

Genetic and Epigenetic Effects of Nanoparticles

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Abstract

Nanoparticles can occur naturally or be intentionally engineered. The field of nanotechnology has varied influence on industry and segments of our daily life. The health effects associated with human exposure to nanoparticles remains elusive and very little has been done with respect to investigating the genetic and epigenetic effects of nano-materials. This is especially concerning given their wide spread applications in the modern world. We reviewed recent findings of the genetic and epigenetic effects of several common nanoparticles that humans are exposed to. Problems and concerns existing in current nano-toxic studies are addressed and discussed.

Introduction

Nanoparticles (NP) are particles with dimensions smaller than 100 nm [1,2]. Engineered NPs are widely used in cosmetics, clothing, sunscreen and food additives, etc. Current applications of nanotechnology have great influence on various industry and medical sectors. The global market for nanotechnology based manufactured goods is expected to be worth US\$ 1.6 Trillion by certain estimations, representing a compound annual growth rate of around 50% during 2009-2013. Engineered NPs with a diameter of less than 100nm are classified as ultrafine particles. Ultrafine particles can occur naturally, or can be generated through combustion sources such as cooking, candle burning, and tobacco smoking, while engineered NPs are produced intentionally for industrial purposes and generally with greater consistency in size and chemistry. These particles readily travel throughout the body, having higher deposition rates in the lower respiratory tract [1,2].

Human exposure to ultrafine particle occurs mostly through ambient atmospheric exposure; therefore the respiratory tract is the preferred target for exposure [2,3]. Exposure to engineered NPs can happen through other pathways (inhalation, dermally, ocularly). The wide spread use and applications such as oral administration through food or drinking water, skin absorption through sunscreen and/or cosmetics application, injection through medical procedures presents a number of potential problems [4]. The fate and risk may differ through different exposure pathways. Most animal studies have found over 90% orally administrated engineered NPs were excreted through feces [5,6]. However, with their small sizes, the retention of NPs in the liver and kidney has been found [7,8]. The employment of nanoparticles in sunscreens has raised the question of whether these particles are photo-clastogenic. Intensive studies have led to controversial results, which will be discussed later.

Much effort has been devoted to understand the toxicity of ultrafine particles. Genetic and epigenetic effects are parts of the toxicity of NPs. The small size and large surface area facilitate the generation of free radicals, and the induction of oxidative stress [3,9,10]. Tissue culture analysis in animal models demonstrates that oxidative stress contributes significantly to the cytotoxicity and genotoxicity associated with NP exposure [2,11,12]. It has been found that lipid peroxidation and oxidative stress are the most important mechanisms of genotoxicity related to NP exposure [13]. An emerging area of concern, are the epigenetic effects of NPs and has attracted growing interests. The findings and their implications will be discussed later.

The biological impact and biokinetic distribution of NPs are

affected by many parameters including size, chemical composition, surface structure, solubility, shape, and aggregation. These parameters can modify cellular uptake, translocation from exposed organs to the targeted sites and the severity of the tissue injury [2]. Therefore, *in vivo*/*in vitro* toxicity assays need to reflect effects on the exposed organs including lungs, skin, and mucus membranes. Additional focus needs to be given to target tissues and systems such as endothelium, blood cells, spleen, liver, nervous system, heart and kidney; most importantly, at a physiological relevant concentration of exposure.

The purpose of this minireview is to utilize several types of NPs as examples to survey the genetic and epigenetic effects of NPs exposure, and to address the importance of their physical /chemical features as well as bioavailability on these effects. Our review is limited to several examples and is no way comprehensive of all types of nanoparticles.

The Genetic Effects of NPs

The genetic effects of NPs, by definition, include DNA damage, possibly leading to mutations, DNA strand breaks and chromosomal aberrations [14]. The mechanism of NPs genetic effects are as follows [15], (1) direct binding to the DNA: some NPs are capable of localizing within the nucleus, directly interacting with the DNA molecule [16,17]; (2) direct binding to DNA associated proteins: where the NPs do not physically interact with the DNA molecule, but with other cellular proteins such as those involved in the chromatin structure or DNA replication process; (3) indirect cellular responses: oxidative stress, inflammation and aberrant signaling activation [18,19].

Two examples, of NPs emitted from laser printers/photocopiers as well as titanium dioxide (TiO₂), are discussed as examples of genetic effects and to consider the importance of physical chemical features as well as bioavailability of NPs to their risk assessment.

