but the toxicity of the NPs still needs more investigations.

Nanomaterials have sizes ranging from approximately 1 nanometer up to several hundred nanometers, comparable to many biological macromolecules such as enzymes, antibodies, DNA plasmids, and others. In this size range, materials exhibit interesting physical properties, distinct from both the molecular and bulk scales, present new opportunities for biomedical research and applications in various areas including biology and medicine.^{12,13} In the latter, carbon nanotubes (CNTs) offer a wide range of applications due to their unique atomic configuration, optical, mechanical and electronic properties, high surface-area-to-volume ratios, and easy functionalization.^{14,15} The use of these NPs in humans for diagnostic or treatment purposes would involve considerable exposure to particles and therefore understanding their effect is of paramount importance.¹⁶⁻¹⁹ Although several *in vitro* and *in vivo* studies have been undertaken in the past few years on their toxicity,^{16,17,20-24} a comprehensive knowledge of their effects is still far from being obtained. This gap is even larger when considering their effects on embryonic development, for which only sparse data are available.²⁵⁻³⁰ Most of these studies have focused on zebrafish embryo because it is easy to manipulate. However, other models were used to explore the effect of CNTs in the embryo such

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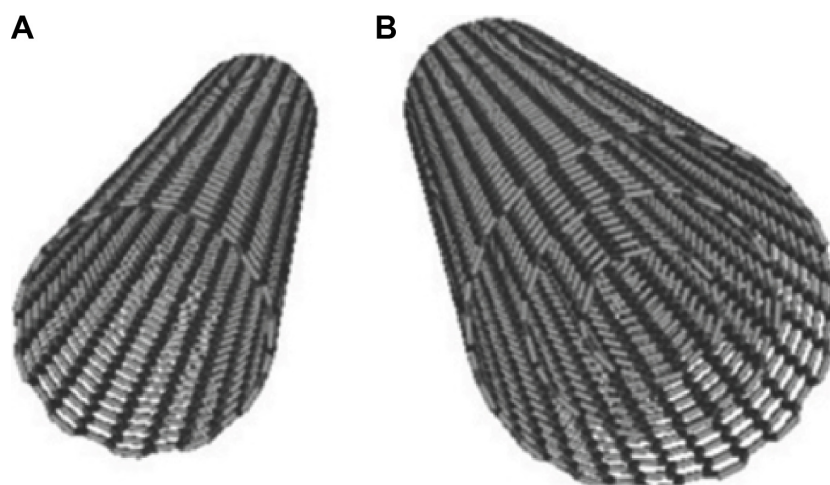


Figure 1 Different types of CNTs: (A) SWCNT and (B) MWCNT.

Abbreviations: CNTs, carbon nanotubes; MWCNT, multiwalled carbon nanotube; SWCNT, single-walled carbon nanotube.

as chicken and mouse.^{28,29} These studies revealed clearly that CNTs could harm the normal development of the embryo. CNTs are classified as single-walled carbon nanotubes (SWCNTs) and multiwalled carbon nanotubes (MWCNTs), which differ in the arrangement of their graphene cylinders. SWCNTs contain only one single layer of graphene, while MWCNTs have many layers,^{31,32} as illustrated in Figure 1. The present review focuses on the toxicity of SWCNTs in the normal development of the embryo.

Single-walled carbon nanotubes

SWCNTs are monocylindrical carbon layers, made of hollow graphitic nanomaterials with a diameter range of 0.4–2 nm, built from carbon atoms; their structures are organized in harmony with helical, armchair, zigzag, and chiral arrangements.^{33–35} These one-dimensional NPs with capability to behave distinctly from spherical NPs in biology offer new opportunities in biomedical research. The nanotubes are flexible and able to bend, facilitating multiple binding sites of a functionalized nanotube to one cell; this leads to a multivalence effect and improved affinity of nanotubes conjugated with targeting ligands.^{36,37}