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NP emitted unintentionally

An unintentional release of potentially dangerous particles can be caused by mechanical manipulation of earth or other processes such as drilling, sawing, or sanding, by abrasion during daily use, or by degradation of the matrix caused by aging or weathering including water absorption, oxidation, or exposure to UV light. One example, that sampled and examined NP using transmission electron microscope (TEM in a sanding mimic abrasion process) showed that free-standing Carbon Nano Tubes (CNTs) were released into the environment during this process [20]. NPs emitted unintentionally are complex non-homogenous in their chemical composition which increases the difficulty of studying their effects. Among some of the more environmentally relevant NPs of interest are ones emitted from printers and photocopiers. These particles have been studied intensively, and therefore their properties are better understood. Toners emit a mixture of organic compounds and inorganic metal oxide additives [21]. The organic fraction of these NPs are formed primarily from the condensation of semi-volatile organic compounds evaporated from the toner and possibly other paper constituents during the printing/photocopying process, and their fraction remains poorly characterized due to its diversity [2,6]. The inorganic fraction of airborne NPs varies with the toner formulation and may contain variable amounts of silicon (Si), sulphur (S), titanium (Ti), iron (Fe), chromium (Cr), nickel (Ni), zinc (Zn) and possibly other elements, most likely originating from the metal oxide additives in toners [21]. The major route of entry of airborne NPs is by inhalation [22,23].

A recent study which recruited young volunteers to spend time in busy photocopy centers (2-3 days a week, 6 hours a day) found higher levels of 8-OH-dG in their urine when compared to the days spent in printer-free environments [24], indicating that the elevated NP levels in these volunteers lead to a measurable level of oxidative stress and thereby modified their genetic material. A549 cells treated with NPs emitted from laser printers exhibited more micronuclei which resulted from DNA double strand break [21].

Various chromosomal aberrations have been found at significantly higher levels in a study of buccal epithelial cell and peripheral blood samples from males working with photocopying machines for more than a year when compared to their age matched unexposed controls [25]. Carbon NP and inflammation induced by carbon deposits might have caused these reported genetic effects [26]. A case report of, a female patient with weight loss and diarrhea after three years of exposed to laser printers in her office showed black material deposited in her submesothelial tissue and associated inflammatory reaction. A scanning electron microscopy study revealed that the submesothelial aggregates consisted of carbon NPs with sizes ranging from 31 to 67 nm [26].

Much effort is still needed to investigate other unintended NP emissions associated with our daily life. The respiratory tract is particularly susceptible to cellular assaults caused by inhaled NPs, which makes the unintended NP emission in workplaces and the daily environmental risk factor that may be detrimental to human health.

TiO₂

Engineered titanium dioxide NPs are a widely used and through their design, exhibit properties that are genotoxic.

Genotoxicity originating from different physical chemical features of NPs: Titanium dioxide is a poorly soluble particulate produced either in its anatase or rutile crystal form in industrial setting

[27]. It is the most widely used white pigment in products such as paints, film, paper, food additives and cosmetics because of its brightness and high refractive index [28,29]. A comparative study using keratinocytes to investigate different crystalline phases of TiO₂ interaction with cells showed that the anatase phase, which is phagocytosed in small clusters and is lodged inside the mitochondria, is more effective in producing free radicals and thereby generating significantly greater amounts of oxidative stress than its rutile phase [30]. Other than the crystalline phases of TiO₂, the agglomeration and dispersion status of the NP can also modulate its genetic effects. A study using TK6 human lymphoblast cells and Cos-1 monkey kidney fibroblasts has shown that less stable dispersion may easily lead to larger agglomerates and thereby inducing DNA damage [31]. This DNA damage included strand breaks and oxidative damage which were analyzed by alkaline and FPG-modified comet assay [31-33].

Genotoxic variability originating from different entry points:

As discussed above, the exposure route and translocation efficiency most certainly will affect the toxicity of the NP. The bright white color, ability to block UV light, and antimicrobial activity of TiO₂ NPs have made it a quite popular component in the food industry, in cosmetics and sunscreen manufacture, which make inhalation, ingestion and dermal exposure a common exposure route for humans [34-37]. The primary route of occupational exposure for TiO₂ NPs is inhalation [2]. Consumer inhalation is also possible during application of antibacterial spray containing TiO₂ NPs [38]. Upon inhalation or instillation, small fractions of TiO₂ NPs are transported from the airway lumen to the blood circulation and reach extra pulmonary tissues such as liver and kidneys [39,40]. *In vitro* studies using cells from extra pulmonary tissues such as immortalized brain microglia (BV2), primarily cultured lymphocytes, and human B-cell lymphoblastoid cell line exhibited chromosome aberrations as well as oxidative DNA damage when treated with TiO₂ [12,41,42]. However, whether the genetic effects reported in these *in vitro* studies are applicable to other routes of entry will largely rely on the biokinetic distributions and whether there is a co-exposure to other pathogens [43].

Oral administration: The Food and Drug Administration (FDA) has allowed 1% by weight of TiO₂ as a food additive (FDA-21 CFR 73.575). Therefore, TiO₂ NP exposure from food-related ingestion is a highly relevant exposure route that needs further study. An *in vivo* study with 13 weeks of repeated oral administration of anatase 80:20 rutile TiO₂ NP to rats, up to 1041 mg/kg body weight, didn't find significant concentration dependent increase of TiO₂ in blood samples. The TiO₂ distribution to the liver, spleen, kidney, and brain was also minimal. No dose-response relationship was seen, meaning that the TiO₂ particles were not significantly absorbed and distributed [7]. This result indicates that gastric ducts will be the major tissues that will be affected by ingestion of TiO₂ NPs. TiO₂ NP have been shown to induce DNA strand breaks by comet assays in gastric epithelial cells [44]. However an *in vivo* murine model study has argued that other organs might be targets for TiO₂ NP genetic effects. Repeated oral administration of anatase75: 25rutile TiO₂ NP, up to 500 mg/kg body weight has led to increased DNA deletion frequency in fetuses after maternal exposure [37]. Nevertheless, a consistent concentration-dependent response of DNA strand breaks and chromosomal damage has been found in bone marrow and peripheral blood from exposed non-pregnant mice, as well [37]. The underlying mechanism driving these results remains elusive. The fact that neither of these studies employed organ deposition analysis as comparison with DNA damage tests has led to a limited interpretation of these data [7,37]. Whether the

in vivo DNA damage effects of TiO₂ were from an indirect mechanism or due to special preparation of TiO₂ samples remains unknown.

Dermal administration: Most of the dermal exposure studies have shown that TiO₂ NPs do not penetrate the stratum corneum, and only penetration into orifices of the pilosebaceous follicles was observed [45]. However, even with preferential distribution, the fact that TiO₂ NPs are widely used in sunscreens and cosmetics has raised the concern of photo-clastogenicity, given that sunscreens are always applied when there's UV exposure. It was reported that TiO₂ produced the OH radicals, H₂O₂ and O₂ under UV irradiation [46,47], while anatase TiO₂ NP lead to higher levels of OH radicals when compared to the rutile form, the OH radicals levels were correlated with the UVA dose [48,49].

In an early *in vitro* genotoxicity study, the single cell gel and chromosomal aberration assay showed that TiO₂ particles induced primary DNA damage and structural chromosome aberrations in cultured L5178Y mouse lymphoma cells when exposed to a UV spectrum similar to natural sun light. These genotoxic effects were dependent upon TiO₂ dose and solar light intensity. Gene mutations were not induced by photo excited TiO₂ particles in microbial or mammalian cell systems. Therefore, it was proposed that the DNA lesion catalyzed by photo excited TiO₂ particles resulted in chromosomal aberration rather than gene mutations [50].

Studies conducted afterwards disputed these findings by showing none of the eight different forms of uncoated, coated and doped TiO₂ NP was able to induce chromosome aberrations in Chinese hamster ovary cells, with or without the presence of simulated solar light [51]. The latter study argued that the previous L5178Y mouse lymphoma cell studies results of comet tail lengths were only evident at concentrations where cell survival was 70% or less, and increased chromosomal aberration frequencies occurred when cells were experiencing >50% cytotoxicity [51].

The Epigenetic Effects of NPs

“Epi” means above, outer and over in Greek, therefore “epigenetic” literally means “above genetic” which are heritable changes in phenotypes or gene expression without a change of DNA sequences [52]. Epigenetic effects involve inducing alterations in DNA methylation patterns, posttranslational modification of histones tails, chromatin remodeling and non-coding RNA. If these changes persist through cell division, heritable altered gene expression pattern will occur [52].

Several NPs have shown epigenetic effects and may lead to health risks to exposed cells which fit within the scope of this mini-review. It goes without saying that engineered NPs that are designed for epigenetic therapy purpose such as NPs formed by histone deacetylase inhibitors [53] and others [54-56] will not be discussed here.

DNA methylation

Methylation on cytosines and their subsequent interaction with methyl-CpG binding proteins (MBDs) act as regulatory marks to induce chromatin conformational change and inhibit the access of the transcriptional machinery, thus altering gene expression [57]. DNA methyl transferases (DNMTs) catalyze the transfer of a methyl group to cytosine [58]. In mammals DNMT1 is primarily involved in the maintenance of DNA methylation patterns during development and cell division, where as DNMT3a and DNMT3b are the *de novo* methyl transferases and establish DNA methylation patterns during

early development [59]. DNMT3L induces *de novo* DNA methylation by recruitment or activation of DNMT3a, while DNMT2 is primarily involved in the methylation of transfer RNA (tRNA) [59].

Promoter hypermethylation is commonly associated with gene silencing [60] with a few exceptions [61] where intragenic methylation might also have a role in regulating gene expression [62,63].

Silica nano particles (SiO₂ NP) are highly stable and can bioaccumulate in the natural environment. SiO₂ NPs are a class of NPs that has great potential for scientific, biological, and medical research applications [64].