SWCNTs have raised considerable interest worldwide due to their unique shape and the resulting versatile and unique properties.^{34,38–40} Numerous studies have presented them in the form of seamless concentric tubes.^{38,41,42} SWCNTs are highly absorbing materials with a strong optical absorption in the near-infrared range because of the first optical transition (E11); therefore, SWCNTs have been utilized in photothermal applications,^{10,43–45} and photoacoustic imaging.^{46,47} Moreover, when semiconducting, SWCNTs with small band gaps (approximately 1 eV), exhibit photoluminescence in the

near-infrared range. The emission range of SWCNTs was found to be 800–2,000 nm,^{48,49} which covers the biological tissue transparency window, and is therefore suitable for biological imaging.

In human health, it is important to rapidly and accurately detect glucose levels in biological environments, especially for diabetes mellitus; for this purpose, Chen et al²⁰ have recently proposed an accurate, highly sensitive, convenient, low cost, and disposable glucose biosensor on a single chip, functionalized through a layer-by-layer assembly of SWCNTs and multilayer films of different needed types. Moreover, Giraldo et al⁵⁰ have investigated the separation and functionalization of SWCNT by their electronic type; this has enabled the development of ratiometric fluorescent SWCNT sensors, used to detect trace analytes in complex environments such as strongly scattering media and biological tissues.⁵⁰ However, their toxic effect on human health could have an important impact on their use worldwide; presently, it was demonstrated that SWCNTs have a toxic effect on cells, including human normal cells, and living organisms.^{24,51–53} The toxic effect of these NPs could be influenced by a number of factors including the surface chemistry, surface area, functional groups, shape, photochemistry, charge, and aggregation as well as preparation method.^{6,24,54} Hence, we will review the recent publications related to the effect of SWCNTs on embryo development, which is unfortunately limited to a few number of studies including one from our group.

SWCNTs in the embryo

Today, SWCNTs have widespread applications in many technological fields; however, several studies demonstrated that pulmonary deposition of SWCNTs causes acute

Table 1 Summarize the outcome of SWCNTs on the embryo

Embryo	Outcome	References
Drosophila	No toxicity	62, 63
Zebrafish	Hatching delay	26, 30
Avian	Cytotoxic effect on glial and neurons cells	64
	Inhibition of angiogenesis, gene deregulation, and abnormal development	28
Mouse	Increase of reactive oxygen species, malformation, and skeletal abnormalities	63, 65
	Cytotoxic effects and DNA damages on embryonic cells	66
	Low cell proliferation and viability of glioblastoma cells	67
	Apoptotic effect and DNA damage on mouse embryonic cells	29
Hamster	Cytotoxic and genotoxic effects on embryonic cells	52

Abbreviation: SWCNT, single-walled carbon nanotube.

pulmonary inflammation, as well as chronic responses such as fibrosis.^{31,55–61} On the other hand, we have identified a list of genes that are differentially expressed between matched primary human normal bronchial epithelial (HNBE) cells exposed to SWCNTs and unexposed ones using microarray technology. Our data showed that SWCNTs inhibit and provoke cell proliferation and apoptosis, respectively, through the deregulation of several important gene controllers of cell survival and apoptosis.⁵¹ These studies suggest that SWCNTs can induce toxicity in bronchial tissues and probably other organ tissues of the exposed organisms. In parallel, it was demonstrated by few investigations, including ours, that SWCNTs can affect the embryo of the exposed organisms. Herein, we will review the outcome of SWCNTs on the embryo of several organisms from *Drosophila* to mammalian (Table 1).