SiO₂ NP has been shown to decrease the mRNA expression of *PARP-1* [65], an important DNA repair gene, in human keratinocyte HaCaT. This decrease of expression could be rescued by knockdown of DNMT1 [65]. DNA methylation levels of *PARP-1* promoter has been found increased gradually with the increasing of SiO₂ NP concentration, suggesting epigenetic effects play a role in regulating *PARP-1* expression level by SiO₂ NP [65]. Nevertheless, it has also been reported that nano and micro-sized SiO₂ decreased global DNA methylation and the related methyltransferase including DNMT1, DNMT3a and MBD2 [66], indicating epigenetic effects of SiO₂ NP might be involving writers, readers, and erasers of DNA methylation.

miRNA induced gene expression change

A large portion of the genome is transcribed into RNA with a significant portion of non-coding RNA (ncRNA) that function as structural, catalytic, or regulatory RNAs, rather than encoding proteins [67]. Although the function of most of the newly identified ncRNAs is yet to be elucidated, emerging evidence has shown that ncRNAs play an important role in chromatin remodeling and epigenetic control of transcription [67]. MicroRNAs (miRNAs) are a group of small ncRNAs that mediate posttranscriptional gene silencing through degradation of mRNA or inhibition of mRNA translation [68]. A complicated feedback network of miRNAs and other epigenetic pathways appears to post-transcriptionally repress gene expression including those signal molecules and thus are critical for many cellular pathways, and to organize the whole gene expression profile [61,69].

Gold NPs (AuNP) has attracted a lot of attention from material scientists for biomedical applications due to their unique features. AuNPs preferentially accumulate at sites of tumor growth/inflammation and their intense photophysical properties facilitate biodiagnostic assays such as HCG pregnancy test [70]. Because of their versatile optical properties, AuNPs have enabled optical imaging of cells with a wide variety of contrast [70].

The epigenetic effects of AuNPs appear most frequently as miRNA levels change [71,72]. Twenty-eight microRNAs were found at significantly altered levels in maternally exposed fetal lungs, and 5 were up-regulated in fetal liver. Let-7a and miR-183 were significantly up-regulated in both organs [71]. The outcome of the up regulation of these miRNA levels remain elusive, given that Let-7a expression level has been found negatively correlated to lung cancer [73] while miR-183 has been found positively correlated to lung cancer [74]. *In vitro* study using Au Nps exposed human fetal lung fibroblast has shown altered gene expression accompanied with up-regulation of miRNA-155 [72]. A reverse correlation has been established between miRNA-155 levels and *PROS1* expression levels, albeit this has yet to be determined if this is a direct effect [72]. The *PROS1* gene encodes for Protein S, a plasma glycoprotein that is involved in thrombus formation in the pulmonary

vasculature giving rise to adverse outcomes such as lung infraction [75,76].

Different NPs might have similar epigenetic effects in terms of regulating miRNA expression. *In vitro* epigenetic effects of co-regulated miRNAs such as miR-34s, miR-21 and miR-29a were found in Fe₂O₃ NPs, cadmium telluride quantum dots (CdTe QDs) and multi wall carbon nanotubes (MW-CNTs) treated cells [77]. Many miRNAs were co-regulated after two out of three nano-material exposure, which suggested the similarity of epigenetic effects of NPs [77]. However, not much overlap was found when comparing regulated miRNA among these three kinds of NPs treated cells with AuNP treated *in vivo* tissues [71,72,77]. This discrepancy might due to different methods that were employed to detect miRNA levels in these studies, which were SOLiD (Sequencing by Oligonucleotide Ligation and Detection) sequencing and miRCURY LNA microRNA Array, respectively [71,77].

Histone code

Histone tail modifications have emerged as important players in epigenetic regulation of gene expression and other chromatin associated processes. The four core histones, H2A, H2B, H3, and H4; are subject to a methylation, acetylation, phosphorylation, and ubiquitination [78]. These marks are thought to exert their function through direct modulation of chromatin structure and thereby formulating a histone code. The signal is then processed through histone code readers that feature modification-specific binding domains [78].

Quantum dots (QDs) are semiconductor nanocrystals with unique optical properties that are used extensively for *in vitro* observations of cellular mechanisms and for *in vivo* studies aimed at understanding the bio distribution of nanoparticles upon systemic injection [79]. Negatively charged CdTe QDs are capable of rapid nuclear accumulation in cells through phagocytosis [80]. These QDs showed a strong interaction to the core histones and cell nuclear extractions when compared with its interaction with bovine serum albumin (BSA), DNA and RNA [81]. Global hypoacetylation of histones was observed in breast cancer cells in an *in vitro* study. This chromatin condensation is associated with decreased gene transcription and increase in transcription of pro-apoptotic genes such as *Bax* upright *Puma* [82].