SWCNTs and *Drosophila* embryo

Few groups investigated the effect of SWCNTs on *Drosophila* embryo; however, they did not observe any toxicity in this organism.^{62,63}

SWCNTs and aquatic embryo

Cheng et al²⁷ explored the impact of raw SWCNTs on the embryo of aquatic organisms using zebrafish embryos. They reported that SWCNTs induce a significant hatching delay in the zebrafish embryos between 52 and 72 hours postfertilization (hpf) at concentrations greater than 120 mg/L. Meanwhile, they revealed that the embryonic development of the exposed embryos (up to 96 hpf) is not affected at SWCNT concentrations of up to 360 mg/L. In parallel, they indicated that the chorion of zebrafish embryos is an effective protective barrier to SWCNT agglomerates. Finally, they stated that the hatching delay observed in their study is likely induced by the Co and Ni catalysts used in the production of SWCNTs, which remained at trace concentrations after purification. However, a recent study revealed that SWCNTs

can provoke hatching delay in the zebrafish embryos; the main mechanism of hatching inhibition by SWCNTs and other NPs is likely related to the interaction of NPs with the zebrafish hatching enzyme.³⁰

SWCNTs and avian embryo

Belyanskaya et al⁶⁴ showed that SWCNT suspensions could induce acute toxic effects in primary cultures from both the central and peripheral nervous systems of chicken embryos. The level of toxicity is partially dependent on the agglomeration state of these particles. Therefore, the authors suggested that SWCNTs are likely to cause adverse effects on glial cells and neurons if the nervous system is exposed to high concentrations.⁶⁴

On the other hand, our group has investigated the effect of SWCNTs on the chicken embryo at the third day of incubation.²⁸ We deposited 25 µg of SWCNTs, diluted in 25 µL of phosphate-buffered saline, on the embryos. We reported that SWCNTs treatment inhibits the angiogenesis of the chorioallantoic membrane and in the chicken embryo, especially in the brain and the liver (Figure 2). Meanwhile, our study revealed that SWCNTs can harm the normal development of the embryo since all SWCNTs-exposed embryos are smaller in comparison with the controls. We also noted that the majority SWCNTs-exposed embryos die before 12 days of incubation. Macroscopic examination did not reveal any anomalies in these embryos. However, histological analysis of liver tissues from these embryos revealed an important necrosis and inhibition of blood vessels development.

In order to define gene targets of SWCNTs in the embryo, we examined the expression patterns of INHBA, ATF-3, FOXA-2, CASPAS-8, MAPRE2, BCL-2, RIPK-1, Cadherin-6 type-2, SPI-4, KIF-14, and VEGF-C genes in brain and liver tissues from SWCNTs-treated and their matched control embryos; these selected genes were recently identified, by our group, as major gene targets of SWCNTs in HNBE cells.⁵¹ Our investigation revealed that INHBA,

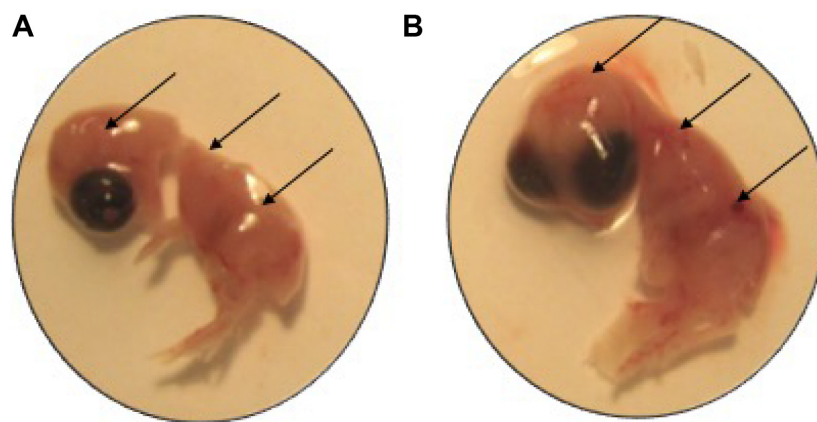


Figure 2 Outcome of SWCNTs on the chicken embryo at 12 days of incubation.