Conclusion Remarks

The controversies associated with NP toxicity studies (not limited to) discussed above are calling for a standard genotoxicity testing battery to cover a wide range of mechanisms. Many toxicology studies are lacking data showing NP aggregation and dissolution which occurs in sample media, let alone the changes in bioavailability and toxicity. It has been proposed that for the purpose of genotoxicity analysis of NPs, the OECD standardized methods should be employed; *in vivo* assays should be included to correlate with *in vitro* results; and more rigorous physicochemical characterization of particle-types should be conducted [83]. The interaction of nanoparticles and natural organic matter that occurs during waste processing results in a nanoscale coating of the nano materials, which dramatically changes their surface chemistry, aggregation, deposition, and toxic properties [84]. Engineered nanoparticles in natural systems are subject to a dynamic physical and chemical environment; therefore the toxicity analysis using their "as manufactured" state might not be thorough and comprehensive. More detailed and thoughtful design is needed for accurate risk assessment of NPs.

References

- Donaldson K, Warheit DB (2011) From Ambient Ultrafine Particles to

Nanotechnology and Nanotoxicology. Cardiovascular Effects of Inhaled Ultrafine and Nanosized Particles: John Wiley & Sons, 525-543.

- Oberdörster G, Oberdörster E, Oberdörster J (2005) Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Perspect* 113: 823-839.
- Warheit DB, Webb TR, Colvin VL, Reed KL, Sayes CM (2007) Pulmonary bioassay studies with nanoscale and fine-quartz particles in rats: toxicity is not dependent upon particle size but on surface characteristics. *Toxicol Sci* 95: 270-280.
- Fischer H, Liu L, Pang K, Chan W (2006) Pharmacokinetics of nanoscale quantum dots: *in vivo* distribution, sequestration, and clearance in the rat. *Adv Funct Mater* 16: 1299 - 1305.
- Lozano O, Laloy J, Alpan L, Mejia J, Rolin S, et al. (2012) Effects of SiC nanoparticles orally administered in a rat model: Biodistribution, toxicity and elemental composition changes in feces and organs. *Toxicology and Applied Pharmacology* 264: 232-245.
- Hughes MF, Long TC, Boyes WK, Ramabhadran R (2013) Whole-body retention and distribution of orally administered radiolabelled zerovalent iron nanoparticles in mice. *Nanotoxicology* 7: 1064-1069.
- Cho WS, Kang BC, Lee JK, Jeong J, Che JH, et al. (2013) Comparative absorption, distribution, and excretion of titanium dioxide and zinc oxide nanoparticles after repeated oral administration. *Part Fibre Toxicol* 10: 9.
- Wang J, Zhou G, Chen C, Yu H, Wang T, et al. (2007) Acute toxicity and biodistribution of different sized titanium dioxide particles in mice after oral administration. *Toxicol Lett* 168: 176-185.
- Razzaboni BL, Bolsaitis P (1990) Evidence of an oxidative mechanism for the hemolytic activity of silica particles. *Environ Health Perspect* 87: 337-341.
- Xia T, Kovochich M, Brant J, Hotze M, Sempf J, et al. (2006) Comparison of the abilities of ambient and manufactured nanoparticles to induce cellular toxicity according to an oxidative stress paradigm. *Nano Lett* 6: 1794-1807.
- Nel A (2005) Atmosphere. Air pollution-related illness: effects of particles. *Science* 308: 804-806.
- Kang SJ, Kim BM, Lee YJ, Chung HW (2008) Titanium dioxide nanoparticles trigger p53-mediated damage response in peripheral blood lymphocytes. *Environ Mol Mutagen* 49: 399-405.
- Nel A, Xia T, Mädler L, Li N (2006) Toxic potential of materials at the nanolevel. *Science* 311: 622-627.
- Durnev AD (2008) Toxicology of nanoparticles. *Bull Exp Biol Med* 145: 72-74.
- Singh N, Manshian B, Jenkins GJ, Griffiths SM, Williams PM, et al. (2009) NanoGenotoxicology: the DNA damaging potential of engineered nanomaterials. *Biomaterials* 30: 3891-3914.
- Papageorgiou I, Brown C, Schins R, Singh S, Newson R, et al. (2007) The effect of nano- and micron-sized particles of cobalt-chromium alloy on human fibroblasts *in vitro*. *Biomaterials* 28: 2946-2958.
- Chen M, von Mikecz A (2005) Formation of nucleoplasmic protein aggregates impairs nuclear function in response to SiO₂ nanoparticles. *Exp Cell Res* 305: 51-62.
- Brown DM, Wilson MR, MacNee W, Stone V, Donaldson K (2001) Size-Dependent Proinflammatory Effects of Ultrafine Polystyrene Particles: A Role for Surface Area and Oxidative Stress in the Enhanced Activity of Ultrafines. *Toxicology and Applied Pharmacology* 175: 191-199.
- Knaapen AM, Borm PJ, Albrecht C, Schins RP (2004) Inhaled particles and lung cancer. Part A: Mechanisms. *Int J Cancer* 109: 799-809.
- Schlagenhauf L, Chu BT, Buha J, Nüesch F, Wang J (2012) Release of carbon nanotubes from an epoxy-based nanocomposite during an abrasion process. *Environ Sci Technol* 46: 7366-7372.
- Tang T, Gminski R, Könczöl M, Modest C, Armbruster B, et al. (2012) Investigations on cytotoxic and genotoxic effects of laser printer emissions in human epithelial A549 lung cells using an air/liquid exposure system. *Environ Mol Mutagen* 53: 125-135.
- Van Landuyt KL, Hellack B, Van Meerbeek B, Peumans M, Hoet P, et al. (2013) Nanoparticle release from dental composites. *Acta Biomater* .
- Svensson CR, Messing ME, Lundqvist M, Schollin A, Deppert K, et al. (2013)

- Direct Deposition of Gas Phase Generated Aerosol Gold Nanoparticles into Biological Fluids - Corona Formation and Particle Size Shifts. PLoS ONE 8: e74702.
24. Khatri M, Bello D, Gaines P, Martin J, Pal AK, et al. (2013) Nanoparticles from photocopiers induce oxidative stress and upper respiratory tract inflammation in healthy volunteers. *Nanotoxicology* 7: 1014-1027.
 25. Goud KI, Hasan Q, Balakrishna N, Rao KP, Ahuja YR (2004) Genotoxicity evaluation of individuals working with photocopying machines. *Mutat Res* 563: 151-158.
 26. Theegarten D, Boukercha S, Philippou S, Anhenn O (2010) Submesothelial deposition of carbon nanoparticles after toner exposition: case report. *Diagn Pathol* 5: 77.
 27. Naya M, Kobayashi N, Ema M, Kasamoto S, Fukumuro M, et al. (2012) *In vivo* genotoxicity study of titanium dioxide nanoparticles using comet assay following intratracheal instillation in rats. *Regulatory Toxicology and Pharmacology* 62: 1-6.
 28. Lin C, Lin W (2011) Sun protection factor analysis of sunscreens containing titanium dioxide nanoparticles. *J Food Drug Anal* 19: 1 - 8.
 29. Pelgriff RY, Friedman AJ (2013) Nanotechnology as a therapeutic tool to combat microbial resistance. *Adv Drug Deliv Rev* .
 30. Jin C, Tang Y, Yang FG, Li XL, Xu S, et al. (2011) Cellular toxicity of TiO₂ nanoparticles in anatase and rutile crystal phase. *Biol Trace Elem Res* 141: 3-15.
 31. Magdolenova Z, Bilaničová D, Pojana G, Fjellsbø, LM, Hudcová A, et al. (2012) Impact of agglomeration and different dispersions of titanium dioxide nanoparticles on the human related *in vitro* cytotoxicity and genotoxicity. *J Environ Monit* 14: 455-464.
 32. Othman EM, Leyh A, Stopper H (2013) Insulin mediated DNA damage in mammalian colon cells and human lymphocytes *in vitro*. *Mutat Res* 745-746: 34-9.
 33. Jackson P, Pedersen LM, Kyjovska ZO, Jacobsen NR, Saber AT, et al. (2013) Validation of freezing tissues and cells for analysis of DNA strand break levels by comet assay. *Mutagenesis* 28: 699-707.
 34. Bhattacharya K, Davoren M, Boertz J, Schins RP, Hoffmann E, et al. (2009) Titanium dioxide nanoparticles induce oxidative stress and DNA-adduct formation but not DNA-breakage in human lung cells. *Part Fibre Toxicol* 6: 17.
 35. Florence A (2005) Nanoparticle uptake by the oral route: fulfilling its potential? *Drug Discovery Today: Technologies* 2: 75 - 81.
 36. Landsiedel R, Kapp MD, Schulz M, Wiench K, Oesch F (2009) Genotoxicity investigations on nanomaterials: Methods, preparation and characterization of test material, potential artifacts and limitations—Many questions, some answers. *Mutation Research/Reviews in Mutation Research* 681: 241-258.
 37. Trouiller B, Reliene R, Westbrook A, Solaimani P, Schiestl RH (2009) Titanium dioxide nanoparticles induce DNA damage and genetic instability *in vivo* in mice. *Cancer Res* 69: 8784-8789.
 38. Lan MY, Liu CP, Huang HH, Lee SW (2013) Both Enhanced Biocompatibility and Antibacterial Activity in Ag-Decorated TiO₂ Nanotubes. PLoS One 8: e75364.
 39. Muhlfeld C, Geiser M, Kapp N, Gehr P, Rothen-Rutishauser B (2007) Re-evaluation of pulmonary titanium dioxide nanoparticle distribution using the "relative deposition index": Evidence for clearance through microvasculature. *Part Fibre Toxicol* 4: 7.
 40. Li Y, Li J, Yin J, Li W, Kang C, et al. (2010) Systematic influence induced by 3 nm titanium dioxide following intratracheal instillation of mice. *J Nanosci Nanotechnol* 10: 8544-8549.
 41. Long TC, Saleh N, Tilton RD, Lowry GV, Veronesi B (2006) Titanium dioxide (P25) produces reactive oxygen species in immortalized brain microglia (BV2): implications for nanoparticle neurotoxicity. *Environ Sci Technol* 40: 4346-4352.
 42. Wang JJ, Sanderson BJ, Wang H (2007) Cyto- and genotoxicity of ultrafine TiO₂ particles in cultured human lymphoblastoid cells. *Mutat Res* 628: 99-106.
 43. Auttachoat W, McLoughlin CE, White KL Jr, Smith MJ (2013) Route-dependent systemic and local immune effects following exposure to solutions prepared from titanium dioxide nanoparticles. *J Immunotoxicol*.