Notes: The SWCNTs-exposed embryo (**A**) is smaller in comparison with its matched control (**B**). Additionally, we note that SWCNTs inhibit blood vessels development in SWCNTs-treated embryo in comparison with the control (arrows). The embryos were treated by 25 μg of SWCNTs at 3 days of incubation, reprinted from *Nanomedicine*, 2013;9(7), Roman D, Yasmeeen A, Mireuta M, Stiharu I, Al Moustafa AE, Significant toxic role for single-walled carbon nanotubes during normal embryogenesis, Pages 945–950,²⁸ Copyright ©2013, with permission from Elsevier.

Abbreviation: SWCNTs, single-walled carbon nanotubes.

ATF-3, FOXA-2, CASPAS-8, MAPRE2, BCL-2, RIPK-1 genes are upregulated, while Cadherin-6 type-2, SPI-4, KIF-14, and VEGF-C are downregulated in brain and liver tissues of SWCNTs-exposed embryos in comparison with their matched tissues from control embryos; these data are consistent with our microarray data in HNBE cells.

SWCNTs and mammalian embryo

Pietrojusti et al⁶⁵ explored the effect of pristine and oxidized SWCNTs on the development of the mouse embryo. In this study, SWCNTs (from 10 ng to 30 $\mu\text{g}/\text{mouse}$) were administered to female mice after implantation (postcoital day 5.5). The authors revealed that there was a high percentage of early miscarriages and fetal malformations in females exposed to oxidized SWCNTs, and lower percentages in animals exposed to the pristine material. The lowest effective dose was identified as 100 ng/mouse. Meanwhile, they reported extensive vascular lesions and increased production of reactive oxygen species in placentas of malformed embryo but not in normally developed fetuses. The data of this investigation clearly suggest that SWCNTs could act as embryotoxic agents in mammals.⁶⁵ Meanwhile, Philbrook et al⁶³ demonstrated that oral administration of SWCNTs (10 mg/kg) to pregnant CD-1 mice during organogenesis leads to increased resorptions, external morphological defects, and skeletal abnormalities.

Later on, Yang et al⁶⁶ investigated the cytotoxicity, genotoxicity, and oxidative effects of SWCNTs on primary mouse embryo fibroblast (MEF) cells. They revealed that

these particles have moderately cytotoxic effect but can induce more DNA damage in comparison with other NPs such as zinc dioxide. The authors also argued that the potential genotoxicity of these NPs could be attributed to the particle shape.⁶⁶ On the other hand, Bobrinetskii et al⁶⁷ examined the effect of SWCNTs on cell viability and proliferation of human embryo fibroblasts and glioblastoma cells. They found that SWCNTs have a low cytotoxic activity on these cells.

Earlier, Tong et al²⁹ explored the role of the p21 and hus1 genes in the toxicity of SWCNTs on wild type and p21^{-/-}, hus1^{+/+} MEF cells. They revealed that the yield of the micronucleus ratio in p21 gene knockout MEF cells is lower than that in their wild type counterpart, which can suggest that p21 might play a role as antiapoptosis factor during the signal transduction of DNA damage caused by SWCNTs in mammalian embryonic cells.²⁹

Recently, Darne et al⁵² examined the outcome of SWCNTs on Syrian hamster embryo cells; they found that SWCNTs induce cytotoxic and genotoxic effects in this cell line.

Finally, we believe that it is important to review the biomedical utility of using SWCNTs with other molecules during gestation in mammals. Bari et al⁶⁸ investigated the outcome of carboxylic acid functionalized single-walled carbon nanotubes (f-SWCNT-COOH) on nonenriched hematopoietic stem and progenitor cells in human umbilical cord blood-mononucleated cells. The authors of this investigation reported that f-SWCNT-COOH can increase the viability of the CD45(+) cells even without cytokine stimulation; it also reduced mitochondrial super oxides and

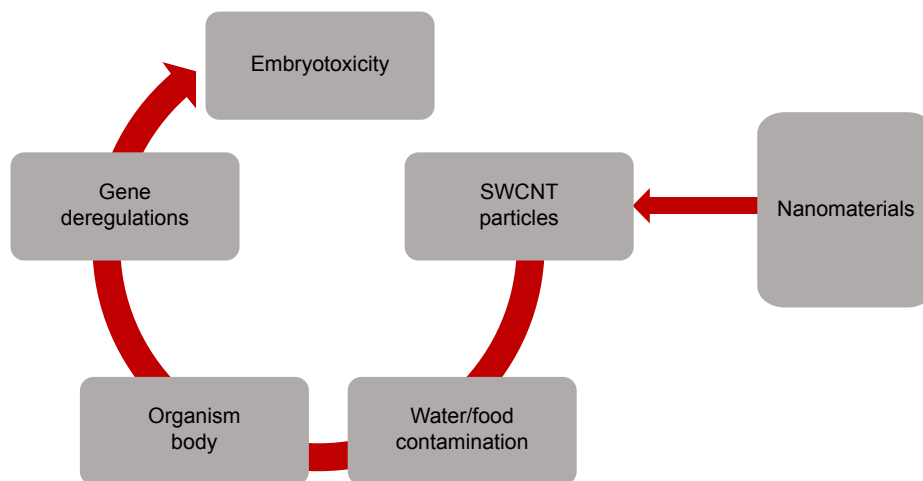


Figure 3 Schematic showing the relationship between SWCNTs and embryotoxicity.

Notes: Water and/or food could be contaminated by SWCNTs; therefore, these particles can penetrate organism and embryonic cells and thereby induce apoptosis and/or cell death via the alteration of their key regulators genes.

Abbreviation: SWCNTs, single-walled carbon nanotubes.

caspase activity in CD45(+) cells. On the other hand, phenotypic expression analysis and functional colony forming units showed significant *ex vivo* expansion of hematopoietic stem and progenitor cells. The data of this study suggested that f-SWCNT-COOH could improve repopulation of immunodeficient mice models with minimal acute or subacute symptoms of graft-versus-host disease.⁶⁸ Separately, Campagnolo et al⁶⁹ examined the effect of SWCNTs with polyethylene glycol (PEG) chains for their use as biomedical carriers in mammalian pregnancy. They reported no adverse effects both on embryos and dams up to the dose of 10 µg/mouse. However, they revealed occasional teratogenic effects, associated with placental damage at a dose of 30 µg/mouse; this dose is equivalent to an ~70 mg dose for a 60 kg pregnant patient. It is reasonable to assume that such a dose might be used for biomedical application of PEG-modified CNTs in humans. However, the authors of this study stated that PEG-SWCNTs might cause occasional teratogenic effects in mice beyond a threshold dose. Therefore, they conclude that the data of this investigation should be considered if exposing women during pregnancy.⁶⁹

Finally, all of the above studies, including ours, suggest that SWCNTs could harm the normal development of the embryo from aquatic to mammalian (Table 1) including human via the deregulation of specific genes related to cell proliferation, apoptosis, survival, cell cycle, and angiogenesis. Meanwhile, it is important to emphasize that organism embryos could be simply exposed to NPs via water and/or food contaminations, which could have a dramatic effect on these organisms and particularly on their embryos (Figure 3).

Conclusion

In this paper, we aimed to provide a concise review of the most updated understanding of embryotoxicity of SWCNTs. Overall, the limited amount of studies published necessitates more systematic and thorough investigations to elucidate the real effect of SWCNTs and their mechanism in the embryo. Such knowledge will allow the determination of a more rounded safety profile and is mandatory toward harmless use of any kind of nanomaterial, which is not restricted to SWCNTs.

Meanwhile, it seems that common critical parameters that determine SWCNTs toxicity include the chemical nature of surface modifications, surface charge, nanotube structure, and nanotube surface area available for interactions;^{31,70} thus, additional studies are necessary to explore the exact role of these parameters in induced toxicity by CNTs on the organisms and their embryos. Finally, we believe that modification of CNTs structure could have an important influence on limiting their toxic effect on human health, including the normal development of the embryo, which could allow us to use them in the industry as well as in the medical field without any hesitation.

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Disclosure

These authors report no conflict of interest in this work.

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