 44. Botelho MC, Costa C, Silva S, Costa S, Dhawan A, et al. (2013) Effects of titanium dioxide nanoparticles in human gastric epithelial cells *in vitro*. *Biomed Pharmacother* .
 45. Filipe P, Silva JN, Silva R, Cirne de Castro JL, Marques Gomes M, et al. (2009) Stratum corneum is an effective barrier to TiO₂ and ZnO nanoparticle percutaneous absorption. *Skin Pharmacol Physiol* 22: 266-275.
 46. Cai R, Kubota Y, Shuin T, Sakai H, Hashimoto K, et al. (1992) Induction of cytotoxicity by photoexcited TiO₂ particles. *Cancer Res* 52: 2346-2348.
 47. Li Z, Pan X, Wang T, Wang PN, Chen JY, et al. (2013) Comparison of the killing effects between nitrogen-doped and pure TiO₂ on HeLa cells with visible light irradiation. *Nanoscale Res Lett* 8: 96.
 48. Uchino T, Tokunaga H, Ando M, Utsumi H (2002) Quantitative determination of OH radical generation and its cytotoxicity induced by TiO₂-UVA treatment. *Toxicol In vitro* 16: 629-635.
 49. Shi H, Magaye R, Castranova V, Zhao J (2013) Titanium dioxide nanoparticles: a review of current toxicological data. *Part Fibre Toxicol* 10: 15.
 50. Nakagawa Y, Wakuri S, Sakamoto K, Tanaka N (1997) The photogenotoxicity of titanium dioxide particles. *Mutat Res* 394: 125-132.
 51. Theogaraj E, Riley S, Hughes L, Maier M, Kirkland D (2007) An investigation of the photo-clastogenic potential of ultrafine titanium dioxide particles. *Mutat Res* 634: 205-219.
 52. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013) The hallmarks of aging. *Cell* 153: 1194-1217.
 53. Ishii Y, Hattori Y, Yamada T, Uesato S, Maitani Y, et al. (2009) Histone deacetylase inhibitor prodrugs in nanoparticle vector enhanced gene expression in human cancer cells. *Eur J Med Chem* 44: 4603-4610.
 54. Brioschi A, Zara GP, Calderoni S, Gasco MR, Mauro A (2008) Cholesterylbutyrate solid lipid nanoparticles as a butyric acid prodrug. *Molecules* 13: 230-254.
 55. Sule N, Singh R, Srivastava DK (2008) Alternative Modes of Binding of Recombinant Human Histone Deacetylase 8 to Colloidal Gold Nanoparticles. *J Biomed Nanotechnol* 4: 463-468.
 56. Shin JH, Metzger SK, Schoenfish MH (2007) Synthesis of nitric oxide-releasing silica nanoparticles. *J Am Chem Soc* 129: 4612-4619.
 57. Brocato J, Costa M (2013) Basic mechanics of DNA methylation and the unique landscape of the DNA methylome in metal-induced carcinogenesis. *Crit Rev Toxicol* 43: 493-514.
 58. Morano A, Angrisano T, Russo G, Landi R, Pezone A, et al. (2013) Targeted DNA methylation by homology-directed repair in mammalian cells. Transcription reshapes methylation on the repaired gene. *Nucleic Acids Res*.
 59. Li KK, Luo LF, Shen Y, Xu J, Chen Z, et al. (2013) DNA methyltransferases in hematologic malignancies. *Semin Hematol* 50: 48-60.
 60. Stocco A, Karlsson HL, Coppè F, Migliore L (2013) Epigenetic effects of nano-sized materials. *Toxicology* 313: 3-14.
 61. Parashar G, Capalash N (2012) Expression of the TIMP2 gene is not regulated by promoter hypermethylation in the Caski cell line. *Oncol Lett* 3: 1079-1082.
 62. Huang YZ, Zhan ZY, Sun YJ, Cao XK, Li MX, et al. (2013) Intragenic DNA methylation status down-regulates bovine IGF2 gene expression in different developmental stages. *Gene* .
 63. Ball MP, Li JB, Gao Y, Lee JH, LeProust EM, et al. (2009) Targeted and genome-scale strategies reveal gene-body methylation signatures in human cells. *Nat Biotechnol* 27: 361-368.
 64. Rothen-Rutishauser BM, Schürch S, Haenni B, Kapp N, Gehr P (2006) Interaction of fine particles and nanoparticles with red blood cells visualized with advanced microscopic techniques. *Environ Sci Technol* 40: 4353-4359.
 65. Gong C, Tao G, Yang L, Liu J, Liu Q, et al. (2012) Methylation of *PARP-1* promoter involved in the regulation of nano-SiO₂-induced decrease of *PARP-1* mRNA expression. *Toxicol Lett* 209: 264-269.
 66. Gong C, Tao G, Yang L, Liu J, Liu Q, et al. (2010) SiO₂ nanoparticles induce global genomic hypomethylation in HaCaT cells. *Biochem Biophys Res Commun* 397: 397-400.
 67. Bierhoff H, Postepska-Igielska A, Grummt I (2013) Noisy silence: Non-coding RNA and heterochromatin formation at repetitive elements. *Epigenetics* 9.

68. Li L-C (2014) Chromatin remodeling by the small RNA machinery in mammalian cells. *Epigenetics* 9: 0-1.
69. Sato F, Tsuchiya S, Meltzer SJ, Shimizu K (2011) MicroRNAs and epigenetics. *FEBS J* 278: 1598-1609.
70. Dreaden EC, Alkilany AM, Huang X, Murphy CJ, El-Sayed MA (2012) The golden age: gold nanoparticles for biomedicine. *Chem Soc Rev* 41: 2740-2779.
71. Balansky R, Longobardi M, Ganchev G, Ilcheva M, Nedyalkov N, et al. (2013) Transplacental clastogenic and epigenetic effects of gold nanoparticles in mice. *Mutat Res* .
72. Ng CT, Dheen ST, Yip WC, Ong CN, Bay BH, et al. (2011) The induction of epigenetic regulation of PROS1 gene in lung fibroblasts by gold nanoparticles and implications for potential lung injury. *Biomaterials* 32: 7609-7615.
73. Lee HW, Lee EH, Ha SY, Lee CH, Chang HK, et al. (2012) Altered expression of microRNA miR-21, miR-155, and let-7a and their roles in pulmonary neuroendocrine tumors. *Pathol Int* 62: 583-591.
74. Vösa U, Voeder T, Kolde R, Vilo J, Metspalu A, et al. (2013) Meta-analysis of microRNA expression in lung cancer. *Int J Cancer* 132: 2884-2893.
75. Zander DS, Baz MA, Visner GA, Staples ED, Donnelly WH, et al. (2001) Analysis of early deaths after isolated lung transplantation. *Chest* 120: 225-232.
76. Alhenc-Gelas M, Canonico M, Morange PE, Emmerich J; Geht Genetic Thrombophilia Group (2010) Protein S inherited qualitative deficiency: novel mutations and phenotypic influence. *J Thromb Haemost* 8: 2718-2726.
77. Li S, Wang H, Qi Y, Tu J, Bai Y, et al. (2011) Assessment of nanomaterial cytotoxicity with SOLiD sequencing-based microRNA expression profiling. *Biomaterials* 32: 9021-9030.
78. Berry WL, Janknecht R (2013) KDM4/JMJD2 histone demethylases: epigenetic regulators in cancer cells. *Cancer Res* 73: 2936-2942.
79. Migita S, Moquin A, Fujishiro H, Himeno S, Maysinger D, et al. (2013) Quantum dots induce heat shock-related cytotoxicity at intracellular environment. *In vitro Cell Dev Biol Anim* .
80. Nabiev I, Mitchell S, Davies A, Williams Y, Kelleher D, et al. (2007) Nonfunctionalized Nanocrystals Can Exploit a Cell's Active Transport Machinery Delivering Them to Specific Nuclear and Cytoplasmic Compartments. *Nano Letters* 7: 3452-3461.
81. Conroy J, Byrne SJ, Gun'ko YK, Rakovich YP, Donegan JF, et al. (2008) CdTe nanoparticles display tropism to core histones and histone-rich cell organelles. *Small* 4: 2006-2015.
82. Choi AO, Brown SE, Szyf M, Maysinger D (2008) Quantum dot-induced epigenetic and genotoxic changes in human breast cancer cells. *J Mol Med (Berl)* 86: 291-302.
83. Warheit DB, Donner EM (2010) Rationale of genotoxicity testing of nanomaterials: regulatory requirements and appropriateness of available OECD test guidelines. *Nanotoxicology* 4: 409-413.
84. Cedervall T, Lynch I, Lindman S, Berggård T, Thulin E, et al. (2007) Understanding the nanoparticle-protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles. *Proc Natl Acad Sci U S A* 104: 2050-2055.

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